Advances in allergy, asthma, and immunology series 2014

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

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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 2013;■■■:■■■-■■■.)

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]

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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

TABLE III. Key advances in allergic skin diseases in 2013

Topic	Clinical or basic research concerns	Advances and observations
AD	Mechanisms	● Multifunctional role of filaggrin in AD pathophysiology was determined. ● Defects of filaggrin-like proteins (hornerin and filaggrin 2) in patients with AD were elucidated. ● Increased IL-13 and IL-22 expression was found. ● A new gene *(Tmem79)* involved in spontaneous development of AD was identified.
	Treatment	● Updated practice parameter was published for the treatment of AD. ● Meta-analysis supports a role for allergen-specific immunotherapy in the management of AD.
Chronic urticaria	Pathophysiology and treatment	● D-dimer is a biomarker for antihistamine-resistant chronic urticaria. ● Omalizumab reduces symptoms of chronic urticaria resistant to antihistamine treatment.

hydrolyzed infant formulas compared with whole cow's milk infant formula (eg, relative risk, 0.72; 95% CI, 0.58-0.88) for an extensive hydrolysate of casein.[13] The effect was accounted for by early protection that was maintained; protection was afforded for AD but not asthma, allergic rhinitis, or sensitization to foods. Regarding the alternative hypothesis that earlier exposure to allergens might be protective, a Finnish birth cohort study (n = 3781), originally developed with infants at genetic risk for diabetes, was evaluated regarding the timing of infant feeding and allergic outcomes.[14] Early introduction of wheat, rye, barley, oat, fish, and egg was associated with protection from asthma, allergic rhinitis, and atopic sensitization at age 5 years. Food allergy as an end point is difficult to assess in these studies. However, Palmer et al[15] used a randomized controlled trial to address the specific question of the effect of the timing of introduction of an allergenic food. They studied 86 infants at risk for egg allergy based on moderate-to-severe AD and randomized egg exposure at 4 months of age. The study became compromised by having a high proportion of these infants; 31% of 49 infants randomized to egg react to egg exposure. At 12 months, a lower but not significant proportion of infants in the egg group compared with control subjects were given a diagnosis of egg allergy (33% vs 51%, $P = .11$), at least suggesting that earlier exposure might not increase egg allergy. Grimshaw et al[16] used a nested, case-control, within-cohort design to evaluate the ability of the infant diet to influence food allergy outcomes by age 2 years and found no difference in the presolid infant diet, but those without food allergies were more likely to ingest a "healthy" diet of fruits, vegetables, and home-prepared foods. Thus studies suggest that the specific allergens ingested might have less to do with allergy outcomes than the healthful components of the foods comprising the diet. Also in agreement with this conclusion is the finding that vitamin D sufficiency is protective against food allergy.[17] Fleischer et al,[18] representing the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma & Immunology, provide recommendations on dietary progression for infants that include recommending exclusive breast-feeding for at least 4 months, considering use of hydrolyzed formula for those unable to breast-feed, and introducing complementary foods without a prolonged delay, including allergens when the infant is doing well. In the meantime, evaluation of prebiotics, probiotics, and bacterial lysates as an active approach to the prevention of atopy and food allergy remain active areas of investigation.[19,20]

Gastrointestinal food allergy

The diagnosis and management of eosinophilic esophagitis (EoE), with particular attention to the role of food allergens, was reviewed by Greenhawt et al,[21] who underscore the need for partnerships between allergists and gastroenterologists for successful management. Diagnosis currently requires invasive testing with endoscopies,[22] and treatment might include empiric or test result–based dietary elimination. Adding to prior studies of dietary treatment primarily in children,[21] Lucendo et al[23] applied a food elimination diet, avoiding milk, egg, cereals, fish/shellfish, peanut/legumes, and soy for 67 consecutive adult patients with EoE, followed by sequential reintroductions by type of food. Overall, 73% had reduced peak eosinophil biopsy counts (to <15/high-power field) on the complete diet. Reintroducing foods revealed that 36% of the responding patients had 1 trigger and 31% had 3 or more triggers. The most common causative allergens were milk (62%), wheat (29%), egg (26%), and legumes (24%). SPTs or serum IgE tests were not helpful. Patients who maintained the diet remained in remission for up to 3 years. However, adherence to a strict elimination diet is challenging. Leung et al[24] challenged 15 patients with proved cow's milk–responsive EoE with foods having extensively heated (baked) milk. Eleven (73%) of the 15 remained in remission, indicating a subset might tolerate these foods, which is similar to those with IgE-mediated milk allergy. Nondietary therapies for EoE are primarily limited to corticosteroids, but insights into the pathophysiology of EoE might inform new therapies.[21] In follow-up to a previous trial of anti–IL-5, in which only a subset of those treated had a response, Otani et al[25] evaluated biopsy specimens, focusing on mast cell accumulation and IL-9, a cytokine that contributes to mast cell activation. Responders had significantly fewer posttreatment mast cells, and this decrease was correlated with eosinophil numbers. Eosinophils were the main source of IL-9, and mast cells and eosinophils were observed in couplets that only decreased in those who responded to therapy. Thus the study suggests a complex interplay between mast cells, eosinophils, and IL-9 that might be a useful target for future therapies.

