Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2014

Scott H. Sicherer, MD,[a] and Donald Y. M. Leung, MD, PhD[b] *New York, NY, and Denver, Colo*

This review highlights some of the research advances in anaphylaxis; hypersensitivity reactions to foods, drugs, and insects; and allergic skin diseases that were reported in the *Journal* in 2014. Studies on food allergy suggest worrisomely high rates of peanut allergy and food-induced anaphylaxis-related hospitalizations. Evidence is mounting to support the theory that environmental exposure to peanut, such as in house dust, especially with an impaired skin barrier attributed to atopic dermatitis (AD) and loss of function mutations in the filaggrin gene, is a risk factor for sensitization and allergy. Diagnostic tests are improving, with early studies suggesting the possibility of developing novel cellular tests with increased diagnostic utility. Treatment trials continue to show the promise and limitations of oral immunotherapy, and mechanistic studies are elucidating pathways that might define the degree of efficacy of this treatment. Studies have also provided insights into the prevalence and characteristics of anaphylaxis and insect venom allergy, such as suggesting that baseline platelet-activating factor acetylhydrolase activity levels are related to the severity of reactions. Advances in drug allergy include identification of HLA associations for penicillin allergy and a microRNA biomarker/mechanism for toxic epidermal necrolysis. Research identifying critical events leading to skin barrier dysfunction and the polarized immune pathways that drive AD have led to new therapeutic approaches in the prevention and management of AD. (J Allergy Clin Immunol 2015;135:357-67.)

Key words: *Dermatology, skin disease, urticaria, atopic dermatitis, eczema, anaphylaxis, allergy, peanut, hypersensitivity disorders, food, drug, insect venom*

Abbreviations used
AD: Atopic dermatitis
BAT: Basophil activation test
EoE: Eosinophilic esophagitis
FLG: Filaggrin
FPIES: Food protein–induced enterocolitis syndrome
OFC: Oral food challenge
OIT: Oral immunotherapy
OR: Odds ratio
sIgE: Allergen-specific IgE
SPT: Skin prick test
TEN: Toxic epidermal necrolysis

This review highlights key advances in allergic skin disease, anaphylaxis, and hypersensitivity to foods, drugs, and insect venom selected primarily from articles published in the *Journal of Allergy and Clinical Immunology* and its sister journal, the *Journal of Allergy and Clinical Immunology: In Practice*, in 2014. Some of the key advances are summarized in Tables I-III, providing additional insights into these topics since our last review.[1]

FOOD ALLERGY

A 2014 updated food allergy practice parameter[2] is available to guide the diagnosis and management of food allergy.

Epidemiology, natural course, risk factors, and prevention

Food allergy appears to have increased in prevalence in the past 2 decades,[3] and Bunyavanich et al[4] provide additional data suggesting a spectacularly high rate of peanut allergy. They evaluated a subset of a prebirth cohort from eastern Massachusetts using various criteria, including self-report of convincing reactions, serum peanut-specific IgE (sIgE) levels, and prescription of self-injectable epinephrine devices, to estimate a rate of peanut allergy between 2% to 5%.

Rudders et al[5] add to this discouraging picture in a study using a database with a random sample from more than 12 million inpatient pediatric discharges from up to 44 states between 2000 and 2009. They found that food-induced anaphylaxis hospitalization rates doubled in this time frame, with the greatest rates of hospitalization in the northeast.

Data from the 2011 and 2012 National Health Interview Survey suggested that among 26,021 children, 5.6% reported possible

From [a]the Elliot and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, and [b]the Department of Pediatrics, Division of Pediatric Allergy/Immunology, National Jewish Health, Denver.

Disclosure of potential conflict of interest: S. H. Sicherer is a member of the American Board of Allergy and Immunology, has received consultancy fees from Food Allergy Research and Education (FARE) and Novartis, has received research support from the National Institute of Allergy and Infectious Diseases and FARE, and has received royalties from UpToDate. D. Y. M. Leung is an advisory board member for Celgene, Novartis, and Regeneron and has received consultancy fees from Biomarin and Alopexx.

Received for publication December 1, 2014; accepted for publication December 11, 2014.

