A Deeper Dive into the Diagnosis and Management of Food Allergies

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Epidemiology and Pathophysiology of Food Allergy

Epidemiology and Increasing Prevalence of Food Allergy

Sandra Hong, MD: Currently, we are in a new place with food allergies. Up until about 5 to 10 years ago, there really weren't many options that we had for patients with food allergies. We would pretty much tell our patients that we could diagnose them with what they were allergic to and we would recommend that they completely avoid those foods because it could cause a life-threatening allergic reaction. But then from there, we would equip them with epinephrine and make sure that they went to the emergency room, but there really weren't many treatment options.

Currently, we have really gone onto a new horizon in food allergies. Not only are there new treatments that are out there, but there are so many in the pipelines that are really going to change the way that we either prevent food allergies or actually treat food allergies. And not only are they out there for our babies and infants, but also for our adolescents and also our adults that are interested in kind of changing their lives and living a totally different life, not only free from the anxiety and the isolation that food allergies can create but also being able to out there and living their lives in a totally different way.

The prevalence of food allergies in the United States. Food allergies are very prevalent in the United States, approximately 32 million people in the United States have food allergies. It's about 1 in 10 adults that have food allergies which is about 26 million adults and about 7% of children have food allergies.

The rates only appear to be rising. The incidence of peanut allergy among 4- to 17-year-olds in the US, between 2001 and 2017, had risen from 1.7 in 2001 to 5.2 in 2017. The study evaluated the number of anaphylactic visits from 2005 until 2013. There was a 173% increase in food allergies-related anaphylactic ED visits during those 8 years. There continues to be an exponential increase in food allergies causing severe systemic reactions requiring ED visits.

Risk factors for food allergies: genetic and environmental determinants. From a prenatal period, the most significant prenatal food determinants appear to be genetic factors and family history. These have the most risk for developing food allergies. Maternal diet during pregnancy and maternal folate: there are some studies that show that there may be some increased risk, however the genetic factors appear to play a much larger role. In the perinatal period, there again appear to be some studies that show the route of delivery, such as vaginal vs C-section, and antibiotic use may play a role, however gut microbiome appears to be increasing, with support to show that that plays a much higher risk of developing food allergies.

What we do know, though, is timing of the introduction of food allergies is extremely important in preventing food allergies. Patients with moderate to severe eczema are at increased risk of developing peanut and egg allergies and we know that introducing these allergens to the diet at 4 to 6 months of age can significantly decrease the rates of these food allergies. There are limited data on maternal diet during lactation and animal exposure during the postnatal period so that it would be limited enough so that we would not recommend any changes in the maternal diet or addition of any pets to the home environment. Science shows early introduction of these foods to be the most effective prevention of food allergies at this time.

Common Food Triggers

As shown in the figure below, common allergens vary geographically. This has been attributed to differing patterns of food consumption by region and culture.[1] For example, prevalent food allergens in Europe include celery, mustard, and stone fruit (commonly peach), while egg, fish, shellfish, and stone fruit (commonly mango) are among the most prevalent allergens in China.[1,2] In this

handout, we will review the most common food allergens in the United States.

Food Allergens in the United States

The 8 most common food allergens in the United States are peanut, milk, egg, tree nut, shellfish, fish, wheat, and soy.[1,3,4] A more detailed review of the prevalence of these food allergies is provided in the table.

Table. Eight Most Common Food Allergens in the United States[1,3,4]

Allergen	Prevalence	Relevance in adulthood
Peanut	~2%-5% of children	Most children continue to be allergic into adulthood
Cow's Milk	~2.5% of children younger than 3 years	Most children outgrow allergy by adulthood
Egg	~2% of children	Most children outgrow allergy by adulthood
Tree nut	~2% of children	Most children continue to be allergic into adulthood
Shellfish	~2% of the population	Most experience their first allergic reaction as adults
Fish	~1% of the population	About half experience their first allergic reaction as adults
Wheat	~1% of children	About two-thirds of children outgrow allergy by adulthood
Soy	~0.4% of children	Most children outgrow allergy by adulthood

About 90% of food allergies in the United States are caused by only 8 allergens.[1,3,4]

Recently, sesame was identified as a major allergen in the US and is now the ninth allergen added by the FDA to food labeling requirements. About 0.5% of the population self-reported sesame allergy, and about 0.2% of the population met symptomatic criteria for IgE-mediated sesame allergy.[5,6] FDA-mandated declaration requirements for sesame began in 2023.[6]

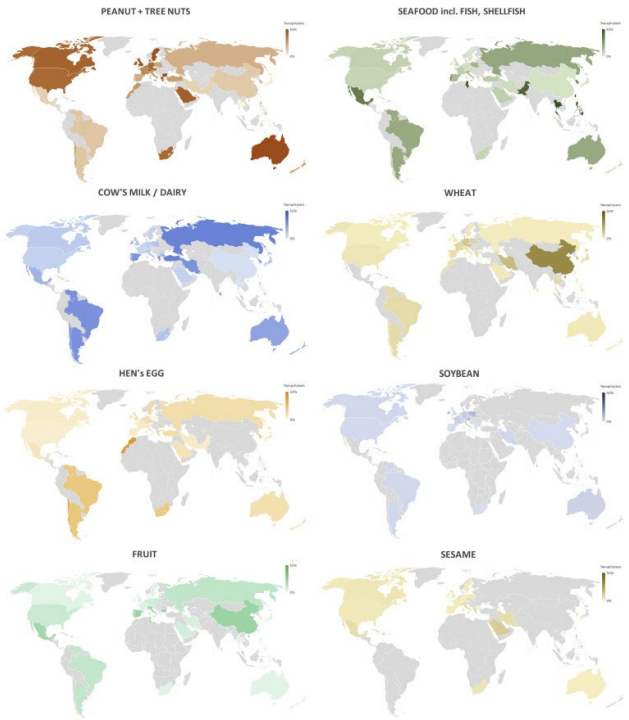

Figure. Variations in the relative frequency of anaphylaxis episodes by specific food allergen[7]
Image without modification courtesy of Baseggio Conrado A, et al. *J Allergy Clin Immunol.* 2021;148(6):1515-1525.e3. CC BY 4.0.

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Inflammatory Pathways Involved in Food Allergy

Sandra Hong, MD: Inflammatory pathways involved in food allergies. Normal physiologic responses to ingested allergens. Oral tolerance is the normal physiologic response to ingested allergens. The mechanism of oral tolerance in the intestinal mucosa requires induction of dendritic cells which produce IL-10 that suppress Th2 cells. There is a generation of the T regulatory cells, suppression of the effector T-cells, a decrease in the B-cell production of IgE, increased B-cell production of IgA and IgG4 and suppression of basophils, eosinophils and mast cell activation. Anything that disrupts any of these processes can induce food allergies to occur.

Immune tolerance vs allergic sensitization. Allergic sensitization can occur by introduction through various pathways, including the respiratory, cutaneous, intestinal or oral tract. Primary sensitization. Before one can have a food allergy reaction, they must be sensitized to the food in question. Food allergens are proteins. Relative epitopes are introduced to T-cells and then these naive CD4 T-cells differentiate into Th2 cells. The Th2 cells produce type 2 cytokines, like IL-4, IL-5, IL-13 and IL-9. These cytokines promote B-cell differentiation into IgE-producing plasma cells. Food allergen-specific IgE is distributed systemically and bind to mast cells.

After sensitization, you can have a secondary response. When the individual is reintroduced to that food protein, there is cross-linking of re-exposed food allergen to allergen-specific IgE that binds to the Fcε receptor on the mast cells which induces deregulation of the mast cells and that releases the preformed histamine and other inflammatory mediators of the immediate allergic reaction. That's what actually causes the allergic reaction, the symptoms that we would actually see in an allergic reaction. This is when patients would have the cutaneous reaction of hives. They can have the swelling of their lips, the angioedema. They can also have bronchospasm, wheezing, shortness of breath, hypotension, GI symptoms of vomiting or diarrhea and that is when they have come into contact again for the second time and third time when they're re-exposed to those allergens.

The skin barrier is a very important contributor to the development of food allergies. There have been many studies that support allergic sensitization to foods without prior ingestion. Food allergies, more specifically egg and peanut, are more prevalent in children with atopic dermatitis and the severity correlates with the risk. Additionally, peanut allergies can be associated with household peanut consumption as opposed to individual consumption.

Risks of Food Allergy

Anna Nowak-Wegrzyn, MD: People who live with food allergies are at risk for having serious and life-threatening reactions. Up to 50%, so 1 in 2 of those diagnosed with food allergy, are considered to be at high risk for anaphylaxis. We know from multiple studies from many different countries, that over the past several decades, food allergy-induced anaphylaxis that results in emergency department visit or hospitalization has increased significantly, and this is predominantly affecting younger patients. It is prevalent in all age groups, but typically most pronounced in infants, young children, as well as teenagers.

It is estimated that every 3 minutes, a food allergic reaction requires an emergency department visit and food allergic reactions, untreated, may produce very serious symptoms and ultimately be fatal, although this is quite rare.