Additional insights into the pathophysiology of EoE are reflected in the observation of a high rate of EoE among those with connective tissue disorders, such as Marfan and Loeys-Dietz syndromes, which are related to excess TGF-β1 levels and pathway signaling. Abonia et al[26] describe 42 patients with EoE and connective tissue disorders (Marfan and Ehlers-Danlos syndrome and joint hypermobility), representing an 8-fold risk of EoE in these patients as derived from their available databases. They additionally found evidence of dysregulation of collagen transcription in patients with EoE and connective tissue disorders that is distinct from those with EoE alone and evidence of potential influence on TGF-β1 signaling. Aside from clinical implications on identification of connective tissue disorders

among those with EoE and *vice versa*, the pathophysiology of the relationship might elucidate therapeutics, possibly involving the TGF-β pathway.

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated disorder characterized by a delayed 2-hour onset of profuse vomiting. Although IgE antibodies to trigger foods might be present or develop in a subset of patients, the disorder appears to be cell mediated,[27] and skin tests and atopy patch tests are generally not helpful in diagnosis.[28,29] Therefore OFCs are required for diagnosis but might induce severe reactions. Holbrook et al[30] report a consecutive case series in which 5 patients experiencing an FPIES reaction during OFCs were treated with ondansetron, a selective serotonin receptor antagonist. Three of the 5 had prompt (usually <15 minutes) cessation of vomiting with intravenous ondansetron, and 2 required a second dose, 1 after an initial oral dose and 1 after an initial intravenous dose. The drug acts both centrally and peripherally, and the results suggest an interesting potential pathophysiologic aspect of FPIES, as well as a potential helpful therapy, although more study is needed to validate the response suggested by this case series. Both EoE and FPIES require careful nutritional management, as reviewed by Groetch et al.[31]

Pathophysiology

Elucidating the pathophysiology of food allergy is necessary for developing better diagnostic, treatment, and prevention strategies. A novel form of food allergy attributed to IgE reactivity to the carbohydrate galactose-alpha-1,3-galactose (α-Gal), likely originating from sensitization caused by tick bites and resulting in delayed allergic reactions and anaphylaxis to mammalian meats, has been increasingly characterized. Hamsten et al[32] followed up on the observation that the α-Gal epitope is a major blood group substance of nonprimate mammals and structurally related to blood group B. They evaluated Swedish patients with red meat allergy and blood donors in Sweden and found that there is a strong relationship with tick bites for the production of IgE to α-Gal and that red meat allergy is strongly associated with B-negative blood groups. It is of clinical relevance to note that gelatin candies and other gelatin-derived medicinal products might have α-Gal as well.[33] Pork allergy can also be attributable to sensitization to cat albumin, resulting in immediate reactions to pork in contrast to delayed reactions attributed to α-Gal.[34] Another interesting "syndrome" of food allergy noted in particular in Japan is wheat-associated, exercise-induced anaphylaxis, which has been linked to the use of facial soaps containing acid-hydrolyzed wheat. Nakamura et al[35] performed a series of experiments showing how patients with this syndrome responded to wheat allergens differently from those with typical wheat allergy in that they recognized epitopes associated with wheat after treatment with tissue transglutaminase and other digestive enzymes. Thus sensitization to the novel allergens corresponds to postdigestion wheat allergens. The cat-pork syndrome and this novel wheat allergy further illustrate the potential for noningestion routes of sensitization to result in food allergies.

