Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2013

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 2013. Studies on food allergy suggest that (1) 7.6% of the US population is affected, (2) a "healthy" early diet might prevent food allergy, (3) the skin might be an important route of sensitization, (4) allergen component testing might aid diagnosis, (5) the prognosis of milk allergy might be predictable through early testing, (6) oral or sublingual immunotherapy show promise but also have caveats, and (7) preclinical studies show promising alternative modes of immunotherapy and desensitization. Studies on eosinophilic esophagitis show a relationship to connective tissue disorders and that dietary management is an effective treatment for adults. Markers of anaphylaxis severity have been determined and might inform potential diagnostics and therapeutic targets. Insights on serum tests for drug and insect sting allergy might result in improved diagnostics. Genetic and immune-mediated defects in skin epithelial differentiation contribute to the severity of atopic dermatitis. Novel management approaches to treatment of chronic urticaria, including use of omalizumab, are being identified. (J Allergy Clin Immunol 2014;133:324-34.)

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

Abbreviations used

AD:	Atopic dermatitis
EoE:	Eosinophilic esophagitis
FPIES:	Food protein–induced enterocolitis syndrome
α-Gal:	Galactose-α-1,3-galactose
LCT:	Long-chain triglyceride
MCT:	Medium-chain triglyceride
OFC:	Oral food challenge
OIT:	Oral immunotherapy
OR:	Odds ratio
OVA:	Ovalbumin
PAF:	Platelet-activating factor
SLIT:	Sublingual immunotherapy
SPT:	Skin prick test
Treg:	Regulatory T
WT:	Wild-type

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 2013. Some of the key advances are summarized in Tables I to III, providing additional insights on these topics since our last review.[1]

FOOD ALLERGY

Epidemiology, risk factors, and prevention

The 2 most recent National Health and Nutrition Examination Surveys performed from 2007-2010 with 20,686 US participants included queries on self-reported food allergies.[2] Overall, 8.96% (95% CI, 8.32% to 9.60%) reported food allergy; among children, the percentage was 6.53% (95% CI, 5.69% to 7.37%). When adjusting for discrepancies in respondents indicating ingestion of some of the foods they reported as allergens, the overall rate was 7.64%. Self-reported food allergy among adults was more common in women, those with higher educational levels, and those of non-Hispanic/black race/ethnicity, whereas among children, prevalence was higher among non-Hispanic black children and more common among persons of all ages with asthma. Increased food allergy among black children was also supported by a meta-analysis of 12 studies.[3] Additional studies are needed to determine whether these discrepancies reflect diet, environment, genetics, or health care disparities.

Another study highlighted the increased asthma morbidity among inner-city children with food allergies: 24% of 300 children with asthma had food allergies, and having food allergy was an independent risk for hospitalization (odds ratio [OR], 2.35; 95% CI, 1.30-4.24).[4] Given the economic burden of childhood food allergies (estimated at 25 billion dollars annually in the United States),[5] the potential for erroneous self-diagnosis,[2]

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 declares that he has no relevant conflicts of interest.

Received for publication November 18, 2013; accepted for publication November 19, 2013.

Available online December 25, 2013.

