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

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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 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

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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

TABLE II. Key advances in anaphylaxis, insect venom, and drug allergy in 2014

Topic	Clinical or basic research concerns	Advances and observations
Anaphylaxis	Epidemiology, risk, pathophysiology, and management	• US population risk is at least 1.6%. • Having an epinephrine autoinjector and having seen an allergist were protective against having an emergency department visit with severe anaphylaxis. • Medications are the most common trigger for fatal anaphylaxis. • Biphasic anaphylaxis was more common for those with prior anaphylaxis, unknown trigger, diarrhea, and wheezing. • Rituximab-treated recalcitrant idiopathic anaphylaxis was shown in a case report.
Insect venom hypersensitivity	Risk, pathophysiology	• Insect venom sensitization without a reaction history is associated with systemic reactions on challenge for 5.3%. • Baseline PAF-AH levels are inversely associated with venom anaphylaxis severity. • Indolent systemic mastocytosis without skin lesions and with insect venom reactivity represents a distinct phenotype.
Drug allergy	Pathophysiology, diagnosis, and management	• Labeling as "penicillin allergic" carries documented adverse consequences, suggesting importance of referral testing. • Safety and efficacy of diagnostic testing (including test doses) for drug allergy has been investigated. • HLA association for penicillin allergy was identified. • microRNA biomarker/mechanism for TEN was identified. • Lactose-containing intravenous methylprednisolone might be a risk for patients with milk allergy.

PAF-AH, Platelet-activating factor acetylhydrolase.

course. *FLG* mutations were associated with food allergy at 10 (OR, 2.9; 95% CI, 1.2-7.0; $P = .02$) and 18 (OR, 2.5; 95% CI, 1.2-5.3; $P = .03$) years of age but not earlier. In a deeper analysis considering direct effects, *FLG* mutations were not directly related to food allergy, but eczema and sensitization were related, and therefore indirect effects of *FLG* mutations on food allergy were modulated over time and influenced through eczema and sensitization. The results and ages of effect from *FLG* mutations suggest the influence of *FLG* mutations through eczema and sensitization, especially on persistent food allergies (eg, peanut and fish over egg and milk). Although this study substantially supports sensitization through an inflamed skin barrier as a risk for food allergy, environmental exposure was not measured.

Brough et al[14] investigated an unselected prebirth cohort evaluated from 1995 to 1997 to age 11 years, during which time assessments included *FLG* genotyping, peanut SPTs, sIgE measurements, component-resolved diagnostics, and some OFCs, and early prenatal/antenatal dust samples were assayed for peanut protein. A total of 623 children had evaluable data, and factors associated with peanut allergy included history and severity of AD, parental report of hay fever, and egg SPT responses at age 3 years. In isolation, environmental peanut exposure was not related to outcomes, but when interactions were considered for *FLG* mutations and peanut exposure, there was a significant effect on SPT sensitization (OR, 5.3, 95% CI, 1.8-15.3; $P < .1$) and a trend for peanut allergy (OR, 2.7; 95% CI, 0.9-8.0; $P = .07$). Multivariate models considering this interaction, egg SPT responses, and AD consistently showed a relationship of *FLG* mutations and environmental peanut exposure to peanut sensitization and allergy with a dose-response effect (environmental peanut exposure with the wild-type *FLG* genotype had no effect on outcomes). Each 2.7-fold increase in house dust peanut levels during infancy was associated with a 3.3-fold increase in peanut allergy at school age.

Considering these 2 studies, one might question whether the risk derives from the *FLG* loss-of-function mutation or the AD itself. In an observational study by the Consortium for Food Allergy Research of 359 atopic children recruited at 3 to 15 months of age with likely milk or egg allergy and/or AD and sensitization to milk or egg, living room dust samples were assayed for peanut allergen and related to the infants' peanut sensitization or likely peanut allergy, the latter based on sIgE levels of greater than 5 kU_A/L.[16] In a multivariate model an increase in 4 $\log_2$ units of peanut protein in house dust increased the odds of peanut sensitization/allergy about 2-fold, with this effect on sensitization augmented in children with a history of AD and more so in those with severe AD. The rate of *FLG* mutations was low in this cohort and not related to outcomes, perhaps suggesting the skin barrier as the important variable in the context of environmental exposure. Animal models suggest a mechanism whereby skin exposure bypasses oral tolerance, resulting in allergy,[12,15] and an anecdotal report suggested[17] that skin exposure to foods could induce food allergy, even in an adult. Roasted peanut in particular might have properties facilitating cutaneous sensitization.[18] Evidently, delaying oral exposure to allergens during a time of environmental skin/respiratory exposure could be a risk factor that is addressable by earlier introduction of foods/food allergens,[19] improving the skin barrier (which already shows promise to reduce AD/sensitization in trials[20,21]) or reducing environmental food exposure.