Food allergy is also a risk for malnutrition and different deficiencies of micro- and macronutrients. We know from longitudinal studies that food allergies limit growth and development at different ages and infants are most susceptible to severe food allergies. The growth impairment can be a side effect of restricted diets, elimination of food allergen which leads to inadequate nutrient intake, but also could be associated with chronic inflammation that is present in many food-allergic conditions, such as atopic dermatitis or gastrointestinal food allergies. And we know that children affected with food allergies may be smaller and shorter, even if they outgrow their allergy, particularly if they have been diagnosed with milk allergy.

Children with more than 2 food allergies are at higher risk to have that, particularly height for age percentile in the lower bracket, so the lower quartile, compared to those who are healthy controls or those that have 1 food allergy.

Food allergy is also associated with increased economic burden and it is estimated that, on average, families of children with food allergy spend more than $4,000 per child every year and, on a population level, this adds up to $25 billion per year. And the annual cost of the food

allergy in the US is mostly reflected in the out-of-pocket costs and also opportunity costs, such as a need to change working arrangement or moving to a different city or having to hire special childcare provider, etc. Direct medical costs are also quite substantial, but they account for a smaller proportion of the financial burden.

In addition to the risk of allergic reaction, nutritional risk as well as financial risk, there are significant psychosocial and emotional burdens of food allergy that have been recognized over the years.

Psychosocial and Emotional Burdens of Food Allergy
Living the life of food allergies | Julia Cecilia

Food Allergies: Simultaneously Over- and Underdiagnosis

Anna Nowak-Wegrzyn, MD: When it comes to recognition of food allergies, diagnosis can be quite difficult or challenging because there's both risk for under- and overdiagnosis of food allergy. Overdiagnosis has adverse consequences. Essentially, this is medicalizing a patient, so turning a healthy individual into a patient with a disease on the basis of a clinical test or examination finding when they are not likely to suffer any of the consequences of the condition. And for food allergy, this leads to unnecessary anxiety and stress. Diagnosis of food allergy causes a lot of worry and stress in all aspects of life. This can also result in unnecessary elimination diet leading to malnutrition. It requires special arrangements for childcare, summer camps and after-school care as well as overuse of treatments and medical resources. Unfortunately, we still are dealing with the overdiagnosis of food allergy on the basis of a positive test without taking into account the actual clinical manifestations or tolerance, clinical tolerance, to food despite having a positive test.

However, under-diagnosis is another facet of food allergy and particularly we'd like to highlight the underdiagnosis in underprivileged populations. We know that compared with White children, Black and Asian children have higher risk for food allergy, particularly Black children. Also, there is a significant increase in prevalence of food allergy most rapid among non-Hispanic Black adults, estimated to be a 2.1% per decade. However, the rates of clinician-diagnosed food allergy are lower among pupils in public schools with more Black and lower-income children than in private schools with more White and higher-income children, 7.4% vs 17.5%. Unfortunately, even among those Black children who have a history of severe food reaction, about 50% of them have never received a clinician diagnosis of food allergy. This is very concerning and certainly points to the need for better recognition and more efforts to provide appropriate care to the patients, Black children with food allergies.

Here are some social determinants of health that are likely to contribute to disparities in food allergy diagnosis and they are multifaceted. There is the issue of food insecurity and lack of varied diet, lack of access to specialty care which is determined by geographic location as well as transportation barriers. There could be cultural and language barriers to care. Lack of insurance or underinsurance that doesn't allow the person to seek specialist care. And then, of course, also discrimination, stress and bias on the part of the healthcare provider. All of these are potentially contributing to disparities in food allergy.

Clinical Features and Diagnosis of Food Allergy

Clinical Presentation of Food Allergy

Anna Nowak-Wegrzyn, MD: Now we will discuss the clinical presentation of food allergy. The most common food allergies are classified as an IgE-mediated food allergy reaction. They account for the majority of the allergic reactions to foods and there are involved IgE antibodies in the pathophysiology of those reactions. Symptoms typically start within minutes to half an hour to an hour and they involve skin, are associated with itching, swelling, hives and flushing. Symptoms from the gastrointestinal tract involve oropharyngeal symptoms, itching in the mouth, itching in the throat, tongue swelling, nausea, abdominal pain, vomiting, diarrhea. Symptoms from the respiratory tract, upper respiratory symptoms involve sneezing, nasal congestion, laryngeal edema, hoarseness or dry cough. From lower airways, the most concerning is wheezing, cough, chest tightness and shortness of breath and, of course, labored breathing. Cardiovascular symptoms tend to more pronounced in older patients, our teenagers, young adults and older patients compared to younger patients. And the symptoms involve tachycardia, although occasionally bradycardia can also be observed, hypotension, dizziness, fainting and loss of consciousness. These tend to be very dramatic, quite obvious. There's also a reported sense of impending doom in severe allergic reactions that the

patient has this sort of overwhelming anxiety and expectation of a catastrophic event.

These are the IgE-mediated food allergic reactions, however there's a category of the non-IgE-mediated food allergies as well as mixed pathophysiology where symptoms tend to be a little bit more obscure and not as obviously associated with the ingestion of the food. For the non-IgE-mediated food allergy, symptoms are usually isolated to gastrointestinal symptoms, to gastrointestinal tract, with nausea, vomiting, diarrhea, stomach cramps, but also could involve skin in the mixed pathophysiology reaction, such as atopic dermatitis. Symptoms start within hours to even days after introduction of the food into the diet. For the most severe manifestation, the IgE presents as anaphylaxis, that is multi-organ system allergic reaction. For the non-IgE-mediated food allergies or mixed pathophysiology, presentation is usually not this dramatic, and life-threatening reactions are quite rare, but are not impossible, in particularly in the food protein-induced enterocolitis syndrome.

In terms of the mechanism, classic IgE-mediated food allergies are an example of type 1 hypersensitivity reactions. For the mixed and non-IgE-mediated food allergy, those are typically type 3 or 4 hypersensitivity reactions. And examples here include reactions to peanut, tree nuts, seafood, milk, eggs, wheat offer the IgE-mediated allergy and specific conditions, such as eosinophilic esophagitis, food protein-induced enterocolitis syndrome or protocolitis or enteropathy in non-IgE-mediated or mixed pathophysiology food allergic reactions.

Diagnosing Food Allergy (NIAID and AAAAI/ACAAI Guidelines)

Sandra Hong, MD: The diagnosis of a food allergy is dependent on a really great history, however neither a history or a physical exam is diagnostic. It's important to know the symptoms that have occurred. It is extremely important to know the timing. When a patient comes into the office, you typically want to know what were the symptoms they had. You want to know if they started to have shortness of breath or wheezing, tightness in their chest, if they developed any vomiting or diarrhea and you also want to know the timing of the reaction. You want to know how soon the reaction actually occurred after ingestion and you also want to know how long the symptoms actually lasted. Typically, a reaction occurs within 4 hours of ingestion. Anything longer than that makes an IgE-mediated reaction very unlikely. You want to know the route of exposure and the amount of food that was ingested. Typically, a patient needs to actually ingest the food product in the vast majority of patients and food products. There are some foods where it can be cooked and you can actually have symptoms from the cooked product, however typically patients need to actually have it exposed to mucosal surfaces or ingested or an open surface, such as patients with eczema and open skin surface areas.

The amount of food that is ingested is important. Certain amounts can cause increased reactions and the form of the food is important. Patients that have oral allergy syndrome will notice that eating a raw apple will cause symptoms, however if they actually eat a baked apple pie or if they drink apple cider, anything that's been cooked, they are able to tolerate it. The other important thing is if a patient has any difficulties with milk, cows' milk, or eggs, hens' eggs, if they're able to tolerate it baked into foods, this can be a very important distinction for these patients. Epidemiologic factors and other potential triggers are extremely important and the presence of cofactors, including exercise, febrile illnesses, alcohol, drugs, aspirin and NSAID use are extremely important in the history of a food allergy.

Physical exams are important, especially in noticing evidence of atopy. In infants, a patient that has eczema is at increased risk of egg and peanut allergies. You want to look for evidence of atopic diseases. Patients that have allergic rhinitis, you may notice that they have nasal congestion, they may have bluish nasal mucosa, they may have allergic shiners. Additionally, if they have atopic dermatitis, you'll notice these areas of excoriation. Babies typically will do this grasping technique of their chest and those will be evidence of atopic dermatitis. And then, on physical exam, obviously if there's evidence of wheezing or they give you a history of asthma, this increases their risk for atopy and increases your concern for a food allergy.

You will also look for other evidence of non-IgE-mediated food reactions. Failure to thrive or autoimmune diseases. If you're concerned about other issues, hemoccult-positive stools, evidence of mucous in the stools, those are other things that you might look for on physical exam.

