Advances in food allergy in 2015

Robert A. Wood, MD *Baltimore, Md*

This review highlights research advances in food allergy that were published in the *Journal* in 2015. The world of food allergy research continues to rapidly accelerate, with increasing numbers of outstanding submissions to the Journal. In 2015, important studies on the epidemiology of food allergy were published, suggesting differential rates of food allergy in specific racial and ethnic groups. Even more importantly, studies were published identifying specific risk factors for the development of peanut allergy, as well as specific prevention strategies. We also saw new studies on the diagnosis of food allergy and potential approaches to the treatment of food allergy, as well as novel mechanistic studies helping to explain the immunologic correlates of food allergy and food desensitization. (J Allergy Clin Immunol 2016;138:1541-7.)

Key words: *Food allergy, peanut allergy, immunotherapy, diagnosis, IgE testing, basophil activation test, allergy prevention*

Abbreviations used

AD:	Atopic dermatitis
BAT:	Basophil activation test
CRD:	Component-resolved diagnostics
DC:	Dendritic cell
ED10:	Dose eliciting reactions in 10% of the allergic population
EPIT:	Epicutaneous immunotherapy
HDM:	House dust mite
LAIV:	Live attenuated influenza vaccine
OFC:	Oral food challenge
OIT:	Oral immunotherapy
PA:	Peanut allergy
SLIT:	Sublingual immunotherapy
SU:	Sustained unresponsiveness
WDEIA:	Wheat-dependent exercise-induced anaphylaxis

This review highlights key advances in food allergy for the year 2015 that were selected primarily from articles published in the *Journal of Allergy and Clinical Immunology.* Although this review focuses only on original research publications, the reader should also be reminded of numerous superb review articles related to food allergy that were also published in 2015, including articles on non–IgE-mediated food allergy, the alpha-gal story, the gut microbiome, the hygiene hypothesis, and the potential application of biologics to food allergy.[1-10]

EPIDEMIOLOGY, NATURAL HISTORY, RISK FACTORS, AND PREVENTION

The epidemiology of food allergy remains a topic of considerable interest, especially given the dramatic and apparently ongoing increase in prevalence that has occurred over the past 2 decades. One specific area of interest relates to possible differences in prevalence in different racial and ethnic groups, even when living in the same geographic region.[11] However, existing data on these potential differences are far from clear, with recent studies from the United States providing conflicting results regarding rates of food sensitization, which were shown to be more common in nonwhite minorities[12]; true food allergy, which was shown to be more common in white than nonwhite groups[13]; and recent changes in the prevalence of food allergy, with a 3-fold higher increase over a 10-year period in nonwhite groups.[14]

Fox et al[15] specifically addressed this question in the United Kingdom, conducting an ethnicity-based study of children with a diagnosis of peanut allergy (PA) between 1990 and 2004, with children with egg allergy from the same clinic used as control subjects. Remarkably, they found that over this 14-year period, the proportion of children with PA from nonwhite backgrounds increased from 26.82% to 50.31%, a highly statistically significant increase of 23.5%. This increase was seen in almost all of the nonwhite subgroups, and it appeared to be specific to PA because there was absolutely no change in the prevalence of egg allergy according to ethnicity over the same time period.

In a study from the United States, McGowan et al[16] looked specifically at the prevalence of food allergy in children living in inner-city environments using data collected in the Urban Environment and Childhood Asthma birth cohort. Through age 5 years, of the 516 children (74% black and 18% Hispanic) included in the analysis, 55.4% were sensitized to milk, egg, and/or peanut (milk, 46.7%; egg, 31.0%; and peanut, 20.9%), with 9.9% categorized as truly allergic to one of these foods based on both sensitization and a convincing clinical history (peanut, 6.0%; egg, 4.3%; and milk, 2.7%; 2.5% to >1 food). An additional 18 (3.5%) children had reported reactions to foods for which IgE levels were not measured. The authors concluded that even though this was designed to be a high-risk cohort, the cumulative incidence of food allergy in this predominantly minority cohort of inner-city children is extremely high, especially considering the strict definition of food allergy that was applied and that only 3 common allergens were included.

In addition to these possible racial and ethnic differences, considerable geographic variability has also been reported.[17] Not surprisingly, these differences are especially significant in patients with food allergies that are pollen associated, and a study by

From the Department of Pediatrics, Division of Allergy and Immunology, Johns Hopkins University School of Medicine.

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Corresponding author: Robert A. Wood, MD, Department of Pediatrics, Johns Hopkins Medical Center, 600 N Wolfe St, Baltimore, MD 21287. E-mail: rwood@jhmi.edu.

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Datema et al[18] developed a clinical and molecular map of hazelnut allergy across Europe. Patients from 12 European cities underwent a detailed evaluation using skin and IgE testing, as well as an oral food challenge (OFC) in a subset. Birch pollen–driven hazelnut sensitization (Cor a 1) dominated in most cities, except in Reykjavik, Sofia, Athens, and Madrid, where reporting of hazelnut allergy was overall less frequent. In Athens IgE against Cor a 8 dominated and was strongly correlated with IgE against walnut, peach, apple, and mugwort pollen. Sensitization to the seed storage proteins Cor a 9 and Cor a 14, which is more likely to be associated with systemic reactions to hazelnut, was observed in less than 10% (mainly children) and correlated with IgE levels to nuts, seeds, and legumes.