Murine models continue to elucidate important pathophysiologic aspects of food allergy.[36-38] In one study evaluating the role of the microbiome,[38] food allergy–prone mice (IL-4 receptor α gain-of-function mutation) and wild-type (WT) control animals were subjected to oral sensitization with chicken egg ovalbumin (OVA), and enforced tolerance was achieved by using allergen-specific regulatory T (Treg) cells. The OVA-sensitized mutant mice exhibited a specific microbiota signature characterized by coordinate changes in the abundance of taxa of several bacterial families that was not shared by the sensitized WT mice, which did not exhibit an OVA-induced allergic response. Transfer of OVA-specific Treg cells to OVA-sensitized mutant mice led to a distinct tolerance-associated microbiota signature coincident with the suppression of the allergic response. The microbiota of allergen-sensitized mutant mice differentially promoted OVA-specific IgE responses and anaphylaxis when reconstituted in WT germ-free mice. Thus the mice with food allergy exhibited a specific gut microbiota signature capable of transmitting disease susceptibility and was subject to reprogramming by enforced tolerance. A review of the influence of the microbiome in human disease was also published this year.[39]

Another murine model was used to explore how fats can affect food allergy.[37] Mice were fed peanut protein in medium-chain triglycerides (MCTs), long-chain triglycerides (LCTs), or LCTs plus an inhibitor of chylomicron formation. MCTs stimulated absorption into Peyer patches and caused spontaneous allergic sensitization and reactions on challenge and stimulated jejunal-epithelial thymic stromal lymphopoietin, *Il25*, and *Il33* expression compared with that seen after LCT feeding. In addition, oral challenges with antigen in MCTs, compared with LCTs, significantly aggravated anaphylaxis. Also, the effects of MCTs could be mimicked by adding a chylomicron formation inhibitor. Thus this study supports the notion that immune response to allergens can be affected by the manner of processing and types of foods in the diet, in this case of MCTs, by affecting allergen absorption and stimulating allergic responses.

Diagnosis

A major stumbling block to food allergy diagnosis is that sensitization can occur without clinical reactivity.[40] Diagnostic tests in which IgE binding is measured to various protein components of an allergen with the hope of improving diagnostic relevance is a major area of investigation. In general, IgE binding to pollen-related labile proteins or any proteins that are less stable to digestion might be less clinically relevant. Studies in the *Journals* this year have addressed the utility of component testing for allergies to egg,[41] milk,[42] wheat,[43] soy,[44] fruits,[45-48] hazelnut,[49] and peanut.[50-55] A major theme among these studies is that the relevant allergens can vary by geographic location and that specific studies might have differing results, reflecting nuances of the study population and methods, the manner of sensitization, the degree of sensitization to various food components, environmental exposure, and numerous other factors. Peanut allergy has garnered the most attention in this regard, where attempting to understand the relationship of clinical outcomes to component testing has uncovered many uncertainties and variations, but most studies emphasize the clinical utility of determining IgE binding to Ara h 2.[50] For example, children in Ghana, where peanut is ingested in large amounts, showed clinically irrelevant sensitization to peanut that appears to be related to cross-reactive carbohydrate determinants, possibly because of parasite sensitization. Variations are noted in the predictive values of Ara h 2; for example, in children in The Netherlands with suspected peanut allergy, a cutoff of 5 kU_A/L or greater had the best overall predictive value (positive predictive

value, 96%; negative predictive value, 71%). In a referral population in the United States, the positive predictive value was 75% at 2 kU_A/L, and the negative predictive value was 91% at 0.23 kU_A/L. Clearly, there are patients with increased test results to Ara h 2 who tolerate peanut,[53,55] and the Ara h 2 level does not seem to clearly predict severity.[52] Nonetheless, component testing, possibly used as a staged approach with standard tests, can assist in diagnosis, as reviewed by Sicherer and Wood.[50] Interestingly, IgE binding to Ara h 1 and 3 might be related to surface-exposed sequences similar to those in Ara h 2.[56]