Testing is an important piece of diagnosing a food allergy. Very frequently, it is very difficult to determine the exact allergen contributing to a reaction based on a history, and

studies show that patients have a low positive predictive value for being able to self-report food allergies. The guidelines for allergy testing are either to do skin testing or serum blood testing. Very frequently a patient will come into the office and they will bring their baby in that's 1 year of age. They had actually come in from their birthday party and they had given their baby a smash cake. And within minutes of been given their smash cake, they developed hives, urticaria, they started to cry, they developed some emesis. And the things that you start to think about when you think about a cake, you think about possibly eggs, you think about dairy, you think about wheat and then you think about possibilities of cross-contamination with peanuts and tree nuts. And this is where you would do a really great history to determine whether or not they've eaten those foods in the past. And so you get a history that, gosh, they've eaten wheat before and they've had cows' milk before, but they really haven't introduced any of the eggs or peanuts or tree nuts that they may have been exposed to.

And in this case, this is where you would want to do further testing. Your choices are either to do skin prick testing or serum IgE testing, also called immunoassays. The beauty of skin testing is that you will get immediate testing results within 15 minutes of this happening. The way that skin testing occurs is that the skin is lanced with purified allergen that's being tested. It activates the IgE antibodies on the cutaneous mast cells and again you'll receive the testing results within 15 minutes of placing the testing. Serum IgE testing or immunoassays are blood samples that evaluate serum IgE specific to the allergens. One is able to obtain a quantitative level for these. Both tests can give false-positive results, and this is the reason that it's important to only test foods that are directed by the history. Skin tests, however, have a very good negative predictive value. Therefore, if a skin test is negative, it generally means that the patient will not have an IgE-mediated reaction. In the patients that I've mentioned, if everything comes back negative to the peanuts and the tree nuts, however egg is positive, one would feel pretty comfortable that the peanuts and tree nuts would be safe for this patient to eat, however you would be concerned about egg as a possible contributor to this patient's history.

Oral food challenges are considered to determine tolerance or to confirm an allergy. It is used to determine the need for an elimination diet. It must be performed under the supervision of a trained clinician prepared to treat an anaphylactic reaction. There are various types of oral challenges. One type is an open challenge, and this is the most common and utilized in practice since it's the most cost-effective. It's unmasked and unblinded, however patients that are anxious can affect the results of these challenges.

The second type is a single-blinded challenge, and this is where the patients do not know which doses have the actual allergen in them. And the third type, and lastly, are the double-blinded, placebo-controlled studies and these are the gold standards in any food allergy diagnosis. This is able to remove the patient's anxiety from the results.

Avoiding Inappropriate Testing for Food Allergy

Sandra Hong, MD: As I've mentioned previously, it is important [for] focus testing to be specific to the patient's medical history. This means that testing panels should not be done on large panels of foods that were not ingested at the time of the reaction. The reason for this is that there are false-positive tests. In other words, patients have positive skin tests and blood work in 8% of patients tested for foods that can clinically ingest them. This can lead to overdiagnosis of food allergies and in turn create unneeded stress and dietary avoidance.

Allergists typically do not promote testing for IgG or IgG4. These levels indicate previous exposure or tolerance to that food allergen. For instance, if there is an elevated IgG to cows' milk, this would imply the patient has been exposed to cows' milk in the past and we typically would not ask for that patient to discontinue drinking or eating any of the foods with cows' milk in them.

Serum antibody allergy testing. You would caution against random testing to screen for food allergies. As an allergist, I would actually recommend against large panels of food for testing. Without a history of ingestion and clinical reaction, there can be risks of false-positives which can lead to overdiagnosis of food allergies. This leads to unnecessary elimination diets, anxiety and malnutrition. On the other hand, misinterpretation of lab work can also lead to underdiagnosis which can lead to serious life-threatening food reactions.

Intradermal testing: similar to TB tests where small amounts of antigen are injected into the dermal layer. This is not recommended in food allergy testing. In those patients that are highly sensitive to foods, these can lead to severe, life-threatening reactions. Additionally, the testing has high levels of false-positive results, therefore

there is no utility to performing this form of testing for any patients with food allergies.

Atopy patch testing is widely used in contact dermatitis testing. This is where a topical solution of the allergen is applied to the skin for extended periods of time. At this time, there is no standardizations of the parameters and it's not recommended in clinical use.

Safe Food Challenge Testing

Sandra Hong, MD: Please consider referring food challenges to allergists who are trained to perform oral food challenges. Oral challenges typically can be safely performed in an allergist's office that is adequately staffed and this is typically a 1-to-1 nursing-to-patient staff ratio and prepared to treat severe anaphylaxis and has rapid access to emergency medical services.

Prior to starting any oral challenge, it is important for the provider to obtain consent for the challenge. Typically, in private practices, allergists can choose to accomplish oral challenges in a variety of ways. These are 2 examples that can be used. The allergist determines a complete serving size and they can divide the serving size into 4 to 6 doses and they divide it by intervals of time, typically anywhere between 15- to 30-minute intervals, watching for any sorts of reactions that may occur.

This is an example of a protocol that would be used in a research setting where the doses of protein would be weighed. This allows for the amount of allergen that elicits the reaction to be calculated, which is standardized between the subjects.

Oral challenges can be extremely difficult for patients, especially as the child gets older or if their reaction was particularly severe. This can very frequently lead to subjective symptoms during these challenges. Patients frequently will describe symptoms that can be attributed to anxiety, and these can be very difficult for patients, families, and the staff, to differentiate. It is very important to determine if the patient and family are ready for challenges, though I would say the only way to get past the anxiety of a food allergy is to do a challenge if they have developed a tolerance. If they are not ready, then it is important to garner the help of a pediatric behavioral health professional for the child or if the anxiety is with the parent or guardian, it would be important for them to have some support in moving forward. Additionally, it is important to avoid terms like "passing" or "failing" because this can sometimes cause patients to feel self-blame.

Case Study: James

Anna Nowak-Wegrzyn, MD: Alright, so our first case is that of a 6-month-old boy, James. His parents present for follow-up of atopic dermatitis that was diagnosed 2 weeks prior to the appointment. They report the use of topical emollient after bathing, as well as topical steroids as recommended by the treating physician, however his atopic dermatitis rash has not improved. You can appreciate the erythema, thickening and hyperlinearity of the skin, with some hyperpigmentation on his hands, in the pictures included on slide 47.

There are additional symptoms from the gastrointestinal tract. He is very colicky, irritable, has frequent random episodes of vomiting and is overall very fussy. He is in the 25th height-for-weight percentile and he has slowed down in his growth.

Medical history reveals worsening symptoms and parents' [reported symptoms] related to introduction of yogurt into James' diet. Solid foods and formula, milk-based formula, were introduced 1 month prior, but he's still partially breast-fed. At this point the allergist recommended evaluation with a skin prick test to the milk extract. Skin prick test results is positive for cows' milk with an 8 mm wheal. The skin prick test results are expressed as average diameter of the wheal, swelling over the erythema, but the wheal measurement is most relevant. This is a pretty high, strong, skin test reaction which, in prior studies, has been identified as 95% predictive of a clinical reaction to cows' milk. Based on that information, and on his clinical history, the recommendation was made to remove dairy from James' diet. Importantly, the cows' milk formula was substituted by a hypoallergenic formula, so appropriate alternative, another potential substitution might be soy-based formula, but this will require additional testing since soy formula is not considered hypoallergenic. And James has been referred to a registered dietician for evaluation because of the concerns of his slower growth.

He will be followed frequently, every 3 to 6 months, to evaluate for resolution of cows' milk allergy. Children with cows' milk allergy usually sort of outgrow their milk allergy by school age, and children that have milder eczema tend to outgrow their milk allergies at a younger age compared to those that have more severe eczema. In

children like James, we sometimes perform oral food challenges to determine if they might tolerate milk in the baked form to allow them to incorporate baked products into the diet.

Case Study: Victoria

Anna Nowak-Wegrzyn, MD: A second study is that of Victoria. She's a 2-year-old toddler and she presents with her parents for evaluation of an acute urticaria on her arms. They've noted that symptoms started 2 days ago and hives are still present. And they are sort of worried about tree nuts and allergy to tree nuts because Victoria ate walnuts for the first time 3 days ago.

And the medical history reveals that Victoria only had walnuts 1 time 2 days ago and has not eaten any walnuts since then. The rash has come and gone over the last 2 days in response to antihistamine. The differential diagnosis of her presentation includes acute postviral urticaria, contact dermatitis, as well as insect bite. This child would not be appropriate for evaluation for food allergy based on her history.

Food Allergy and Nutrition

Changes in Food Allergy Prevention Recommendations

Anna Nowak-Wegrzyn, MD: There have been important changes in the approach to food allergy prevention, and you can appreciate the timeline of those changing guidelines from the American Academy of Pediatrics for Prevention of Food Allergy. In 2000s, the empiric recommendations were made to delay the introduction of potentially allergenic foods, so milk until 1 year, eggs until 2 years, and nuts and fish until 3 years. But it has been observed that when those recommendations have been implemented at the same time, there was an increase in prevalence of food allergy, particularly peanut allergy. The guidelines from 2008 stated explicitly there is no evidence for delaying introduction of allergenic foods and sort of strongly recommend adding those allergenic foods into the diet because there is no evidence for that intervention. In 2015, a landmark study learning early about peanut allergy, so-called LEAP study, has been published and the study has generated evidence that early introduction of peanut was associated with an 80% reduction in peanut allergy.