NATURAL HISTORY

Another key aspect of food allergy epidemiology relates to its natural history. Although there have been several retrospective studies on the natural history of PA,[19-21] no prospective studies had been published until the recent study by Peters et al.[22] They followed 1-year-olds with challenge-confirmed PA (n = 156) from the population-based HealthNuts Study through 4 years of age. They conducted skin tests, peanut-specific IgE measurements, and even OFCs irrespective of risk profile and found that PA resolved in 22% of children by age 4 years. Decreasing wheal size predicted tolerance, and increasing wheal size was associated with persistence, as was a peanut IgE level of 2.1 kU/L or greater at age 4 years. These results are similar to those published in the retrospective studies, although those all included much older children, suggesting that the eventual proportion of children who outgrow their PA might be far higher than the 18% to 20% previously reported, especially if OFCs are performed routinely.

RISK FACTORS

Although an association between atopic dermatitis (AD) and food allergy has been recognized for decades, there has been a great deal of recent interest in the specific mechanisms that might underlie this connection. A series of studies have led to the hypothesis that infants can frequently have sensitization to food allergens through cutaneous exposure, especially if the skin barrier is impaired.[23-27] Additional studies supporting this hypothesis were published in 2013 and 2014 by Brough et al,[28-30] studying the distribution of peanut allergen in home environments and demonstrating relationships between early-life environmental peanut exposure and the development of PA, particularly in children who carry a filaggrin mutation. In their 2015 study, they took this a step further in collaboration with the Consortium of Food Allergy Research Observational Study, which specifically studied relationships between the history and severity of AD, environmental peanut exposure in infancy, and the development of peanut sensitization.[31] They demonstrated an exposure-response relationship between peanut protein levels in household dust and peanut sensitization, as well as likely PA, and that this effect was augmented in children with any history of AD, especially severe AD, adding further evidence to support the role of cutaneous peanut exposure, especially through an impaired skin barrier, in the development of PA.

PREVENTION

2015 saw the publication of the Learning Early About Peanut study by Du Toit et al.[32] Although not published in the *Journal*, this landmark study clearly deserves note. In brief, the study randomly assigned 640 infants (4-11 months of age) with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age. Among the 530 infants who initially had a negative peanut skin test result, the prevalence of PA at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group. Among the 98 babies who initially had positive skin test results, the prevalence of PA was 35.3% in the avoidance group and 10.6% in the consumption group. Based on these data, the authors concluded that early introduction of peanut significantly decreased the frequency of PA in this exceptionally high-risk population.

This study spawned a number of other studies, as well as the development of guidelines seeking to operationalize the Learning Early About Peanut results in the clinic. Although formal guidelines from the National Institute of Allergy and Infectious Diseases (NIAID)–sponsored working group are currently being finalized, preliminary recommendations were published by Fleischer et al[33] in the *Journal*, highlighting the potential benefits of early peanut introduction during the period of complementary food introduction in infants. This is a rapidly evolving field, with additional studies focused on other common food allergens and other patient populations.[34]

In addition to the concept of early introduction, there is great interest in other approaches to prevention.[27] In particular, strategies that might provide more general rather than food-specific protection would be most ideal, especially if they might also provide some protection against the development of other atopic diseases. Probiotics and prebiotics have been proposed to fill this role, although prior studies have yielded inconsistent and overall disappointing results. Cuello-Garcia et al[35] published a meta-analysis focused on probiotics and allergy prevention, concluding that they can reduce the risk of eczema when used by women during the last trimester of pregnancy or while breast-feeding or when given to infants. Therefore although we still have no evidence that probiotics help to prevent food allergy, hope remains that interventions that might interrupt the atopic march, which usually begins with eczema, could have an effect on the risk of other allergic diseases, including food allergy.

A prevention trial with longer-term follow-up was recently published by Grüber et al,[36] who previously reported that supplementation of the infant diet with a specific mixture of prebiotic and immunoactive oligosaccharides reduced the occurrence of AD in the first year of life.[37] In the present study they report results through 5 years of age and found that the early effects on eczema were not sustained beyond the first year of life and that there was no apparent effect on the development of respiratory allergy. Unfortunately, they did not include food allergy as an outcome. Additional studies of probiotics, prebiotics, and other approaches to reduce the incidence and severity of infantile eczema are ongoing.

DIAGNOSIS

Diagnostic testing for food allergy remains a major challenge to patient care. In addition to significant limitations in diagnostic accuracy, there is an ongoing need for tests that might help predict the risk of more severe reactions or patients at risk of reacting to smaller allergen exposures. Several articles were published in 2015 regarding each of these issues.

It has long been established that the majority of patients with sensitization to peanut or other foods will not be clinically allergic