Studies continue to elucidate the diagnostic utility of standard tests as well. In a unique population-based Australian cohort of infants who underwent testing and OFCs, 95% predictive values for allergic reactions were determined as follows for egg (SPT wheal, ≥4 mm; serum IgE level, ≥1.7 kU_A/L), peanut (SPT wheal, ≥8 mm; serum IgE level, ≥34 kU_A/L), and sesame (SPT wheal, ≥8 mm).[57] Attention is also drawn to using combinations of tests and clinical factors to predict allergy.[58] With regard to distinguishing children who tolerate extensively heated cow's milk from those who do not, a number of factors were informative,[59] including casein- and milk-specific IgE levels, casein-specific IgG_4 levels, and casein IgE/IgG_4 ratios; milk-specific to nonspecific basophil activation ratios, median basophil reactivity, and spontaneous basophil activation; and milk SPT wheal diameters. Casein- and milk-specific IgE levels, milk-specific basophil reactivity, and milk SPT wheal diameters were all significantly greater among patients with milk allergy who react to baked milk than among those who tolerate it. Ultimately, food diagnostic studies typically conclude that the OFC is required for diagnosis in a substantial number of patients. The procedure must include the form of the food that will be eaten after testing. For example, Turner et al[60] identified children with wheat allergy who tolerated whole-grain wheat cereal biscuits on challenge, likely because processing of the biscuits removed or altered a relevant protein.

A holy grail for diagnostics is long-term prognosis. In evaluating children with milk allergy in a longitudinal study sponsored by the Consortium of Food Allergy Research, milk allergy resolved in 154 (52.6%) subjects at a median age of 63 months.[61] Baseline (determined at age 3-15 months) characteristics that were most predictive of resolution included milk-specific IgE level, SPT wheal size, and AD severity (all $P < .001$). Baseline expression of GATA-3, IL-10, IL-4, IFN-γ, or T-bet by using real-time PCR in CD25-selected, casein-stimulated mononuclear cells was not informative. A calculator to estimate resolution probabilities by using baseline milk IgE levels, SPTs, and AD severity was devised for use in the clinical setting (available at www.cofargroup.org), although additional validation is needed.

Treatment

Oral immunotherapy (OIT) or sublingual immunotherapy (SLIT) continues to be a significant focus of food allergy research. Peanut SLIT was evaluated in a multicenter randomized controlled trial with 40 participants age 12 to 37 years (median, 15 years) randomized 1:1 for 44 weeks of treatment (at which time a 5-g OFC was performed), aiming for a maintenance dose of 1386 μg of peanut protein.[62] After unblinding, placebo-treated subjects crossed over to a daily maintenance goal of 3696 μg of peanut protein, whereas subjects receiving active treatment continued the 1386-μg dose. Subjects successfully consuming 5 g or at least 10-fold more peanut powder at 44 weeks compared with the baseline OFC threshold were considered responders, and those not crossed over were re-evaluated on treatment at 68 weeks. Fourteen (70%) of 20 subjects receiving peanut SLIT were responders compared with 3 (15%) of 20 subjects receiving placebo ($P < .001$). In peanut SLIT responders the median successfully consumed dose increased from 3.5 to 496 mg. After 68 weeks of SLIT, this significantly increased to 996 mg (compared with week 44, $P = .05$). The median successfully consumed dose at the week 44 crossover OFC was significantly higher than baseline (603 vs 71 mg, $P = .02$). Seven (44%) of 16 crossover subjects were responders, increasing from a median of 21 to 496 mg. Overall, no one tolerated 5 g of peanut powder at 44 weeks, although 5 were able to consume this amount or more at 68 weeks. Of 10,855 peanut doses through the week 44 OFCs, 63.1% were symptom free; excluding oral-pharyngeal symptoms, 95.2% were symptom free. Thus peanut SLIT safely induced a modest level of desensitization in a majority of subjects, with evidence that longer duration of therapy might increase the threshold of desensitization.

