

The Natural History of Food Allergy



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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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Activity Objectives

Learning objectives:

1. To understand the natural history of food allergy on a population level.
2. To understand how to use clinical and laboratory information to predict the natural history of food allergy on an individual level.

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On a population level, it is well recognized that some IgE-mediated childhood food allergies, such as milk and egg allergies, are more likely to resolve than others, such as peanut and tree nuts allergies. Unfortunately, some studies suggest that resolution rates may have slowed compared with impressions from past decades. The clinician can apply the knowledge of the epidemiology of these allergies to describe likely patient outcomes, and direct management in a general manner. However, the ability to evaluate and predict the natural course of specific food allergies for individual patients is essential to inform

personalized patient care. Data are accumulating to assist in identifying whether a child's allergy has likely resolved, informing the timing of oral food challenges or subsequent testing. Exciting recent studies are increasingly identifying early prognostic markers as well. Emerging food allergy therapies carry risks and costs. Identifying which egg-allergic patient has likely persistent allergy, and which patient with peanut allergy may experience natural resolution, is becoming an important goal to identify the best candidates for these therapies. Although more work needs to be done to identify reliable predictive markers and validate them, there is already much known about the natural course of food allergies that can be applied by the clinician to improve patient care. © 2016 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2016;4:196-203)

Key words: Food allergy; Natural history; Milk; Egg; Peanut; Tree nut; Wheat; Soy

Food allergies are increasingly common, can cause life-threatening anaphylactic reactions, lead to significant morbidity and impaired quality of life, and result in high health care costs.¹⁻⁶ Ensuring a proper diagnosis and prognosis and identifying the possibility of allergy resolution are therefore key components of management to ensure that the least number of foods is being avoided. Here, we discuss the clinical and laboratory

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Abbreviation used
SPT- skin prick test

factors associated with the natural history of pediatric IgE-mediated food allergy and the natural history of allergies to the most common food allergens. This information provides a general understanding of the natural course of specific food allergies, identifies when specific parameters can be used to predict when an individual will experience resolution of his or her food allergy or estimate his or her prognosis, and aids in guiding the timing to assess for resolution. To date there have been few well-designed studies regarding the natural history of food allergy. The estimates of the resolution rate or prognostic ability of various tests vary widely, likely attributable to methodology and the populations studied. However, a number of general findings are of clinical utility and will be emphasized here.

THE PROVIDER'S TOOLKIT: FACTORS ASSOCIATED WITH THE NATURAL HISTORY OF FOOD ALLERGY

A number of clinical features as well as laboratory measures, some of which are not yet clinically available, have been associated with the development of tolerance or persistence of a food allergy. These markers have been most studied for allergy to egg, milk, and peanut.

Clinical characteristics

Symptom severity on ingestion has been associated with the timing of resolution of allergy to foods, and allergy persistence has been associated with more severe symptoms or lower threshold dose required to elicit a reaction.⁷⁻¹¹ An earlier age at diagnosis¹¹ and the presence of other comorbid allergic diseases (eg, allergic rhinitis, asthma, and eczema)¹¹⁻¹⁴ and their severity^{8,15} are also associated with a more persistent food allergy phenotype.

Allergic sensitization

Routinely available assays of IgE sensitization include the skin prick test (SPT) and serum food-specific IgE levels. In general, larger SPT wheal size^{8,10,15,16} or higher food-specific IgE levels^{7,8,12,15-20} are associated with persistent food allergy. The rate of change of food-specific IgE levels²¹ or SPT wheal sizes¹⁶ can also help predict the likelihood that a food allergy has resolved. Less readily available assays such as IgE epitope specificity,²² IgE/IgG₄ ratio,²³ and specific IgA and IgA₂ levels²⁴ have also been associated with the development of tolerance. Allergen component-resolved diagnostics^{25,26} and cellular-based assays^{27,28} have shown promise in the diagnosis of food allergy, and may in the future prove to have a role in predicting the natural course of this disease.²⁹ Further work on the identification and refining of biomarkers associated with persistent allergy or tolerance would be of great clinical benefit to reduce the need to conduct time-intensive and potentially risky oral food challenges to assess for resolution of food allergy.

PROGNOSIS AND ASSESSMENT FOR RESOLUTION

Because the natural history of food allergy can vary so substantially, the provider should incorporate all available data to provide each patient with as much information as possible about

the likely course of the allergy. This can range from providing an overall estimate of the likelihood of outgrowing the allergy, based on general epidemiologic studies, to providing an age range and likelihood that resolution may occur on an individual basis. During follow-up, the provider may use knowledge of the natural history to inform the current diagnosis, that is, whether or not the child may have outgrown the allergy, helping to guide the decision on when to assess for resolution by performing an oral food challenge.

Some food allergens are difficult to avoid and fortunately have a generally high likelihood of resolution (eg, milk and egg; Table I). Safely liberalizing the diet to include these foods has important nutritional and quality-of-life benefits. In contrast, other food allergens such as peanuts and tree nuts have a lower likelihood of resolution and anticipatory guidance regarding prognosis is valuable to families in navigating the stages of childhood and adolescence.

During follow-up, we generally recommend yearly reevaluation by food-specific IgE levels and/or SPT results until the individual picture has stabilized. In general, reevaluation using specific IgE testing provides more prognostic information regarding the long-term timing of tolerance acquisition¹² and the short-term likelihood of passing a food challenge,³⁷ and more studies have been done using specific IgE testing rather than SPT. Although it is critical to manage each patient individually, we generally use a specific IgE level cutoff that provides a 50% positive predictive value of passing a food challenge to determine when to assess for resolution. Values have been published for some foods (Table II), but these should be interpreted with caution because studies are small and other factors beside IgE levels (such as the clinical history as described above) may influence the chance of resolution, and more information regarding prognosis is needed. In those patients without a history of reaction, whose diagnosis was made on the basis of sensitization alone, higher IgE level cutoffs may be appropriate. For example, among children with peanut-specific IgE levels of less than 5kUA/L, 77% tolerated peanut at food challenge if their peanut allergy diagnosis was made on the basis of sensitization only, whereas none passed a food challenge if they had a history of reacting to peanut.³⁷ In patients with high and unchanged specific IgE levels over several years, testing can be performed less frequently.⁴⁴ For example, a school-aged child with a peanut-specific IgE level of more than 100 kUA/L for several years or a high school student with a peanut-specific IgE level of more than 100 kUA/L is very unlikely to benefit from yearly reassessment. Factors to consider before deciding to pursue a food challenge to assess for resolution include the chance of success, the potential for risk, and preferences of the patient and family including the importance of the food to the diet.⁴⁵ Other important considerations may include patient age, history of reactions, family characteristics, and comorbidities (eg, severe atopic dermatitis or eosinophilic esophagitis). For some patients, such as a teen getting ready to attend college, a 10% to 20% chance of passing a food challenge may be worth the risk of having a reaction to a challenge, whereas in a younger child with multiple food allergies, a 50% chance of passing a food challenge may not be worth the risk of reaction.

SPECIFIC FOOD ALLERGIES

The ideal study design to define the natural history of food allergy would require a food challenge at diagnosis and at specified intervals, according to preselected criteria (see Peters et al⁴⁶

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