The most recent guidelines from the American Academy of Pediatrics reiterated that there's no evidence for delaying introduction of allergenic foods, that they should be--all of the foods should be—introduced within the first year of life and that the early introduction of peanuts, in particular, may be beneficial for infants with high risk for allergy to peanuts, and peanuts should be introduced between 4 to 6 months in those high-risk infants who are defined as those with severe eczema or allergy to egg.

You can appreciate the results of the LEAP study. Those infants, aged between 4 to 11 months, who had a high risk for peanut allergy, defined as having severe eczema, egg allergy or both, were randomized to either avoidance of peanut for 5 years or to introduction of peanut into the diet for those 5 years, and then the prevalence of peanut allergy was evaluated at the end of 60 months. And the children were stratified based on the outcomes of the skin prick test to peanut at the time of enrollment, and you can appreciate that those who had negative skin prick test at the time of randomization into the study had substantial reduction in the peanut allergy when they're consuming peanuts. This is the orange bar compared to the avoidance group which is shown as the blue bar. However, there was also very significant reduction among those who had skin prick test positive results to peanut at the entry into the study, although there was a smaller subset of overall participants in the study.

Among both cohorts, there is again a significant reduction, over 80% reduction, in peanut allergy at the end of 5 years in the study, suggesting that early introduction of peanut had a very significant protective effect against development of peanut allergy.

An additional study, focused on patients from the general population, was the EAT study, and this was a large clinical trial that compared early vs standard introduction of multiple potentially allergenic foods. So, cows' milk, peanut, cooked egg, sesame, white fish, as well as wheat. It was a large study that involved over 1,300 infants at 3 months of age who were exclusively breast-fed. Those infants were from the general populations without any risk factors, and while, in the intention-to-treat analysis, there was no significant difference between the 2 groups, it was observed when the adherence to the protocol was taken into account, which was significantly lower for early feeding group, 42% vs 92% for the standard feeding group, there was a significant reduction in peanut and egg allergy per protocol analysis. Those who were able to add at least 2 grams of the peanut or egg protein into the diet

per week were protected from development of peanut and egg allergy compared to those who were unable to adhere to the protocol. This study highlighted the potential challenges associated with early introduction of multiple allergenic foods into the diet of infants without any risk factors.

Current Recommendations for Food Allergy Prevention

Anna Nowak-Wegrzyn, MD: Current recommendations for prevention of peanut allergy have been published in 2017 by the National Institute of Allergy and Infectious Diseases, and they were based on the outcome of the LEAP study. And they recommended that infants that have severe eczema or egg allergy are evaluated for peanut sensitization. Both tests, either serologic testing or skin prick testing to evaluate for detection of sensitization, so IgE against peanut and then the patients who have detectable specific IgE to peanut or those who have positive peanut skin prick test should be referred for a specialist consultation and evaluation. Those who are estimated to be at a low risk of reaction, which represents the largest proportion of the general population, would be recommended to introduce peanut at home or, in cases of hesitant caregivers, it could be done as a supervised feeding in the office. The important part of the guidelines is that the introduction of peanut should be followed by regular intake of peanut at home, so at least a couple of times a week at a substantial amount going forward. It is not a single event.

The implementation of the guidelines, the NIAID guidelines, has been hampered by the practical aspects of testing or assessing for severity of eczema in general clinical care as well as access to the specialist for evaluation of allergic sensitization. Based on the LEAP study, as well as subsequent smaller clinical trials and the collective evidence from different countries from Europe, from Canada, from Australia, *A Consensus Approach to Primary Prevention of Food Allergy Through Nutrition* has been published in 2021 which emphasized that although infants with severe eczema are at highest risk for food allergy, peanuts should be introduced to all infants around 6 months of age, but not before 4 months. And that also eggs should be introduced at around 6 months of age, but not before 4 months. There should be no delayed introduction of other allergenic foods in the general patient population. The recommendation was to feed a diverse diet or traditional diet and which potentially might prevent development of food allergy. There was a recommendation to not use hydrolyzed formulas which are hypoallergenic, cows' milk-based formulas for prevention of food allergy. Those formulas are appropriate for management of cows' milk and multiple food allergies, but have not proven to prevent food allergy. And then there's absolutely no evidence to support recommendation for maternal exclusion of common allergens from her own diet for the purpose of preventing food allergy. Recommendation is that the breast-feeding mother or pregnant mother should be on an unrestricted diet, sort of prepregnancy diet, that is overall healthy and includes all of the allergens in moderation.

Optimizing Nutrition in Patients with Food Allergy

Anna Nowak-Wegrzyn, MD: We covered the risk of food allergy in the context of nutrition, and this also ties to the overdiagnosis of food allergy, and a big proportion or population of patients that are unfortunately overdiagnosed with allergy are infants and children with atopic dermatitis. It is really important to focus on minimizing those unnecessary restricted diet because they place children at risk for poor growth and nutritional deficiency and you can appreciate the results of a study that showed that, through the food challenges, there's only 2% of patients who had challenge-proven cows' milk allergy with the use of a double-blind, placebo-controlled food challenge which is the gold standard for diagnosis of food allergy because it minimizes the risk of bias the best. 22% of those were found to be on an unnecessary milk elimination diet to those who underwent challenges, and then 76% were not on any restricted diet.

It is important, you know, when you suspect food allergy and you eliminate the allergens--obviously elimination of allergens is necessary because we don't want patients experiencing allergic reactions and having chronic inflammation in the form of atopic dermatitis or gastrointestinal inflammation--but it's very important to provide appropriate substitution. Alternative sources of nutrition. This table nicely outlines the nutritional risks with the potential deficiencies of protein, fat, calcium, riboflavin, phosphorus and vitamins A, D and B12 in a diet that is restricted for milk. And here is a potential alternatives list which should be modified based on the patient's age, the ability to ingest certain forms of food. And usually in patients who are milk-allergic in the first year of life or even up to 18 months of age, we do recommend feeding with an appropriate infant hypoallergenic infant formula as opposed to commercially-available fortified drinks or milks, so-called

milks, which are not really milks but are beverages based on soy, rice, oats or almond and other sources.

For eggs, you can see the alternatives for soy, wheat, peanuts and tree nuts as well as fish and shellfish. And I just want to point out that even with peanut and tree nuts that are not considered as essential nutrients, there are nutritional advantages, such as fiber and stabilizing a healthy diet, blood sugars, so currently we do encourage patients to introduce peanut and tree nuts into the diet through oral food challenges if there's a possibility they might tolerate 1 of the tree nuts or they might tolerate peanut but are allergic to tree nut and vice versa to minimize the number of the avoided foods and the restricted diet.

It really, for the patients, the infants that are struggling with growth or patients who are allergic to multiple foods or on a severely restricted diet, having consultation with a registered dietician with experience in food allergy is optimal. And registered dieticians can be important allies in managing those patients and encouraging a diverse and balanced diet. Infants who are breast-fed: it's important to encourage breast-feeding and if the baby is reacting, although it is rare, but it's possible that the baby may experience reactions to allergens present in the maternal breast milk, then we would recommend restricted, elimination of those allergens in maternal diet, but continue breast-feeding. However, it is very critical that we pay attention to adequate maternal nutrition with replacement of the eliminated foods and supplementing vitamin D as well as calcium and potentially iron. And there are known risk factors that are associated with high nutrition risk, so multiple food allergies, feeding difficulties, delays or lack of financial resources for specialty formulas, and those should be identified, and the appropriate solution should be offered to the patients.

Current Food Allergy Treatment Approaches

Overarching Treatment Principles

Sandra Hong, MD: Standard-of-care: is to remove the suspected allergen or food from the diet, being aware of possible cross-reactivity from the foods and possibly cross-contamination. Very frequently, it is helpful to have the patient see a registered dietician if there is some concern about the ability for the patients to be able to do this. It is necessary to undergo testing for confirmation and then possibly to do a diagnostic elimination followed by reintroduction that is supervised challenges by the allergist. There can be exposures through inhalation, especially with seafood. Typically, contact is not a problem unless [there are] open skin lesions or ingestions. Children sometimes need to worry about different products at school. School projects sometimes include food products that they need to stay away from and it's very necessary to teach families regarding reading labels.

It is extremely important to review signs and symptoms of anaphylaxis. It is important to ensure families are aware that the earlier they use epinephrine, the less severe the reaction. I tell patients that if they wonder to themselves should I use epinephrine, they most likely should be using it. They should always have 2 epinephrines with them at all times and the reason for this is that they may have a rebound reaction. I ask that they always call 911 and seek emergency care. Provide families and patients with a written treatment plan so that they know what to do in the case of an emergency.