It has generally been assumed that OIT might induce more robust results than SLIT but with a greater chance of side effects caused by larger doses. Chin et al[63] confirmed this impression when they compared their published and extended results of their peanut OIT and SLIT trials. They found that OIT, compared with SLIT, produced a more robust clinical effect at 12 months and greater changes in peanut IgE and IgG_4 levels and basophil activation at 2 years. Of special interest, epitope analysis of patients undergoing peanut OIT for more than 3 years (compared with control subjects with peanut allergy) revealed that OIT differentially altered Ara h 1 to 3 binding patterns that are otherwise generally stable during avoidance.[64] The changes were variable between patients and included a progressive polyclonal increase in IgG_4 levels, with a concurrent reduction in IgE amounts and diversity but without significant changes in affinity. Interestingly, the IgE repertoire expanded throughout the years of treatment. The correlation of these changes with regard to clinical outcomes remains to be determined. However, the larger question is whether these treatments can induce tolerance, a permanent ability to ingest the allergen without daily therapy.[65] Given that OIT and SLIT studies have not yet clearly indicated that tolerance can be achieved and various safety and quality-of-life issues are not well addressed with regard to long-term treatment and follow-up, some conclude that this treatment for peanut allergy is not yet ready for clinical practice.[66] Regarding side effects, however, combining peanut (or other food) OIT with omalizumab might represent an advantageous modality to reduce reactions and facilitate desensitization. In a pilot study, Schneider et al[67] were able to reach 992 mg of peanut flour in 1 day in 13 children who reacted to less than 100 mg of peanut flour during an OFC. Twelve of the subjects reached a maintenance does of 4000 mg of peanut flour in a median of 8 weeks and went on to continue dosing off omalizumab. Overall, 2% of 3502 doses resulted in reactions, and epinephrine was given once during treatment on omalizumab and twice during maintenance off omalizumab. Although the results are encouraging, randomized placebo-controlled studies are needed to further address safety and long-term efficacy.

Keet et al[68] provide some insight on the long-term outcomes of OIT by reporting on nearly 5 years of follow-up of 32 participants in 2 milk OIT trials. They found that many subjects

lost desensitization over time, and no more than 31% were tolerating full servings with minimal or no symptoms. One participant had been using epinephrine about twice per month for reactions to milk. These disappointing observations for milk might be different when OIT is applied to other foods or used for other manifestations of food allergy (eg, perhaps OIT or SLIT is a more effective approach for pollen-related food allergy[69,70]), but much more study is required.

Alternative treatment strategies were investigated in murine models. Liu et al[71] tested a novel peanut-human fusion protein composed of Ara h 2 and human IgG Fcγ1, the rationale being that it can cross-link inhibitory FcγRIIb with peanut-specific IgE bound to FcεRI, inhibiting degranulation. In a series of experiments, the novel protein inhibited histamine release induced by whole peanut extract from basophils of patients with peanut allergy and inhibited passive cutaneous anaphylaxis in transgenic mice. In a more general approach to typical allergen desensitization, Khodoun et al[72] used serially increasing doses of mAbs to IgE (activating antibodies), FcεRIα, or allergen. Rapid desensitization with anti-IgE mAb suppressed IgE-mediated immediate hypersensitivity; however, some mice experienced mild anaphylaxis during treatment. The anti-FcεRIα mAb that only binds FcεRI not occupied by IgE suppressed both active and passive IgE-mediated anaphylaxis and temporarily suppressed IgE-mediated anaphylaxis by decreasing mast cell signaling through FcεRI; it also slowly induced longer-lasting mast cell unresponsiveness by removing membrane FcεRI. Rapid desensitization with anti-FcεRIα mAb induced less reaction and was longer lasting than rapid desensitization with antigen. These interesting approaches will need more investigation before embarking on clinical studies.

Current food allergy management requires instructions on avoidance for a variety of settings[73-75] and provision of self-injectable epinephrine, which affects quality of life.[76] An area of concern and confusion concerns the risk related to products with voluntary precautionary labeling, such as "may contain."[77] Several studies[78-80] were reported that focus on establishing thresholds doses at which most allergic patients would not react or at most have minimal symptoms, which might eventually be applicable for improved labeling. There also remains confusion among physicians about vaccination of persons with egg allergy,[81] and therefore it is helpful to be aware of the increasing leniency (and no need for testing or splitting doses) in providing influenza vaccinations to persons with egg allergy, as reflected in a practice parameter update.[82]

ANAPHYLAXIS

Using a US nationwide cross-sectional telephone survey, Wood et al[83] estimated that the prevalence of anaphylaxis in the general adult population is at least 1.6%. Medications were the most common trigger (35%), followed by foods (32%) and insect stings (19%). A majority of respondents with anaphylaxis had 2 or more anaphylactic reactions in their lifetimes. Importantly, the need for improved patient and health provider education is illustrated by the observation that most respondents with a history consistent with anaphylaxis had not been provided with an emergency care plan; only 32% reported that they planned to use epinephrine with future reactions, 52% had never received a prescription for self-injectable epinephrine, and 60% did not currently have self-injectable epinephrine available. A Canadian study of pediatric anaphylaxis[84] in the emergency department of Montreal's Children's Hospital found 0.21% of 81,677 visits were due to anaphylaxis. Food was the primary trigger (84.5%). Like the US study and others, anaphylaxis was undertreated with epinephrine.