Maternal and infant diets have been a target for prevention of atopic disease, although proof of effect specifically on food allergy is elusive.[2] Bunyavanich et al[22] evaluated the association of maternal pregnancy diets to atopy outcomes in an unselected prebirth cohort of 1277 children followed to about age 8 years and found higher first-trimester peanut intake was associated with lower peanut allergy, higher milk intake with reduced asthma/rhinitis, and higher wheat intake in the second trimester with reduced AD. In a murine model Song et al[23] evaluated offspring of mice with peanut allergy, finding them more susceptible to peanut allergy than offspring of nonallergic mice, and this susceptibility was associated with epigenetic

TABLE III. Key advances in allergic skin diseases in 2014

Topic	Clinical or basic research concerns	Advances and observations
AD	Mechanisms	• Pollution might contribute to increasing prevalence of AD. • *FLG* mutations define a specific AD endotype. • T_H2 and T_H22 cytokines impair keratinocyte differentiation in patients with AD. • Eczema herpeticum is associated with deficient interferon responses.
	Prevention and treatment	• Early emollient intervention might prevent AD. • Vitamin D prevents winter-related exacerbation of AD. • Blockade of IL-4 and IL-13 action reduces AD skin severity.
Chronic urticaria	Pathophysiology and treatment	• Omalizumab is effective as treatment for chronic urticaria unresponsive to antihistamines and other drugs.

modifications of the *IL4* gene promoter, suggesting that early-life interventions that could modify T_H2-biased epigenetic marks might reduce the risk of allergy in high-risk infants.

Regarding the infant's diet, 2 large cohort studies investigated food diversity, one Finnish cohort[24] finding that a greater food diversity by age 12 months (eg, ≥11 items) was associated with less risk of asthma and rhinitis at age 5 years, and another European cohort of rural children[25] finding a protective effect of increased first-year food diversity on asthma and food allergy at age 6 years. Whether these associations are related to earlier allergen exposure, diversity leading to better maturational effects or other factors, such as nutrient properties, remains uncertain. However, Grimshaw et al[26] noted in a nested, case-control, within-cohort study using prospective food diaries that ongoing (not necessarily early) higher intake of fruits, vegetables, and home-prepared foods (ie, a healthy diet) was associated with less food allergy by age 2 years, suggesting the latter aspect, nutritional value, might play a role.

Another active means to potentially prevent atopic disease is the use of probiotics. Bertelsen et al[27] evaluated a cohort of more than 40,000 infants from Norway born between 2003 and 2009, where data were available about maternal and infant diets that might have included milk-based probiotic products. A small reduced risk of AD at 6 months was noted for maternal ingestion of these products (relative risk, 0.94; 95% CI, 0.89-0.99) that was lost by 18 months unless the infant also consumed these products, and there was no effect on asthma evaluated at age 3 years (food allergy outcome was not reported). Overall, these studies suggest that intervention trials addressing diet, probiotics, and environmental exposures are warranted to address prevention of food allergy and atopy.

Diagnosis

Component-resolved diagnostics remains an active area of interest.[28] For example, Sirvent et al[29] cleverly noted that persons with negative test results to kiwifruit who yet react might be responding to allergens in the small crunchy seeds of the fruit rather than the pulp. They elegantly proved this to be the case, identifying 2 relevant seed allergens that might be needed to improve diagnosis.

A controversy in diagnosis is whether total IgE levels influence the predictive capacity of sIgE levels. Gupta et al[30] evaluated the sIgE/total IgE ratio among persons undergoing OFCs to multiple types of foods, noting that the ratio was higher for those who reacted to (ratio, 1.5) versus those who tolerated (ratio, 0.5) OFCs. This overall result reflected differences in the ratio that were prominent among "persistent" food allergens, such as peanut, tree nuts, shellfish, and seeds (passed ratio, 0.4; failed ratio, 2.2) rather than transient allergies to egg, milk, wheat, and soy (passed ratio, 0.8; failed ratio, 0.8).