Allergen immunotherapy is a novel therapy to treat very select patients with IgE-mediated food allergies. It is similar to the process that you may be aware of for allergy shots for pollen allergies. Food allergen immunotherapy is a process where desensitization is pursued by oral immunotherapy, sublingual immunotherapy (SLIT) or epicutaneous (EPIT) immunotherapy. This is where slow, increasing amounts of the allergen are exposed to the individual at regular intervals. The only FDA product currently is an oral immunotherapy product for peanut allergies, [for] ages 4 to 17 years of age. There are research protocols available for various other foods for OIT and SLIT and EPIT.

Introduction to Allergen Immunotherapy

Sandra Hong, MD: The goals of allergen immunotherapy are to increase the threshold at which the patient has a reaction which means if they have an accidental exposure, they can tolerate more than prior to treatment. Another goal is to decrease the need for the lifestyle changes and the need to read packaging, continue to ask about food safety at restaurants, fear of the accidental exposure. This would hopefully improve the quality of life and decrease their anxiety.

The Global Allergy and Asthma European Network 2022 guidelines state that patients must meet all of the following indications for OIT: IgE-mediated systemic

allergic reactions after ingestion and/or positive oral food allergy; evidence of allergic sensitization, so they need to either have a positive skin test or a serum IgE specific to the food. They must have primary food allergy. It can't be oral allergy syndrome. There is a low likelihood that they would spontaneously develop a tolerance to the food allergy. The patients and/or the caregivers or guardians must understand the efficacy, adverse effects, logistics and the potential for lifelong duration of therapy. The patients and/or the caregivers are motivated. They need to be adherent and capable of administering epinephrine treatment. Previous severe reactions to allergens or impaired quality of life due to the burden of their food allergies. They need to be willing to incorporate the allergen into their diet and the patient needs to be living in a stable and family situation. These are all extremely important and I would actually say that these are extremely reasonable for any patient considering oral immunotherapy.

The guidelines also have broken the OIT into contraindications, both absolute and relative contraindications. The absolute contraindications are for patients, if they are not patients that could adhere to the therapy and the reason for this is that if patients miss any dosing, they can have an anaphylactic and life-threatening allergic reaction. Uncontrolled or severe asthma, because this can increase their risk for a life-threatening reaction and respiratory distress. Active malignancy, active systemic autoimmune disorder, systemic immunosuppressive disorder. If the patient has untreated or uncontrolled active EOE or other eosinophilic GI disorders and partially this would play a role because OIT can actually cause EOE. Or initiation during pregnancy, again because this can cause anaphylaxis for the patient.

Relative contraindications would be severe systemic conditions, so cardiovascular disease, systemic autoimmune disorders, uncontrolled atopic dermatitis since this can exacerbate and make it difficult to determine if the patient is having an anaphylactic reaction. Again, similarly, chronic urticaria. The use of beta blockers or ACE inhibitors, this would partially be due to the fact it could be difficult to treat an anaphylactic reaction. Systemic mastocytosis, because this can also increase their risk for anaphylaxis. Ongoing up-dosing with other immunotherapy, chronic GI symptoms of uncertain etiology, the inability to consume the study product, the aversion to the taste, the allergy to the vehicle or vomiting, and a psychological disorder or eating disorder. All of these would be relative contraindications.

Desensitization: what is the difference between desensitization vs tolerance? When discussing OIT, these are 2 terms that are extremely important to discuss. Desensitization is when there is a temporary increase in the amount a patient can tolerate due to frequent exposure to an allergen. This is the primary outcome of most food allergen immunotherapy studies. Tolerance, on the other hand, is a permanent state of nonresponsiveness. This is where an allergen can be started and stopped in one's diet for extended periods of time without developing a reaction. This is the ultimate goal of food allergy immunotherapy. Sustained unresponsiveness is also another term that is used.

How does OIT occur? OIT occurs through chronic stimulation and exhaustion of allergen-specific Th2 cells. This then leads to shifts in IgE and IgG4 ratios. Early initiation increases the Th2 cells and decreases the Tregulator cells. It causes mast cells, eosinophils and basophils to increase and there's an increase in the B-cell production of IgE. You end up causing late initiation and Th2 cell exhaustion with increased Treg cells and basically you end up continuing to have the process where the whole cycle continues upon itself. And patients develop increased IgG4, increased tolerance to the product and ability to increase the amounts that they are able to tolerate of the allergen.

This is a sample OIT schedule. Typically, for the OIT process, there is an initial dose escalation on day 1. There are multiple doses given on day 1. The patient is continued on the dose that they are able to tolerate. They continue the dosing at home and typically up-dosing occurs every 2 weeks. They come back into the allergist's office every 2 weeks and they get a higher dose which they go through the up-dosing, they are monitored for typically an hour, they go home and they continue that dose for 2 weeks. And this continues on every single week going through an up-dosing. This process takes about 6 to 9 months of these every-2-week up-dosing until they are able to obtain maintenance phase. This typically takes, again, about 6 to 9 months and then they stay at their maintenance dose for months to years, and possibly lifelong.

Safety and Efficacy of OIT for Single-Food Allergies

Sandra Hong, MD: OIT is effective for desensitizing patients while on therapy, however it may not always prevent clinical reactions in the real-world setting. Being able to attain sustained unresponsiveness may be

dependent on the age of induction with patients at younger ages being more successful and those with lower severity being able to be more successful.

A systematic review of the literature on efficacy and safety of OIT, looked at 36 trials that included over 2,000 subjects, mostly children. They showed that, while on OIT, these patients increased their tolerance to peanut with a relative risk of 9.9, cows' milk and egg. They also found that the number needed to treat to increase the tolerance from 300 to 1,000 mg of peanut protein was 2.

Systematic review of allergen immunotherapy safety. They found that OIT did not increase adverse or severe adverse reactions, however they found that there may be an increase in mild adverse reactions to milk and egg. Of note, extremely food-allergic patients were excluded in some of these studies.

Peanut (Arachis hypogaea) Allergen Powder-dnfp Clinical Trials

Sandra Hong, MD: The PALISADES trial was the peanut allergen phase 3 trial that was a double-blind, placebo-controlled trial that enrolled patients ages 4 to 55 years of age with peanut allergies. The primary endpoint was the portion of participants 4 to 17 years of age who can ingest a challenge dose of 600 mg or 2 peanuts or more without dose-limiting symptoms. Sixty-seven percent who received active treatment vs 4% who received placebo were able to tolerate 600 mg or more of peanut protein with only mild symptoms at the exit interview after 24 weeks of treatment.

ARC004 was an open-label follow-up to PALISADES. Basically, this was an open-label, follow-on study to PALISADES where they used 5 dosing cohorts to explore treatment with the peanut therapy and alternative therapy dosing regimens. They were the patients in the active arm that tolerated more than 300 mg or about 1 peanut dose. They could continue daily or nondaily dosing. Overall, the study showed sustained safety and efficacy after the first year and there were ongoing immunomodulations that persisted into the second year of treatment.

The safety profile during the clinical trials were that revealed that during the dose escalation phase, mild symptoms of abdominal pain, vomiting, oral pruritus, nausea and oral paresthesias were common. Systemic reactions occurred in about 8% and severe systemic reactions occurred in about 4%. While on maintenance, meaning they were on their stable dose during both PALISADES and the follow-up study, there were less adverse symptoms but GI and respiratory symptoms still occurred. Severe adverse reactions occurred less than 3% of the time.

Peanut (Arachis hypogaea) Allergen Powder-dnfp Prescribing

Sandra Hong, MD: Peanut allergen powder-dnfp prescribing. There are 3 phases to dosing. Day 1 is the initial dose escalation which is made up of 5 doses. The patient tolerates the dose to the final dose of 6 mg. Each dose is monitored for a reaction and separated by a 20- to 30-minute interval. The patient returns the next day for day 2 of dosing and they maintain that dose daily at home. Every 2 weeks, they present to the office for their up-dosing. There are 11 dose levels which starts at 3 mg. These dose escalations are supervised in the office by trained, licensed providers equipped to treat anaphylaxis. The final dose is 300 mg or the equivalent of 1 peanut at maintenance.

The Global Allergy and Asthma European Network 2022 guidelines recommends OIT prescribing only occur by staff trained and experienced in food allergy immunotherapy. This includes both nursing and providers trained in recognizing and treating anaphylaxis. It is necessary to have emergency medications and treatments available immediately and the ability to provide emergency medical services within minutes is imperative.

It is extremely important to discuss OIT with the parents or guardians and also the patients. It is a very difficult decision to make for patients because there are many things that we ask the patients to do because different things can actually increase the risks for reactions. It starts with a physician's role, patient selection for OIT. Not every patient is a great patient for OIT. You want to start with a firm diagnosis of a food allergy and that starts with a great history, either skin testing or lab testing and either a food challenge or, again, a great history. You want to know about their atopic history, including atopic dermatitis, asthma. Additionally, if they have severe allergic rhinitis, you want that to be under great control, especially when you're dosing during their pollen season. Very frequently, when patients take their dose, if they start to sneeze and it's just because of their seasonal allergic rhinitis, they will actually wonder to themselves was it the dose that they had taken or was it because of

their allergic rhinitis. If they have asthma, at times patients' providers will consider actually increasing their asthma therapy as they're doing up-dosing to ensure that the asthma is extremely well cared for and it is very important to ensure that parents, patients and anyone else who may be caring for the patient understand that necessity for adherence. Again, it is very possible to have anaphylactic reactions during these times, so you want the families to understand the necessity of adherence, not missing dosing and making sure that they will tell anyone who's caring for them that they are having allergic reaction and the need to treat.