Corresponding author: Scott H. Sicherer, MD, Division of Allergy/Immunology, Mount Sinai Hospital, Box 1198, One Gustave L. Levy Place, New York, NY 10029-6574. E-mail: scott.sicherer@mssm.edu.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2014.12.1906

TABLE I. Key advances in food allergy in 2014

Clinical or basic research concerns	Advances and observations
Epidemiology/natural course/risk factors/prevention	• Peanut allergy rates exceed 2%. • Increased rates of food-induced anaphylaxis hospitalizations are seen. • Transition to having detectable sIgE associated with persistent allergy is found in patients with FPIES. • Resolution of egg allergy is associated with tolerance to and incorporation of "baked" egg, lower sIgE levels, and isolated skin reactions. • Environmental exposure to peanut through an impaired skin barrier (*FLG* loss-of-function mutations/AD) increases allergy risk. • Maternal early-trimester intake of peanut is associated with lower infant risk of peanut allergy. • Murine model suggests epigenetic mechanism for increased susceptibility to peanut allergy for offspring of peanut-sensitized mice. • Diverse, "healthy" early infant diets are protective against atopic disease.
Diagnostic testing	• Improved test utility is seen with component-resolved diagnostics. • Total IgE levels might influence the diagnostic utility of sIgE for some foods (peanut, tree nut, and sesame). • BAT shows promise for increased diagnostic utility. • *IL9* expression in peanut-activated memory T_H cells distinguishes clinical peanut allergy.
Treatment/management	• Sustained unresponsiveness is noted in approximately 50% receiving long-term peanut OIT. • Insights in the mechanism of OIT include the role of IgG and regulatory T cells. • Patients with aspirin-induced respiratory disease are at high risk of alcohol-induced respiratory symptoms. • High rates of bullying of patients with food allergy need to be addressed. • Threshold doses of numerous allergens have been identified. • Nutritional concerns for patients with food allergy have been noted.
Gastrointestinal allergy/EoE	• Studies suggest EoE is as common in black as white subjects. • Environmental factors, including microbial exposure, strongly influence development of EoE. • Phospholamban, a smooth muscle contraction–related protein, might play a role in EoE. • Molecular, histopathologic, and clinical features distinguish EoE from eosinophilic gastritis. • Effectiveness of a 4-food/food group elimination diet in adults has been examined.

food allergy, and among these, high rates of poor access to food (33.5%), prescriptions (4.5%), and specialist care (2.8%) were noted, with worse access among nonwhites.[6] These data underscore the scope, costs, and disparities that underlie management of food allergy and need to be addressed through research and social action.

Several studies investigated the natural course of food allergy. Arshad et al[7] report 18-year follow up on peanut allergy and sensitization from the Isle of Wight cohort (n = 1465), finding that sensitization increased over time and was associated with grass pollen allergy. Peanut allergy rates were 0.47% at age 2 years, 0.62% at 4 years, 0.58% at 10 years, and 0.71% at 18 years, with remission in 17%.

Caubet et al[8] describe outcomes for food protein–induced enterocolitis syndrome (FPIES) among 160 subjects, observing the age of tolerance was a mean of 4.7 years for rice, 4 years for oat, and 6.7 years for soy. Interestingly, 24% of the subjects had sIgE to the incriminated food. For cow's milk, 41% of those with sIgE experienced acute reactions rather than the delayed gastrointestinal reactions characteristic of FPIES; none with sIgE resolved the allergy, whereas the median age of resolution was 5.1 years for the IgE-negative children with milk allergy.

Tan and Smith[9] further elucidate the potential course of FPIES. They describe a case series of adults, several of whom exhibited symptoms consistent with FPIES to foods such as seafood and egg, with initial presentation as adults and without documented resolution.

Two studies addressed the natural course of egg allergy. Peters et al[10] used a population-based cohort and identified 140 infants with oral food challenge (OFC)–proved raw egg allergy who were offered OFCs to egg in baked goods at age 1 year and to raw egg at age 2 years. They noted a 47% resolution rate by age 2 years that was more likely (odds ratio [OR], 5.3) if the infant tolerated baked egg, and among those who tolerated baked egg, ingestion at least 5 times per month increased the likelihood of tolerance compared with less frequent ingestion (OR, 3.5). The magnitude of egg skin prick test (SPT) size and sIgE levels at age 1 year also predicted the persistence of egg allergy at age 2 years, but filaggrin *(FLG)* gene mutations were not predictive.

Sicherer et al[11] reported egg allergy outcomes from the National Institute of Allergy and Infectious Diseases–sponsored Consortium for Food Allergy Research, showing that among 213 children followed from infancy for a median of 74 months, 49% resolved their egg allergy. The strongest predictors associated with egg allergy resolution on multivariate analyses were infant sIgE levels and the type of presenting clinical reaction (eg, isolated skin reactions were lower risk vs other presentations), and a calculator was devised to estimate the rate of resolution by using these parameters (see www.cofargroup.org).

Considering the high prevalence, slow resolution, negative effect on quality of life, and financial burdens of food allergies, there is great interest in identifying and modifying risk factors.[12] Several new studies support the hypothesis that exposure to food allergens through the skin, particularly when there is poor barrier function from atopic dermatitis (AD)/*FLG* loss-of-function mutations, is associated with an increased risk of sensitization and allergy.[13-16]

Venkataraman et al[13] used the 1989 Isle of Wight birth cohort followed to age 18 years to investigate food sensitization/allergy outcomes to multiple foods in light of *FLG* loss-of-function mutations and eczema, taking into consideration models of time