Another approach to diagnostics is the basophil activation test (BAT). Santos et al[31] evaluated children with peanut allergy, peanut-sensitized but nonallergic children, and healthy children (total 104 children) based on BAT results, SPT responses, sIgE levels, and Ara h 2 levels and then validated their results in an additional group of 65 children. They found that BAT results were superior to any of the other modalities and that BATs far outperformed specialists' predictions in a subgroup of 44 children with equivocal results on standard tests for whom 3 pediatric allergists attempted to predict outcomes. In a BAT-as-second-step approach focusing on those with equivocal standard test results, the BAT was able to reduce the need for an OFC by 97%. Additional studies will need to further validate these promising results and address the best BAT cutoff values, the costs and labor intensiveness of the test, and limitations, such as standardizing the test and addressing basophil nonresponders.

In a series of investigations of gene expression in peanut-activated memory T_H subsets, Brough et al[32] found that *IL9* showed the greatest difference between children with peanut allergy and those with only sensitization (as well as those who were nonsensitized) and that the IL-9–producing cells were a distinct T_H subset, suggesting a biomarker and potential therapeutic target.

Diagnosing the trigger of acute allergic reactions is difficult, but when reactions occur at a time distant from eating, the challenge to determine whether food is causal is even greater. Indeed, delayed anaphylaxis to meats caused by alpha-gal, likely related to sensitizing exposures to tick bites, could be misdiagnosed as idiopathic anaphylaxis.[33]

Commins et al[34] formally documented reactions at 3 to 7 hours after red meat OFCs in 10 of 12 subjects with sIgE to alpha-gal. Tryptase levels were positive in only 3 patients, but BAT responses correlated with the timing of clinical symptoms, suggesting that reactions occurred as the proteins entered the bloodstream. Additional studies regarding alpha-gal noted that patients might have allergic reactions to initial placement of porcine or bovine heart valves[35] and that pork kidney apparently has high levels of or very accessible alpha-gal and is likely to elicit reactions more often than red meat and would especially be a risk for those with red meat allergy.[36]

Treatment

Jones et al[37] performed a comprehensive review concerning recent advances in food allergy immunotherapies. Several peanut allergy–related immunotherapy studies were published in the

journals this year, including a long-term follow-up study of peanut immunotherapy by Vickery et al.[38] Their report represents a follow-up from prior studies in which 24 of 39 children undergoing peanut oral immunotherapy (OIT) were followed up to 5 years, eventually reaching a 4000-mg daily maintenance dose of protein that was confirmed to protect them from a 5000-mg OFC. After a month without treatment, 50% were still protected against this OFC, and among those who lost full protection, the range of amounts ingested to elicit a reaction was 1500 to 5000 mg. Those with sustained unresponsiveness off treatment at 1 month were more likely to have had smaller skin test results and lower sIgE levels at baseline and the time of the OFC without a difference in peanut IgG_4 levels compared with those without sustained unresponsiveness. These are very promising results, especially because those who "failed" sustained unresponsiveness were still protected at well above the 50-mg doses to which they all reacted on their initial escalation days years before. Having biomarkers of sustained unresponsiveness or tolerance off therapy would be important, as would understanding the mechanisms involved.

Syed et al[39] evaluated several immune markers and found that T-cell function and demethylation of forkhead box protein 3 CpG sites in antigen-induced regulatory T cells were significantly different between those with or without evidence of sustained unresponsiveness, suggesting a role for antigen-induced regulatory T cells in tolerance during OIT and the role of epigenetic changes that enhance these functions.