The things that are necessary to consider are actually the triggers that can increase the risks of reaction. Those are things up in the top right. We discussed things that may increase the reactions. Some can actually be having upper respiratory tract infections. If patients are having any asthma exacerbations, any increase in metabolism and this can be hot showers, increased temperatures, so fevers, exercise, we ask that patients don't dose or take hot showers or baths within 2 hours. If they are menstruating or taking NSAIDs, this can increase their risk for anaphylactic reactions. Alcohol use can also increase these risks. Patients can have symptoms of itchy mouth or throat or abdominal discomfort. Typically, you want to know those symptoms prior to starting. There is the risk of eosinophilic esophagitis, so you want to know their baseline symptoms to ensure that they don't have baseline evidence of EOE prior to starting. And then, everyone needs to know that this is something that may occur and that there are lifestyle changes that occur with it. Typically, again, we'll have patients rest for 2 hours after taking their dose. We ask that they eat with their dose of medication or food OIT. Really important to make sure that everyone, including the individuals that are going to be doing the OIT, especially a teenager or if they're about to launch into college, they are onboard because this can be a lifelong therapy and if they're not willing to proceed and continue the therapy and they're going to stop the therapy once they head off on their own, there may not be much utility to going forward and increasing the risk for anaphylaxis for these individuals.

Case Study: Julian

Sandra Hong, MD: Julian is a 13-year-old boy who is referred to your practice after a severe anaphylactic reaction to peanuts at school. He has recently joined a traveling soccer team and his parents are concerned that there may be more potential for accidental exposure. Julian has had a workup that included skin testing 3 years ago and 2 accidental reactions recently that were severe and systemic, requiring epinephrine. Julian has no atopic conditions, and his family asks about immunotherapy. Would Julian be considered eligible for OIT?

This would be a shared decision-making between Julian and his parents and his providers and, again, anyone else who may care for Julian when his parents are not around. The factors that need to be discussed are the goals of OIT. Typically, with oral immunotherapy, the studies have shown that although patients on 1 peanut a day, after about a year and a half, these patients are able to tolerate 6 to 9 peanuts. In addition to that, their reactions have been significantly mitigated and their reactions are much less severe. Talking about possible goals and efficacy of OIT. However, there are risks of OIT and Julian is an extremely active individual. It is finding the time in his day to be able to take 2 hours out where he'll be at rest, where he won't raise his body temperature. Julian will need to come in every 2 weeks for his up-dosing for the next 6 to 9 months, depending on if he has reactions. And then the need for Julian to stay on lifelong therapy. At this time, we do not know which patients will have sustained unresponsiveness, so they typically will need to continue the 300 mg a day lifelong. And then the question is the cost of therapy for the individual. These are all questions that Julian and his parents need to think about and in discussions with their providers before going forward with therapy.

Anaphylaxis and Food Allergy Management in School Settings

Food Allergies at School: Reducing Risk of Allergen Exposure

Anna Nowak-Wegrzyn, MD: Many of the patients who are affected by food allergies are school age, so we're dealing frequently with management of food allergies in a daycare or school setting, and it's very important to be familiar with approaches to reducing risk of allergen exposure. Children with food allergy are protected under the Americans with Disabilities Act, so they should be provided with access to education in the least restrictive environment. There is also the 2011 Food Allergy and Anaphylaxis Management Act that resulted in development of voluntary guidelines for food allergy and anaphylaxis management for schools, however it is quite complex and difficult to manage the situation because

those guidelines and requirements vary significant by state, by county, and even by school district.

However, we know that school is a common location where children experience food allergic reactions, so in 1 study, between 16% and 19% of children reported food allergic reactions in the school setting. Obviously, there should be good, appropriate attention paid to managing food allergies at school.

The allergist plays an important role in ensuring that the children with food allergies are safe. Their evaluation and diagnosis of food allergy should be combined with a discussion with the patient and family and caregivers about food allergy care. There is a recommendation to provide a written allergy and anaphylaxis emergency treatment plan that outlines what are the food allergens, what is the route of exposure; and the student and family should have input into that plan regarding potential self-administration of the medication for older children and this should be provided to the school by the family. The patients are given prescriptions for epinephrine, so epinephrine autoinjectors, to be available for immediate administration in case of a more severe allergic reaction, and there is requirement for collaboration with the school personnel for creating plans that are associated with effective avoidance, as well as communicating with the school team as needed.

Although food allergic reaction can result from inhalation or skin contact, the most reactions in school occur from oral ingestion. It would be incredibly uncommon to have severe reactions from cutaneous or inhaled exposures, especially in the school setting. There are some commonsense practices that should be enforced, such as teaching children that sharing foods or eating and drinking utensils should be avoided. It is important to be aware that some hidden allergens may be found in school supplies, such as for art or science projects, like Play-Doh or paint, but those would be most typically associated with more contact reactions. Food allergens can be effectively eliminated by standard cleaning methods. The surface soap and water, some detergent or wipes are sufficient to clean the surfaces.

For younger children, having a special peanut-free lunch table can reduce the risk of severe allergic reactions. This is not so important for older patients, teenagers who actually prefer not to be isolated at a special table, but for younger children who really don't control their behavior and are more vulnerable having the free lunch table can be, create a safer environment. However, it should be realized that allergen exposure is not limited to the lunchroom. It can occur anywhere in the school because children bring food from home, and this is particularly challenging for food-allergy patients during the COVID-19 pandemic which led to change in CDC recommendations regarding the presence of food in the classroom. To minimize mixing of students, in 2020, CDC recommended that snacks and lunch should be eaten in the classroom and then, in 2021, this recommendation has been discontinued. Instead, CDC left it up to the schools to determine. So again, there is a huge variability between the approaches that the schools undertake.

And for many students with food allergies, being in the vicinity of the food in the classroom, they have pretty significant adverse effects and there may be heightened anxiety regarding spills and accidental exposures. There could be relaxation of food separation protocols due to the change in the routine and obviously there could be sharing of snacks and other foods outside of mealtimes, increasing the risk of potential ingestion.

Food Allergies at School: Emergency Plans

Anna Nowak-Wegrzyn, MD: Every patient with food allergy, but particularly pediatric patients, should be provided with an individualized written document that utilizes simple lay terms to describe guidance about symptoms and treatment of anaphylaxis. Anaphylaxis and multiorgan system allergic reaction can be fatal if untreated. The emergency plan should include demographic and allergy history if relevant, the foods that are being avoided and then symptoms, potential signs and symptoms of allergic reactions, and clear instructions for treatment, as well as appropriate doses of medication.

It is not sufficient to just provide an emergency plan. It is important that school staff is trained regarding the appropriate management and how to recognize the symptoms as well as how to respond to those potential emergencies that may happen at school, during the school trips, on the bus, on the school bus, etc.

This is an example of the American Academy of Pediatrics' emergency treatment plan which may include a child photo, include demographic information and historical information about the asthma, prior anaphylaxis, whether a child may self-carry or may self-administer the medicine, and outlines what are the symptoms of severe allergy and anaphylaxis and what actions should be taken,

vs mild allergic reaction and how [it] could be best managed. Epinephrine is the first line of management of anaphylaxis, so it should be immediately available and administered if anaphylaxis is recognized and then, after using epinephrine, we recommend to activate emergency medical services, calling ambulance vs using oral antihistamines that could be sufficient for milder reactions. This is available for downloading from the American Academy of Pediatrics' website.

Anaphylaxis: Appropriate Use of Epinephrine

Anna Nowak-Wegrzyn, MD: Epinephrine autoinjectors. They are being routinely prescribed to patients with food allergy, particularly to peanut, tree nuts or the patients with a history of anaphylaxis or those who are considered to be at high risk for anaphylaxis, and those with asthma. As you can see, there are many different types of epinephrine autoinjectors that are available on the market, and they have a different mode of administration. It is important to train the patient in the use of the device that they have access to and, also, physicians need to be aware that [with] some pharmacies, in some states, there could be a substitution of a device that is covered by the patient's plan over the device that has been prescribed. The patient should be advised to notify the physician and to discuss the training in use of the device. Some of them have multiple steps required to activate the device and they're not straightforward. [For] patients who are older patients, who are being evaluated for their allergies on an annual basis, we do offer training. We review the administration, sort of the practical aspect as well as the indication for the use of epinephrine and anaphylaxis.

At this time, almost all states have epinephrine stocking laws that allow for having non-student-specific epinephrine in school, however there are very few states that require actually stocking of epinephrine in school. It is voluntary. Again, there is a huge variability depending on the state, depending on the location, depending on the public vs private school. And so for the physician who cares for patients with food allergy, it is important to be up to date with local stocking and self-carry laws. And it is important to ensure that students' families have emergency medications to provide to schools and then the school personnel should be available to administer epinephrine if needed. It requires the parents investigating who is the primary designated person to administer emergency medication, what is the school emergency protocol. Sometimes physicians are asked to provide training to the staff at school to ensure that the children are in a safe environment.