As indicated by the epidemiologic studies, anticipatory anaphylaxis education is important to promote appropriate care. Simons et al[85] surveyed parents to determine when they were comfortable transferring anaphylaxis management responsibilities to their children and found that parents most often believed responsibility to self-inject should be expected at 9 to 11 years, approximately 3 years earlier than pediatric allergists had suggested in another study. Although transferring responsibility might be an important step toward independence, self-treatment by the child should not be depended on; an adult should be responsible. It will remain to be seen whether alternative injection devices[86] or future alternative routes of treatment[87] improve appropriate use.

Several studies investigated risks and biomarkers regarding anaphylaxis severity. Lee et al[88] analyzed 302 adult emergency department patients presenting with anaphylaxis, and after adjusting for age, sex, suspected trigger, and pre-existing lung disease, they found β-blocker, angiotensin-converting enzyme inhibitor, diuretic, or antihypertensive use in aggregate were associated with involvement of 3 or more organ systems (OR, 2.8; 95% CI, 1.5-5.2; $P = .0008$) and hospitalization (OR, 4.0; 95% CI, 1.9-8.4; $P = .0001$). These medications could act in numerous ways to promote hypotension and bronchospasm, which suggests their use should be considered when counseling patients at risk for anaphylaxis.

Biomarkers of anaphylaxis would aid in diagnosis and might inform better therapies. Vadas et al[89] scored anaphylaxis severity in 41 patients from "1" (least severe) to "3" (most severe) and correlated severity against measurement of platelet-activating factor (PAF), tryptase, and histamine levels. Increased PAF levels were observed in 20%, 66.7%, and 100% of the patients with grade 1, 2, and 3 allergic reactions, respectively. PAF showed the best correlation with severity and among the most severe episodes. Histamine levels were increased in only 70%, and tryptase levels were increased in 60%, suggesting a primary role for PAF. Brown et al[90] investigated anaphylaxis severity and clinical course while also measuring levels of numerous cytokines, anaphylatoxins, tryptase, histamine, and PAF acetylhydrolase. Among 315 episodes of anaphylaxis, 97 were categorized as severe, and severity was associated with older age, pre-existing lung disease, and drugs triggers. Delayed deterioration, which was noted in 9.2%, was associated with hypotensive reactions and lung disease. All of the mediators were associated with severity of anaphylaxis, and principal component analysis identified a group of mediators (mast cell tryptase, histamine, IL-6, IL-10, and TNF receptor 1) to be associated with delayed deterioration. Low PAF acetylhydrolase levels were associated with severe reactions. These studies suggest that mediators resulting in disruption of vascular integrity during anaphylaxis (which in part might relate to generation of endothelial nitric oxide) are pivotal in the most severe reactions and poor outcomes. Cui et al[91] used murine models and pharmacologic intervention to show that sphingosine-1-phosphate receptor 2, which is expressed in vascular endothelial cells, inhibits the generation of nitric oxide through interaction with an activating kinase of an enzyme involved with generation

of nitric oxide. The results suggest that agonists of this receptor could be novel therapeutic agents for anaphylaxis.

HYPERSENSITIVITY TO STINGING INSECTS

Insights into diagnosis included the identification that the conventional yellow jacket venom ImmunoCAP might have reduced sensitivity because of incomplete capture of Ves v 5–reactive IgE antibodies (spiking with rVes v 5 resulted in an increase in sensitivity from 83.4% to 96.8%)[92] and clarification that serum tests for paper wasp do not have relevant interference from cross-reactive carbohydrate determinants.[93] Although sting challenge is not routinely used for diagnosis or determination of treatment response, Fischer et al[94] noted that this challenge test improved quality-of-life scores. Insights on tolerance induction were reported in evaluating beekeepers who endure multiple stings without experiencing anaphylaxis.[95] Sera from beekeepers in and out of sting seasons, both those with venom allergy and healthy control subjects, were used in various binding and inhibition assays. Among the beekeepers, allergen-specific IgG_4 levels were markedly increased compared with those seen in control subjects and decreased modestly out of season, although there was not as strong a decrease as seen in nonbeekeepers, and IgE was virtually absent, overall suggesting that tolerance was due to high levels of immunoreactive IgG_4 with blocking activity, low IgE levels, or both. The authors contrast their findings to a persistent increase in IgG levels associated with serum inhibitory activity observed 2 years out from grass pollen immunotherapy, suggesting that the differences might be due to the intermittent systemic exposure to venom compared with more prolonged seasonal mucosal re-exposure to pollens.