Burton et al[40] used a murine model and an *in vitro* assay of patients' sera before and after OIT to investigate the role of specific IgG, levels of which have been observed to increase during OIT, in the prevention of reactions and found that these antibodies act through FcγRIIb to block IgE-mediated reactions. Safety is paramount for OIT because dosing can result in allergic reactions.[41] Alternative methods of immunotherapy are being investigated. For example, using boiled peanuts for OIT might have an advantage, at least initially, because levels of major allergens are reduced,[42] and the epicutaneous and sublingual routes are active areas of research.[37]

A number of clinical reports provide practical advice about food allergy management.[43] There are many ways in which alcohol can induce allergic-type reactions, but Cardet et al[44] point out that a high percentage of patients with aspirin-exacerbated respiratory disease experience alcohol-induced nasal symptoms (75%) and wheeze/dyspnea (51%) that correlate with the severity of their aspirin-induced reactions. Patients with food allergies must worry about food proteins in medications and vaccines; Kelso[45] catalogued the foods and types of medication that are of concern, providing a very practical review. Another concern is labeling, where "may contain" and other advisories have proliferated; cogent means to address these labeling quandaries require a better understanding of allergen thresholds (which might require studies that provide doses at intervals longer than those of standard OFCs[46]).

Allen et al[47] describe thresholds to 11 allergens that might help to improve product labeling in the future. Two reports highlight a very high rate of bullying related to food allergies, emphasizing the importance of bringing this up at clinical evaluations and advising parents to discuss concerns with their child and the school administration.[48,49] Finally, several studies underscore nutritional issues for children on restricted diets,[50,51] including Nachshon et al,[52] who remind us that patients with milk allergy are at high risk of having reduced bone mineral density and early osteoporosis, making it imperative to address calcium and other nutrients in the diet.

Eosinophilic esophagitis

Several studies published in the journals this year address the epidemiology, pathophysiology, and treatment of eosinophilic esophagitis (EoE). Two studies addressed the observation that most reports of pediatric EoE include primarily white subjects, possibly suggesting a racial or ethnic disparity in diagnosis or risk. Gill et al[53] compared EoE records from a black inner-city cohort and a rural white population, noting similar rates of EoE per the general population, younger age of diagnosis in black subjects, typical endoscopic findings reported more often in white subjects, greater midesophageal eosinophilia in black subjects, and more allergic symptoms among black subjects.

Weiler et al[54] reported on 50 consecutive children given a diagnosis of EoE at Children's National Medical Center in Washington, DC, where 42% were white and 42% were black. The black children had a comparatively higher rate of failure to thrive, vomiting, AD, and younger age at presentation and diagnosis; however, with adjustment for age and insurance type, only AD remained a distinction. Together, the report suggests that the scope of EoE requires further study with attention to racial and ethnic diversity and the potential effect of health care disparities.

Regarding risk factors for EoE, Alexander et al[55] evaluated gene and environment influences, reporting a 1.8% risk overall for first-degree relatives and a 2.3% risk for a sex-matched first-degree relative (2.8% for male and 0.8% for female subjects), with risks varying from a high for a brother (3.5%) or father (2.4%) to a low for a mother (0.6%) or sister (1.3%). In the same report twin analyses suggested a high degree of influence of common environment (81%) compared with heritability (14.5%). The effect of environment was also suggested by a study showing early antibiotics and caesarian section delivery were EoE risk factors.[56] Insights on mechanisms include an *in vitro* study by Beppu et al[57] showing that TGF-β1 induces phospholamban, a smooth muscle contraction–associated protein, which they also showed was expressed more in smooth muscle cells from patients with EoE compared with control cells, providing a target for potentially interrupting the mechanisms of dysphagia in this disease.

EoE is the most common disease among other eosinophilic gastrointestinal disorders, and Caldwell et al[58] described molecular, histopathologic, and clinical characteristics of eosinophilic gastritis, suggesting distinctions between these disorders. Their study suggested that eosinophilic gastritis is a systemic T_H2 disorder with peripheral blood eosinophilia, extragastric eosinophil involvement, and a gastric transcriptome that is distinct from that in patients with EoE, a finding that will undoubtedly help with diagnosis, management, and eventual treatment.

Regarding therapy of EoE, prescribed diets remain a key approach. Colson et al[59] remind practitioners to address nutritional adequacy during dietary trials, and Molina-Infante et al[60] report on the efficacy of a 4-food group elimination diet for adult EoE. In the latter study 52 adults were treated with diets removing all milk, egg, wheat, and related grains and all types of legumes, and 54% had complete resolution, with an additional

31% of the group responding after removal of additional foods, nuts, fish, and shellfish. Patients typically were responsive to a more narrow elimination diet (2 foods/food groups) after single-food re-exposure trials following success on the 4-food group diet. Also regarding diet and EoE, the clinician should be attuned to the possibility that EoE can be triggered by a food to which a subject experienced resolution of acute IgE-mediated reactions.[61] Taken together, these EoE studies are encouraging for improved recognition and treatment for EoE, with insights that might help identify novel prevention and treatment strategies.