As presented before, we realize there are barriers to epinephrine access in underserved populations in the United States and there's definitely lack of access to personal epinephrine and undesignated epinephrine. There's limited education among school staff in recognizing and managing anaphylaxis if the school's located in underserved areas. And there's obviously a lack of access to allergist care and limited training for primary care providers. And some of the studies have shown that undesignated epinephrine autoinjectors are less likely to be available in schools serving lower socioeconomic status communities than the high socioeconomic status schools, however the utilization of those undesignated epinephrine autoinjectors was significantly higher among those lower socioeconomic schools. That's sort of inverse relationship showing this discrepancy.

Case Study: Casey

Anna Nowak-Wegrzyn, MD: This is a case of a 12-year-old girl, Casey, who has a history of multiple allergies. She's avoiding peanuts, soy, egg and wheat. In the past year, Casey has had 2 allergic episodes at school, both occurred to peanut, 1 of which was quite serious and required epinephrine treatment. Casey's rather on the small side. She is thin and underweight. She has had evaluation for peanut allergy that was positive 6 years ago, so positive skin prick test. Also, soy was positive on a skin prick test 6 years ago. She is avoiding egg and wheat because of self-reported allergies and the symptoms that were observed by the parents after ingestion. The question is what would be the most appropriate management for Casey? Would you do any testing? How would you like to, are you concerned about any of the information particular to her growth, nutrition and multiple dietary restrictions?

For Casey, we would recommend skin prick testing to the foods she's avoiding for which she … we don't have a clear history of anaphylaxis. We don't need to perform skin prick test to peanuts since she has had recent reactions, quite severe, but we would definitely perform skin prick test to egg, wheat and soy to assess whether she is still sensitized to those allergens. Her skin prick testing was positive for soy, but was negative for egg and wheat. This patient, Casey, is invited to undergo oral food challenges to soy, egg and wheat under physician supervision to improve her nutrition.

Oral food challenge in the clinic actually shows symptoms after ingestion of 2 grams of soy, but no symptoms after eating a full serving of egg and wheat. This results in adding egg and wheat into Casey's diet, but continued elimination of peanut and soy. And because of her growth concerns, she should be optimally referred to a registered dietician for development of balanced elimination diet. And Casey needs an emergency plan for school, as well as review of the principles of avoidance of peanut in her diet.

Emerging Food Allergy Treatments

Unmet Needs in Food Allergy & Emerging Treatments

Sandra Hong, MD: There are many unmet needs in our current state of therapies for food allergy. There is only 1 FDA-approved product and it is only for peanut. There continues to be risks of reactions to the therapy, whether it be mild symptoms such as abdominal pain or oral symptoms or more severe, such as eosinophilic esophagitis and anaphylaxis. Patients typically are extremely taste-averse to peanut when they are peanut-allergic. The peanut therapy is a defatted peanut product which continues to taste like peanut which can be unsavory for the patients. Sometimes it is possible to hide the taste in other foods, such as savory foods like tomato or others, like mint, which can mask the taste. However, very frequently these patients and children can actually taste the peanut still, despite this.

There are varying rates of sustained unresponsiveness. Some are only desensitized as long as therapy lasts, while others have achieved sustained unresponsiveness, and the ability to distinguish those patients is not available at this time. Therefore, all patients need to continue lifelong therapy. Again, since it is only peanut, it does not address the issues of all of the other food allergies.

Biologics that are currently under investigation are drugs that are key inflammatory mediators in the food allergy pathway. The emerging biologics for food allergy are those directed towards IgE, including monoclonal and antibodies directed at IgE including omalizumab and ligelizumab; IL-4 receptor, such as dupilumab which binds to the IL-4 receptor which blocks IL-4 and IL-13 intracellular signaling; IL-13 etokimab which is an IgG1 anti-IL-33 monoclonal antibody; and TSLP or tezepelumab which blocks TSLP.

Omalizumab: Early Evidence in Food Allergy

Sandra Hong, MD: Omalizumab is an anti-IgE monoclonal antibody currently FDA-approved to treat IgE-mediated perennial asthma, nasal polyposis and chronic spontaneous urticaria. It is currently being evaluated as both monotherapy and in conjunction with OIT for food allergies. Sampson et al had evaluated omalizumab as monotherapy to determine peanut flower tolerance as compared to placebo. The study was discontinued early due to severe anaphylactic reactions during initial food challenges and primary endpoints were not obtained. However, the limited data suggested an increase in tolerability to peanut powder in the omalizumab-treated subject vs placebo.

In the first study, Fiocchi et al described a real-world study of omalizumab in patients with severe asthma and multiple food allergies or failed OIT to 1 food. Patients initiated omalizumab after oral challenge at baseline. After 4 months of treatment, patients underwent repeat oral challenges. Seventy percent of the patients tolerated complete challenge doses. The remaining foods were partially tolerated. The number of reactions to unintended ingestion of allergic foods or accidental allergic reaction had dropped from 47 to 2. Asthma control improved and both patient and parent quality of life improved.

In the second study, Just et al described food allergies improved in 38% of both children and adult patients being treated with omalizumab for 12 months for severe allergic asthma as a post-hoc analysis of the STELLAR study.

There are increasing numbers of studies looking at omalizumab as an adjuvant to OIT. The studies have evaluated both the possibility of achieving higher tolerance to doses and achieving desensitization rapidly. In 1 study by Schneider et al, patients were able to obtain a maintenance dose of 4,000 mg within 8 weeks. In other studies, they have found that between 82% to 100% of patients are able to be rapidly desensitized by adding omalizumab as an adjuvant. It may reduce the risk of serious adverse reactions from OIT.

MacGinnitie et al randomized 37 patients to omalizumab or placebo. After 12 weeks, the patients underwent a rapid desensitization to 250 mg, then weekly increases to 2,000 mg. Omalizumab was discontinued and the subjects were maintained on 2 grams of peanut protein. They

then underwent a 4-gram challenge at 12 weeks after stopping omalizumab. The study found that omalizumab allowed patients to be rapidly desensitized in 8 weeks to peanut OIT and, in a majority of patients, the desensitization was sustained after omalizumab was discontinued.

Omalizumab: Ongoing Phase 2 and 3 Studies (BOOM and OUTMATCH)

Sandra Hong, MD: The BOOM trial is a phase 2 trial, 90 participants, ages 6 to 25 years of age, with 3 or more food allergies at 4 sites in Canada. They were randomized to omalizumab 8 mg per kg per month or 16 mg per kg per month or placebo. They were given it for 12 weeks, then it's dropped to 15% for 4 weeks, then 25% for 4 weeks. After a treatment period of 8 weeks, then they start an OIT mix with 3 allergens until they reach a target of 1,500 mg of protein. Every 2 weeks, they have an escalation. The primary endpoint will be the time from their start to the target maintenance of 1,5000 mg.

The OUTMATCH trial is looking at omalizumab as monotherapy or adjuvant. This is a multistage clinical trial with 2 parts, enrolling patients ages 1 to 55 years of age with a peanut allergy and at least 2 other food allergies: peanut, egg, wheat, cashew, hazelnut and/or walnut. Stage 1 is efficacy of omalizumab for the treatment of multiple foods, stage 2 comparison of the efficacy or omalizumab monotherapy vs omalizumab-facilitated multiallergen OIT, and stage 3 is the long-term efficacy and safety of these treatments, including the use of dietary forms of food allergens. Basically, stage 1 is taking a look at omalizumab as monotherapy or placebo, giving oral food challenges and then going through an open-label extension and then continuing on to stage 3 where it is for looking at the long-term efficacy and safety. And then stage 2 is omalizumab given either with a multiallergen OIT or with placebo OIT and the study will be completed December 2023.

Ligelizumab Next Generation Anti-IgE Antibody

Anna Nowak-Wegrzyn, MD: Among the emerging biologic treatments for food allergy is ligelizumab. This is a next generation anti-IgE antibody that has a greater affinity for human IgE than omalizumab, 88-fold higher. And it binds to the human IgE at a different epitope, so it has a different binding site and it does bind to the high affinity binding site, but not to the low affinity receptor binding site. Ligelizumab is actually a derivative of a HU901 which was the first humanized monoclonal IgG antibody directed against IgE that was studied for peanut allergy in adults who were peanut-allergic and showed some protective effect after 4-month injections. But it has not been developed until recently and has not been evaluated for food allergy until now.

We know that preclinical studies show that ligelizumab binds free IgE molecules. It does lead to the reduction of Fcε receptors, so binding of IgE, removing the IgE does decrease the expression of the high-affinity IgE receptors on the surface of the cells, such as mast cells and basophil. This may reduce allergen-induced activation of those effector cells and then also decrease the granulation of proinflammatory molecules. It does also block IgE/CD23 signaling, but which might potentially affect antigen presentation and IgE transport. This antibody, ligelizumab, is expected to have effect on the reactions in the skin, in the gastrointestinal tract, in the airways, as well as in the cardiovascular system.