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.2013.11.013

TABLE I. Key advances in food allergy in 2013

Clinical or basic research concerns	Advances and observations
Epidemiology/risk factors/prevention	● The National Health and Nutrition Examination Survey suggests a food allergy prevalence of 7.6%. ● Multiple studies implicate the skin as a route of sensitization. ● Use of specific hydrolyzed infant formulas in comparison with cow's milk might reduce rates of eczema out to 10 years. ● Studies suggest earlier introduction of allergens does not promote atopic disease. ● A "healthy diet" (fruits and vegetables) might protect against food allergies.
Gastrointestinal allergy	● Food elimination diets are effective in adults with EoE. ● Foods with "baked milk" can be tolerated in a subset of patients with milk-induced EoE. ● Importance of the mast cell–eosinophil–IL-9 axis to EoE was determined. ● The relationship of EoE to connective tissue disorders was elucidated. ● The potential for ondansetron to ameliorate vomiting during FPIES reactions was determined.
Molecular aspects/pathophysiology	● IgE to α-Gal in red meat allergy is associated with B-negative blood groups. ● A murine model elucidates strong relationship of food allergy and microbiome. ● A murine model suggests type of fats associated with allergen might affect allergen absorption and immune responses.
Diagnostic testing	● Numerous studies elucidated the role of allergen component testing. ● Predictive values of SPTs and IgE tests for egg, peanut, and sesame were evaluated in infants. ● Prognostic testing for milk allergy (calculator) was developed.
Treatment/management	● Trials of peanut OIT and SLIT suggest OIT produces more robust results. ● Combining OIT with omalizumab may facilitate desensitization. ● Murine models suggest novel immunotherapy strategies using allergen and IgG Fcγ1 and desensitization strategies using anti-FcεRIα mAb. ● Studies of allergen threshold might result in opportunity to improve ingredient labels.

α-Gal, Galactose-α-1,3-galactose.

TABLE II. Key advances in anaphylaxis, insect venom, and drug allergy in 2013

Topic	Clinical or basic research concerns	Advances and observations
Anaphylaxis	Epidemiology, risk, pathophysiology, and management	● US national prevalence is estimated to be at least 1.6% of adults. ● Antihypertensive medication use, in aggregate, is a risk for severe anaphylaxis. ● PAF and additional mediators are related to anaphylaxis severity. ● Identification was made of a potential new target for therapy.
Insect venom hypersensitivity	Risk, diagnosis, and treatment	● Sensitivity of yellow jacket and wasp venom serum tests was elucidated. ● Mast cell disease is a risk factor for Hymenoptera venom anaphylaxis, but mast cell load does not correlate with risk. ● Venom immunotherapy is safe and effective in patients with systemic mastocytosis.
Drug allergy	Pathophysiology, diagnosis, and management	● Characterization of T-cell responses in patients with delayed-type hypersensitivity was performed. ● Potential for false-positive penicillin serum test results was elucidated. ● Procalcitonin might be a marker differentiating symptoms caused by drug reaction versus bacterial infection.

and insufficient diagnosis by physicians,[6] as well as the vulnerabilities among special groups with comorbidities, these studies underscore the need for increased attention to improved diagnosis, management, and prevention of food allergies.[7]

Numerous theories have been proposed to explain the apparent increase in food allergies and other atopic diseases, with goals of identifying prevention and treatment strategies. In developing a cohort of infants age 4 to 10 months for entry into an interventional study of peanut allergy,[8] it was noted that egg allergy and severe eczema were the strongest predictors of peanut sensitization, although many children with detectable serum peanut-specific IgE had negative skin prick test (SPT) responses to peanut (black race increased the risk for serum sensitization but was relatively protective for having skin sensitization). Although these discrepancies require more study, the observation that severe eczema is a risk factor adds credence to the theory that a poor skin barrier might promote sensitization though the cutaneous route, thus bypassing oral tolerance. An interesting murine model compared epicutaneous with oral sensitization and noted that only the skin-sensitized mice had expansion of intestinal mast cells, increased serum IL-4 levels, and anaphylaxis after oral food challenge (OFC).[9] In human subjects loss-of-function mutations in filaggrin related to a defective skin barrier are associated with peanut allergy.[10] Peanut allergen is prevalent in homes in relation to household consumption, appears to be distributed throughout the home, and maintains biologic activity,[11,12] adding further plausibility to the concern that skin sensitization is a potential contributor to peanut allergy, especially when the food has not been ingested.

The notion that earlier exposure to a food allergen might promote tolerance contrasts older dogmas that avoidance could prevent sensitization and allergy. On the notion that allergen avoidance is a potential strategy, a 10-year follow-up of a randomized trial of 4 substitute formulas as breast milk substitutes in infants at risk of atopy continued to show a reduced cumulative relative risk of atopic dermatitis (AD) for specific