ANAPHYLAXIS

A national random telephone survey of the general adult population, interviewing 1000 participants, suggested that the population risk of anaphylaxis is at least 1.6% (95% CI, 0.8% to 2.4%).[62] A population-based survey of 1059 subjects reporting allergic reactions in the prior 10 years revealed 33% with anaphylaxis, with most not being adequately prepared to manage a subsequent episode.[62]

The importance of being prepared for anaphylaxis was underscored by a study of risk factors for severe anaphylaxis leading to hospitalization among those receiving treatments in emergency departments.[63] In this study 11,972 cases of anaphylaxis were identified from commercial research databases, and 22% of the cases were severe. In multivariate analyses filling a prescription for an epinephrine autoinjector was protective (OR, 0.64; 95% CI, 0.53-0.78), as was having seen an allergist/immunologist (OR, 0.78; 95% CI, 0.63-0.95). Thankfully, fatality from anaphylaxis is rare, with 1 US study suggesting a case fatality rate of 0.3%,[64] but data also suggest increasing rates of hospitalization.

A review of 2458 US anaphylaxis fatalities from 1999 to 2010 suggested medications as the most (58.8%) and foods as the least (6.7%) common triggers, with disparities including increased risk of fatality for African American race and older age.[65] Another study provided insight on risks for biphasic anaphylaxis. Among 541 patients presenting with anaphylaxis, 4% had biphasic reactions, with a median onset at 7 hours, and this was associated with prior anaphylaxis (OR, 2.6), unknown triggers (OR, 2.6), diarrhea (OR, 4.5), and wheezing (OR, 2.6),[66] suggesting risk factors warranting longer observation before discharge.

Idiopathic anaphylaxis is a treatment challenge.[67] An interesting case report[68] addressed the observation that this disorder is associated with having activated B cells. A teenager with highly recalcitrant idiopathic anaphylaxis unresponsive to omalizumab, antihistamines, and steroids was treated successfully with rituximab, suggesting a role in some for IgG antibodies or other mechanisms. Together, these and additional studies underscore the need and potential benefits to address proper identification and avoidance of triggers,[67,69] referral to an allergist, education,[70] proper treatment and a search for better treatments, and addressing disparities.[71]

HYPERSENSITIVITY TO STINGING INSECTS

Diagnostic testing for insect venom allergy is maturing. Screening tests for venom hypersensitivity are not recommended because of the well-known fact that many persons are sensitized but will not react on sting. Sturm et al[72] actively investigated this situation by performing sting challenges in 94 subjects with sensitization and no reaction history. Overall, 5.3% had systemic reactions, but 44% had large local reactions, representing a 9.5-fold higher rate of large local reactions but no increased risk of systemic reactions over the general population. About 1 month after being stung, IgE levels increased, but subjects selected for re-sting did not have systemic reactions. Studies are also elucidating the role of component testing in venom allergy.[73,74]

Two studies investigated the interaction of insect venom reactions and underlying disease or metabolic status. Pravettoni et al[75] measured baseline platelet-activating factor acetylhydrolase activity levels and graded venom anaphylaxis in 169 patients. In a multivariate analysis considering variables such as IgE and tryptase levels, age, and sex, only platelet-activating factor acetylhydrolase levels were significantly associated with anaphylaxis severity grading, with decreased levels associated with more severe reactions.

Alvarez-Twose et al[76] identified a subtype of indolent systemic mastocytosis characterized by lack of skin lesions and mast cell mediator release triggered almost exclusively by insect stings. Those with this proposed distinct phenotype showed a male preponderance and had serum baseline tryptase levels that were lower than those of others with indolent systemic mastocytosis without skin lesions (who were not primarily insect reactive) or those with skin lesions. This subgroup less often had bone marrow mast cell aggregates, and they systemically showed mast cell–restricted *KIT* mutations. This distinct subgroup also had fewer episodes of urticaria, flushing, cramping, and diarrhea; were typically symptom free between stings; and typically had detectable venom IgE when using expanded testing methodologies with whole venom.