Early evidence of potential utility of ligelizumab for food allergy came from the pharmacokinetic and pharmacodynamic studies for patients that have been overall atopic or allergic. They were noticed to have reduced free IgE and basophil receptor expression relative to omalizumab and particularly the skin prick test. Wheal size to inhalant allergens were reduced by more 95% at 6 weeks post-treatment. Monoclonal antibodies are being administered as injections. Patients with allergic asthma, in a small study, ligelizumab was associated with reduction in skin prick test wheal to the inhaled allergens relative to omalizumab. And those reductions were dose- and time-dependent. Provided an initial basis for studies of ligelizumab.

Currently there is a phase 3 clinical trial ongoing. This study involves individuals between 6 and 55 years of age, with a history of peanut allergy who have to meet specific criteria for having evidence of IgE sensitization and reacting on the positive, on the peanut, double-blind, placebo-controlled food challenge with a total IgE less than 2000 IU/mL. And the study compares 2 different doses of ligelizumab, 240 vs 120, and it also evaluates the necessary duration of the treatment with ligelizumab before the patient undergoes a food challenge. The primary endpoint of this study is the proportion of patients who are able to tolerate at least 600 mg of peanut protein dose, which translates into a 1044 mg cumulative dose of peanut protein without any dose-limiting symptoms at week 12. The design with the

different duration of placebo of 8 weeks vs 16 weeks vs 2 different doses of ligelizumab as a monotherapy will provide important insight into the mechanism and the efficacy of ligelizumab for limiting allergic reactions and increasing the threshold for developing allergic symptoms in patients with peanut allergy. It should be noted that ligelizumab, like other monoclonal antibodies and biologic treatments [that] are antigen agnostic, is an antigen agnostic treatment so even though it is being evaluated for patients with peanut allergy, it would be expected that it would exert similar effects for the other food allergens. It will be very interesting to see whether ligelizumab really is translating into improved thresholds for the patients.

Dupilumab: Early Evidence in Food Allergy

Anna Nowak-Wegrzyn, MD: Another monoclonal antibody that has been evaluated in clinical trials is dupilumab. Dupilumab is a monoclonal antibody that inhibits IL-4 and IL-13 receptor and inhibits signaling through that receptor. And it sort of globally decreases Th2 inflammatory signaling. It is currently FDA-approved for atopic dermatitis down to age 6 months, for asthma, chronic rhinosinusitis, sinusitis with polyposis, as well as eosinophilic esophagitis. It covers the spectrum of allergic conditions, and it is currently being evaluated as a monotherapy or as a combination immunotherapy with the allergen-specific immunotherapy.

You can appreciate the shutting down of the signaling through IL-4 and IL-13 results in the significant down-regulation of the allergic inflammation in the target tissues.

Initial studies with dupilumab have been conducted in adolescents with atopic dermatitis. It has really significant benefit to the patients and, in addition to improving atopic dermatitis, dupilumab was noted to be associated with better control of asthma, allergic rhinitis, as well as food allergen sensitivity. After 16 weeks of treatment as an injection every 2 weeks, in a small number of patients, there was a significant reduction in allergen specific IgE concentration. If you look at the reduction in peanut IgE, egg white and cows' milk, they are all about 40% to 50% reduced compared with baseline, suggesting that even as a monotherapy, dupilumab may be effective for management of food allergy.

However, the monotherapy clinical trial has not shown such spectacular results, so it was evaluated in a small trial in patients with peanut allergy between 6 and 7 years old. Only 8.3% of patients achieved the primary outcome of tolerating 444 mg cumulative peanut protein treatment after 24 weeks of treatment, so 6 months. And the secondary outcomes were positive. There was a cumulative tolerated dose of peanut protein increased at the end of the treatment period, however one-third of the patients still experienced quite severe allergic reactions during the food challenge at the exit from the study, but there was evidence of median peanut-specific IgE levels that decreased through week 36. It doesn't appear that dupilumab as a monotherapy is a highly efficacious therapy for patients with peanut allergy.

However, there are ongoing trials of an adjuvant dupilumab to allergen-specific oral immunotherapy with milk and peanuts, so those are registered at ClinicalTrials.gov. The first study is evaluating dupilumab vs placebo as an adjunct to peanut oral immunotherapy, and the primary outcome is the proportion of patients who tolerate 2044 mg cumulative dose of peanut protein after up-dosing. Results have not been posted. Another study is evaluating dupilumab as an adjunct to milk oral immunotherapy and this is comparing dupilumab vs placebo run-in and maintenance with milk OIT in patients 4 to 50 years [of age] who are allergic to cows' milk. And the primary outcome is the proportion of patients who tolerate 2044 mg cumulative dose of milk protein at the exit food challenge.

Dupilumab is really a very interesting, as [are] other biologics, because of their broad spectrum and not being an allergen nonspecific approach, as well as the not daily administration is definitely attractive to older patients, patients who have sort of lifestyle restrictions that lead them to not be able to participate in the oral immunotherapy, oral desensitization. And those patients are the best target population for biologics.

Next-Generation Peptide Immunotherapy

Anna Nowak-Wegrzyn, MD: The alternative to the biologics is next generation allergen immunotherapy with a mixture of peptides. Different peptides have been identified from different allergenic proteins and those peptides can modulate responses by T cells, but they are unable to cross link IgE antibodies and trigger a release of allergic mediators. The peptide immunotherapy is administered by intradermal injection and the hypothesis is that those peptides that are unable to induce IgE-mediated reactions but are still able to modulate T cell responses, would ultimately lead to reduction in the

amount of allergen-specific T cells. Compared to the currently available oral immunotherapy options, the peptide immunotherapy has some advantages, such as reduced risk of acute adverse reaction due to activation of basophils and mast cells and, importantly, no need for supervised daily dosing or dose escalations. And it may, through further reduction of the allergen-specific T cells, it may provide potentially long-term effects but this is a … large studies are currently in preparation.

To date, there's some preliminary studies done with the peanut peptide vaccine. In vitro, blood samples from people with peanut allergy, there's no evidence of activation of basophils and in phase 1 study of 66 adults with peanut allergy, adverse events were mostly mild to moderate. That was a safety study. Patients were randomized 2:1 either to peptide vaccine or placebo. As far as I know, the phase 2 clinical trial is underway.

Summary

Anna Nowak-Wegrzyn, MD: Food allergies remain an important public health problem that has significant implications and burdens for the effected individuals. The mainstay of therapy remains avoidance and avoidance obviously reduces the risk of allergic reactions, but is associated with dietary restrictions. Attention must be paid to appropriate replacement of the avoided nutrients. Patients have to be educated about the symptoms and management of acute allergic reactions and anaphylaxis treatment plans should be provided to individuals at risk for anaphylaxis, particularly children of school age. Students need to receive a written anaphylaxis treatment plan that outlines the actions needed in case of an exposure, in case of the symptoms of an allergic reaction.

There are exciting developments on the horizon regarding prevention. Benjamin Franklin said that an ounce of prevention is worth a pound of cure. Many studies are focusing on developing preventive, preventative approaches to food allergy through early introduction of the allergenic foods, from diet diversity, probiotics and other, such as meticulous skin care and aggressive treatment of eczema. Those are ongoing. At this point, the only proven approach for prevention of peanut allergy is early introduction of the peanut into the diet of infants, particularly those at high risk, such as those with eczema and/or egg allergy.

In terms of the treatment, at this point there is no cure for food allergy. Although for some children this is a transient condition and they may outgrow it with age. This is particularly true for milk, for egg, wheat allergies, but not so much for peanut or tree nut allergies. There is definitely a big interest in developing effective treatments that reduce the risk of allergic reactions and potentially might result in permanent cure. Currently, there is an oral immunotherapy product that is approved by FDA for the purpose of desensitization and reduction of accidental anaphylactic reactions in patients with peanut allergy and this is approved for individuals 4 to 17 years old. Not available for adults, or not available for infants, and there are ongoing studies evaluating various modalities at younger ages, in infants and toddlers.

On the other hand, there is a big interest in biologic therapies that are allergen-non-specific that don't require daily dosing and are not associated with allergic reactions and don't require significant lifestyle modifications that are associated with oral immunotherapy or other forms of allergen-specific immunotherapy. And those treatments may be more attractive for teenagers, for young adults and older patients. And this is a very sort of active area of investigation. We are looking forward to having some more options for our allergic patients.

Sandra Hong, MD: This is an extremely exciting time for patients that have been suffering with food allergies. Currently, there are so many food therapy options, either currently in existence or in the pipelines that will be coming out in the coming years. This will be extremely important for these patients that have been suffering for so many years with the risks of true anaphylaxis from life-threatening reactions to their food allergies that have caused either psychosocial issues with isolation or bullying. In addition to it, this may allow them to be able to live a totally different life with these new therapies and I'm very excited to be able to share this with our patients going forward.

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