Van Anrooij et al[96] explored recent observations about increased baseline serum tryptase levels being a risk factor for Hymenoptera venom–induced anaphylaxis by evaluating 328 patients with different subtypes of mastocytosis. Counterintuitively, anaphylaxis prevalence did not increase constantly with increasing levels of mast cell markers; after a gradual increase to a maximum of near 50%, it decreased with a further increase in these markers, and in patients with indolent systemic mastocytosis, all markers of mast cell load were independent negative predictors of venom-induced anaphylaxis. The results suggest a complex pathophysiologic association between mast cell load and anaphylaxis risk that will need additional study.

Given the general increased risk of insect sting anaphylaxis identified previously, Bonadonna et al[97] reviewed their experience in using venom immunotherapy in 84 patients with systemic mastocytosis, concluding it was well tolerated, safe, and effective (43/50 patients restung were protected).

DRUG ALLERGY

There is a clear need to increase drug allergy testing to reduce unnecessary avoidance of medications caused by presumed allergy.[98,99] For example, Macy and Ngor[100] evaluated 500 patients with a history of penicillin allergy and cleared 98% of them using skin tests with penicilloyl-poly-lysine, penicillin, and oral drug challenge (when test results were negative). Also regarding penicillin allergy diagnostics, false-positive serum test results for penicillin were identified as possibly occurring in 26% of tested patients attributable to a nonrelevant determinant, suggesting caution in interpretation.[101] Another diagnostic quandary is determining whether nonspecific rashes occurring during infections are the result of medications or the infection itself. Yoon et al[102] studied 95 patients with delayed drug hypersensitivity, 47 patients with proved bacterial infection, and 45 healthy control subjects to evaluate potential biomarkers distinguishing those with allergy and those with infection. They found procalcitonin levels to be increased preferentially in those with infection, with the best cutoff value being 1.67 ng/mL (sensitivity, 85%; specificity, 96%), but validation is required. Studies on the mechanisms of cell-mediated drug hypersensitivity, which might become easier to explore with new murine models,[103] included the following observations: T-cell activation without metabolizing the drug (shown with carbamazepine)[104] and systemic reactions to abacavir likely induce resident memory T cells that home to the skin.[105] Regarding drug allergy risks, a high incidence of delayed-type hypersensitivity reactions to heparin was noted among pregnant women,[106] as was a relationship of quinolone allergy to neuromuscular blocking agent sensitization.[107]

AD

AD has been a hot area of investigation during the past year (Table III). It has been documented that patients with AD can have significant mental health comorbidity.[108] The clinical phenotype of AD is influenced by multiple factors, including pollution[109]; pet exposure[110]; endogenous antigens, including sweat proteins[111]; and intestinal microbiota.[112] IL-10 polymorphisms were reported to influence Treg cell expression and the development of AD.[113]

Skin barrier dysfunction

Filaggrin deficiency in the skin resulting from gene mutations or cytokine-mediated downregulation has emerged as one of the strongest risk factors for AD. The importance of filaggrin in contributing to various aspects of the biophysical, immune, and microbiome abnormalities observed in patients with AD are now emerging.[114] Recent studies also indicate an important role of filaggrin in protecting human skin keratinocytes against staphylococcal toxins.[115] Interestingly, using a mouse genetics approach, 2 groups[116,117] found that separating the filaggrin gene mutation from the matted gene in flaky tail mice revealed that filaggrin-deficient mice displayed impaired skin barrier function but lacked the propensity for spontaneous skin inflammation. In contrast, the mice with the matted phenotype and a loss of function mutation in *Tmem79* had spontaneous development of dermatitis. *Tmem79* is expressed in the granular layers of the epidermis, where its absence correlates with abnormal function of lamellar granules and failure to transfer lipids and proteases to the upper part of the epidermis. These data suggest that abnormal trafficking of lamellar granules might contribute to AD.[118] Aside from filaggrin, other filaggrin-like proteins, such as hornerin and filaggrin 2, have also been found to be decreased in AD skin.[119] Taken together, these data suggest that loss of multiple epidermal proteins is likely to contribute to the skin barrier dysfunction in patients with AD.