DRUG ALLERGY

It is clear that the allergist-immunologist has a huge opportunity to intervene with testing to address concerns of drug hypersensitivity. Macy and Contreras[77] showed that being labeled as allergic to penicillin is associated with important health and financial consequences. They evaluated a matched cohort of 51,582 patients hospitalized with notation of penicillin allergy and found that compared with matched control subjects without this possible diagnosis (which is typically disproved when evaluated), there were longer lengths of stay, more use of broad-spectrum antibiotics, and more complications, such as drug-resistant and *Clostridium difficile* infections. Studies also documented a lack of understanding of drug allergy among physicians[78] and poor treatment and low referral for drug allergy testing from the emergency department,[79] whereas another study showed how educational interventions could improve a physician's understanding of drug allergy.[80]

Several studies addressed drug allergy testing.[81] Fox and Park[82] suggested the safety and efficacy of penicillin skin testing. They reviewed 778 children tested (90.4% had negative results), showing they tolerated the tests; they also performed challenges on 369 of those with negative test results, finding 14 (3.8%) reacted (11 with rash or itch, 2 with serum sickness, and 1 with erythema multiforme). Iammatteo et al[83] evaluated 456 adult patients undergoing 497 test doses or multistep challenges to various drugs, typically in the context of negative skin test results or lack of suspicion of severe reactivity. Overall, 53 (11%) reactions occurred, typically of mild severity, with half receiving

treatment; 3 patients received epinephrine but on author's review did not have objective evidence of findings necessitating epinephrine. Drug desensitization protocols and reviews of approaches were presented in a number of studies.[84-87] Of clinical note, a case series suggested that intravenous use of methylprednisolone sodium succinate resulted in allergic reactions in children with milk allergy that was traced to likely milk protein contamination of lactose in this preparation,[88] and a case report added to the limited literature with the suggestion that antihistamines can induce urticaria.[89]

Several insights of importance for diagnosis and potential future management of drug allergy were reported. HLA associations with adverse drug reactions are well described,[90] but Gueant et al[91] have now identified HLA-DRA variants predicting penicillin/amoxicillin allergy but not cephalosporin allergy. Insight into the mechanism of keratinocyte apoptosis in patients with toxic epidermal necrolysis (TEN) was noted in a study of microRNAs extracted from tissues and sera of patients and through supporting *in vitro* studies.[92] A specific upregulated microRNA, miR-18a-5p, was detected in lesions from patients with TEN and was distinct from other types of rashes tested, and a dose response was noted for milder drug eruptions on the spectrum of TEN. Additional studies noted that a target of miR-18a-5p is the apoptosis gene *BCL2L10*, further indicating pathologic significance. The investigators were able to measure miR-18a-5p levels in sera and noted they were increased in patients with TEN more than in patients with skin eruptions that were less dramatic on the TEN spectrum, thus providing a possible biomarker of disease activity with as yet unknown potential as a therapeutic target.

ATOPIC DERMATITIS

During the past year, research in AD has focused on identifying the abnormalities in terminal differentiation of the epidermal epithelium that contribute to skin barrier dysfunction in patients with AD, as reviewed by Leung and Guttman-Yassky.[93] Data continue to grow that these abnormalities occur as the result of both genetic and acquired or immunomodulatory influences. Triggers of AD include not only allergens, microbes, and stress but also pollution.[94] As such, it is important to characterize pathways of polarized immune activation because they can be targeted for the treatment of patients with severe AD.

Skin barrier dysfunction

The October 2014 issue of the *Journal of Allergy and Clinical Immunology* focused on skin barrier dysfunction in patients with AD. Elias and Wakefield[95] reviewed how diverse inherited and acquired abnormalities in epidermal structural and enzymatic proteins converge to produce skin barrier dysfunction and abnormal host defense in patients with AD. *FLG* mutations have been found to be the strongest risk factor for AD[96] and might form the basis of a distinct AD endotype. These patients have a characteristic phenotype of palmar hyperlinearity, dry skin, and early-onset AD that is more persistent and often associated with development of asthma and food allergy. RNA sequencing to analyze the whole transcriptome of skin biopsy specimens from patients with AD with *FLG* mutations versus patients with AD without *FLG* mutations revealed 2 different mechanistic pathways: patients with wild-type *FLG* showed dysregulation of genes involved with lipid metabolism, and patients with *FLG* mutations had increased IL-1β levels and a type 1 interferon–mediated stress response.[97]

However, the majority of patients with AD do not have *FLG* mutations. Interestingly, a recent study of South African amaXhosa patients with AD reported that they had decreased levels of FLG breakdown products but no loss-of-function mutations in *FLG*.[98] These findings are consistent with the observation that T_H2 cytokines can inhibit FLG expression, highlighting an interplay between the skin barrier and the immune response.[99] This work also raises the possibility that other epidermal genes might be involved in causing skin barrier dysfunction in patients with AD, particularly in African populations. Indeed, Margolis et al[100] reported *FLG2* gene variations in African American patients with more persistent AD. Pellerin et al[101] also found bleomycin hydrolase downregulation in AD lesions independent of *FLG* gene mutations. Because bleomycin hydrolase is involved in FLG breakdown, its absence might lead to reduced production of amino acids that comprise the natural moisturizing factor, thereby leading to increased dryness of the stratum corneum.

Samuelov and Sprecher[102] recently reviewed the genetics of AD-like congenital disorders, including Netherton syndrome, highlighting mechanisms by which dysregulation of epidermal differentiation can lead to atopic responses.

Immunologic responses in patients with AD

The predisposition of AD skin to infection and colonization with microbes, including the propensity to warts, suggests that AD is associated with aberrant skin immune responses.[103] This was more formally investigated by Slifka et al[104] as part of the National Institutes of Health/National Institute of Allergy and Infectious Diseases–funded Atopic Dermatitis Research Network by comparing the immune response of patients with AD versus nonatopic control subjects after transcutaneous yellow fever vaccination. After transcutaneous vaccination, both groups mounted similar neutralizing antibody responses to yellow fever virus, but patients with AD demonstrated lower antiviral T-cell responses by 30 days after vaccination. Among transcutaneously vaccinated subjects, a significant inverse correlation was observed between baseline IgE levels, and the magnitude of antiviral antibody and $CD4^+$ T-cell responses was observed. These data suggest that high baseline serum IgE levels provide a biomarker for predicting reduced virus-specific immune memory after transcutaneous infection with a live virus. Identification of the critical polarized immune responses that impair skin barrier function and promote microbial colonization and infection are of critical importance in the development of targeted biologic therapies, which can be used for treatment of severe AD refractory to conventional therapy with topical corticosteroids and calcineurin inhibitors.[105]

The application of next-generation sequencing to characterize tissue samples from patients with different phenotypes of AD at the genomic, transcriptomic, and epigenetic levels will likely revolutionize our understanding of molecular subtypes of AD and improve our personalized approach to the treatment of various types of severe AD. During the past year, a series of publications have advanced our understanding of the role of abnormalities in innate and adaptive immune responses in patients with AD.[106-111] A polarized IL-13/IL-22 immune response is emerging as of

critical importance in patients with AD.[112] This is supported by the observation that dupilumab, a humanized mAb that blocks the action of IL-4 and IL-13, can improve the skin severity of AD and the molecular signature of the inflammatory skin response in the majority of patients.[113] In the subset of patients with AD prone to eczema herpeticum, by using RNA sequencing, it has been found that these patients have a defective interferon response.[107]

Prevention of AD

Because AD is often the first step in the atopic march, there has been considerable interest in management strategies to prevent the development of AD. During the past year, 2 studies were reported that assessed the effectiveness of early intervention with skin emollient therapy to prevent AD by protecting the skin barrier during infancy. Simpson et al[20] performed a randomized controlled trial of 124 neonates at high risk for AD. Infants less than 3 weeks of age in the intervention arm received full-body emollient therapy. Infants in the control arm used no emollients. The primary outcome was the cumulative incidence of AD at 6 months. Their results demonstrated a statistically significant protective effect with the use of daily emollient on the cumulative incidence of AD, with a relative risk reduction of 50%.