Although much of the focus has been on keratinocytes, recent studies also highlight the potential role of fibroblasts.[120] Atopic compared with normal fibroblasts were found to downregulate terminal differentiation of epidermal keratinocytes because of

reduced expression of the differentiation-associated cytokine leukemia inhibitory factor. These data suggest fibroblast-derived factors might be new therapeutic targets for AD.

Immunologic responses in patients with AD

Whether AD is due to a primary skin barrier defect or is the result of a polarized immune response is hotly debated. Proponents in the skin barrier camp point to Netherton syndrome as an example of a primary skin barrier abnormality associated with a high level of allergen sensitization. Indeed, a leaky epithelial barrier defect that allows easy penetration of allergens and resultant thymic stromal lymphopoietin release can induce allergic responses.[121] However, primary immunodeficiencies are often associated with eczema.[122] Furthermore, the development of skin lesions in filaggrin-deficient mice has been found to be dependent on adaptive immune responses.[123] The truth undoubtedly lies somewhere between these 2 extreme perspectives, with various combinations of different skin barrier abnormalities and immune pathways being activated, leading to the complex phenotype of AD. Most patients with AD have strong activation of their T_H2 and T_H22 pathways contributing to a lack of epithelial differentiation and atopy.[124] These adaptive responses might be influenced by defective innate immune responses.[125]

There is evidence that in addition to T_H2 responses, patients with intrinsic AD have increased T_H17 immune responses compared with those seen in patients with extrinsic AD.[126] However, the overall IL-17 response in patients with AD is much weaker than that observed in patients with psoriasis.[127] A functional IL-6 receptor variant has also been identified as a risk factor for persistent AD.[128] Even after clinical resolution of AD skin lesions with narrow-band UV light therapy, certain inflammatory and differentiation pathways remain abnormal in AD skin, potentially predisposing to the development of new lesions.[129] A combination of intrinsic barrier and immune abnormalities in patients with AD might predispose these patients to the development of contact dermatitis.[130]

Management of AD

An update of the practice parameters for treatment of AD was published during the past year, summarizing diagnostic criteria, mechanisms, first-line management, identification and elimination of allergen triggers, role of microbes and emotional stress, patient education, and treatment of difficult-to-manage AD.[131] This was reinforced by reviews on the ABCs of managing patients with severe AD[132] and systemic therapies for severe AD.[133] A meta-analysis of randomized controlled trials of allergen-specific immunotherapy suggests they might be effective in the management of AD.[134]

Advances in urticaria

A polymorphism in the thromboxane A1 synthase gene *(TBXAS1)* was reported to have an increased association with acute urticaria induced by nonsteroidal anti-inflammatory drugs.[135] Increased plasma levels of D-dimer, a marker of fibrinolysis, were found in patients with antihistamine-resistant chronic urticaria.[136] Canakinumab, a long-acting fully humanized anti–IL-1 mAb, was reported to reduce the disease activity of patients with urticarial vasculitis.[137]

Investigators evaluated the safety and efficacy of 24 weeks of treatment with omalizumab in patients with persistent chronic idiopathic urticaria despite treatment with H_1-antihistamines at up to 4 times the approved dose plus H_2-antihistamines, leukotriene receptor antagonists, or their combination.[138] Omalizumab was well tolerated and reduced the signs and symptoms of chronic idiopathic urticaria, including weekly itch severity scores.

CONCLUSIONS AND SUMMARY

In the year since our last review, numerous exciting advances have been reported in the *Journal*. Although studies suggest an increase in food allergy, we are also seeing outcomes of prevention studies that show promise and the result of the first randomized controlled trial to investigate earlier introduction of allergenic foods as a means of prevention. EoE treatment is becoming more refined, and studies continue to elucidate phenotypes that might provide more insights into pathophysiology and treatment. Murine models showing a close relationship of food allergy and the microbiome will spur additional investigations that might result in new avenues for the prevention, treatment, or prediction of allergy. As we learn about desensitization through OIT and SLIT, we are better positioned to move studies toward clinical care or look for alternatives. Exciting studies on anaphylaxis could result in better markers for predicting outcomes and treating more effectively. New insights into AD reveal the importance of an impaired skin barrier in combination with a dysfunctional immune response, leading to persistent skin inflammation. New therapeutic advances included the observation that omalizumab might be effective in the treatment of chronic urticaria. Overall, these advances show promising steps toward improved diagnosis and management and include many observations that can be used immediately to improve patient care.

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