Horimukai et al[21] performed a randomized controlled trial with early moisturizer intervention in 116 neonates at high risk for AD. The primary outcome was the cumulative incidence of AD as of week 32. Intervention with moisturizer reduced the risk of AD by 40% compared with the control group ($P = .002$). These 2 studies suggest that early intervention with emollient therapy represents a safe and effective approach for AD prevention. In future studies, it would be of interest to determine whether skin barrier therapy could prevent food allergy. Alternatively, enhanced barrier function can be achieved by developing new therapeutic strategies to upregulate FLG expression in the skin.[114]

Nutritional supplementation is an alternative and complementary approach for prevention of AD or its exacerbation. Vitamin D has been shown to have multiple beneficial effects, including a reduction in allergic inflammation, enhanced corticosteroid responsiveness, and improvement in skin barrier function.[115,116] Low vitamin D levels have been associated with increased burden of allergic disease, particularly AD.[117,118] The greatest benefits are likely in populations with extremely low levels (25-hydroxyvitamin D, <20 ng/mL), such as persons living in upper latitudes during the winter or darkly pigmented subjects, and who require vitamin D supplementation for their bone health. In a recent study Camargo et al[119] presented data from a randomized placebo-controlled trial demonstrating that winter-related AD can be improved with vitamin D oral supplementation.

The use of probiotic therapy or bacterial lysates early in the course of illness to prevent AD remains an area of active investigation, but results have been inconsistent. This might be due to lack of standardization of the bacterial preparations, age at which the probiotic is introduced, or lack of biomarkers to identify which AD phenotype would benefit from this approach. Colonization with intestinal clostridia at the age of 5 and 13 weeks has been reported to be associated with an increased risk of AD.[120] More recently, Fyhrquist et al[121] reported that *Acinetobacter* species in the skin microbiota protects against allergic sensitization and inflammation.

Management of severe AD

An update on practice parameters for the management of AD has recently been published[122] and focused on the importance of identifying he triggers that exacerbate AD, skin barrier repair, and anti-inflammatory action. Other publications have also reviewed the importance of treating subclinical inflammation to induce and maintain a state of remission.[123] However, there remains an unmet need in the use of systemic therapies for the treatment of severe AD.[124,125] Although systemic therapies are capable of reversing epidermal pathology, there is often residual genomic profiles reflecting ongoing skin inflammation, which might lead to AD reoccurrence.[126,127] This suggests that combination therapies will be needed for the treatment of severe AD. Furthermore, standardized measures are needed to assess clinical signals of AD in future clinical trials.[128]

Advances in urticaria

During the past year, the practice parameters for chronic urticaria were updated.[129] One important development that has been highlighted in the *Journal* is the effectiveness of omalizumab in patients with chronic urticaria that does not respond to the H1- and H2-antihistamines or leukotriene receptor antagonists.[130,131] The importance of mast cells in patients with chronic urticaria was further supported by the observation that Mas-related gene X2, a receptor for neuropeptides on mast cells, is upregulated in the skin of patients with chronic urticaria.[132] Uysal et al[133] have also proposed an algorithm for treating chronic urticaria with omalizumab individualizing the dose interval for optimal control of urticaria. Weller et al[134] also developed and validated an urticaria control test based on a patient-reported outcome instrument to assess urticaria control.

CONCLUSIONS AND SUMMARY

In the year since our last review, numerous exciting advances have been reported in the *Journal*. For food allergy, studies suggest a potentially increasing prevalence, although better means to predict outcomes, diagnose reactivity, and possibly prevent and treat this disease are emerging. Insights into anaphylaxis underscore the tremendous need to better educate medical providers and patients to reduce morbidity and mortality, and referral to an allergist-immunologist appears to be an important step in this direction. A means to predict the severity of insect sting reactions might be at hand. For drug hypersensitivity, insights into the utility and safety of diagnostic testing and negative consequences of not evaluating patients clearly underscore the role of the allergist-immunologist in evaluating patients with suspected drug allergy.

Research in AD reveals abnormalities in terminal differentiation of the skin epithelium, leading to a defective stratum corneum that allows enhanced allergen penetration and systemic IgE sensitization. AD skin is also predisposed to microbial colonization. These skin barrier abnormalities are caused by a combination of genetic, environmental, and immunologic factors. Recent studies suggest that the prevention of AD can be achieved by early interventions protecting the skin barrier. Optimal management of AD requires control of local and systemic immune activation. Effective treatment of AD might reduce systemic allergen sensitization and reduce the prevalence and severity of associated allergic diseases in the gastrointestinal and

respiratory tract. The use of omalizumab for treatment of chronic urticaria provides a new tool for management of refractory 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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