

Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2010

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This review highlights some of the research advances in anaphylaxis; hypersensitivity reactions to foods, drugs, and insects; and allergic skin disease that were reported in the *Journal* in 2010. Key epidemiologic observations include an apparent increase in peanut allergy, with more than 1% of children affected, and increasing evidence that early food allergen exposure, rather than avoidance, might improve allergy outcomes. Advances in food allergy diagnosis include improved insights into prognosis and estimation of severity through component-resolved diagnostics and characterization of IgE binding to specific epitopes. Regarding treatment, oral and epicutaneous immunotherapy show promise. Studies of drug allergies show insights into pathophysiology, and studies on insect hypersensitivity reveal improved diagnostic methods. Genetic and functional studies have revealed the important role of epidermal differentiation products in the pathogenesis of atopic dermatitis. Cross-talk between the atopic immune response with the innate immune response have also been found to predispose to infection in patients with atopic dermatitis. New therapeutic approaches to control chronic urticaria have also been identified during the past year. (*J Allergy Clin Immunol* 2011;127:326-35.)

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

This review highlights key advances in allergic skin disease, anaphylaxis, and hypersensitivity to foods, drugs, and insect venom selected primarily from more than 100 articles on these topics published in the *Journal of Allergy and Clinical Immunology* in 2010. Some of the key advances are summarized in Table I.

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Disclosure of potential conflict of interest: S. H. Sicherer is a consultant for the Food Allergy Initiative and receives research support from the National Institutes of Health/National Institute of Allergy and Infectious Diseases. D. Y. M. Leung had declared that he has no conflict of interest.

Received for publication November 15, 2010; accepted for publication November 16, 2010.

Available online December 28, 2010.

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0091-6749/\$36.00

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doi:10.1016/j.jaci.2010.11.024

Abbreviations used

AD:	Atopic dermatitis
ADEH-:	Atopic dermatitis without a history of eczema herpeticum
ADEH+:	Atopic dermatitis with a history of eczema herpeticum
EH:	Eczema herpeticum
EoE:	Eosinophilic esophagitis
FACU:	Familial atypical cold urticaria
FLG:	Filaggrin
NIAID:	National Institute of Allergy and Infectious Diseases
NMF:	Natural moisturizing factor
OR:	Odds ratio
PPAR:	Peroxisome proliferator-activated receptor
TCI:	Topical calcineurin inhibitor
TCS:	Topical corticosteroid
TSLP:	Thymic stromal lymphopoietin
WTVZV:	Wild-type varicella zoster virus

FOOD ALLERGY

A milestone publication toward improving care of patients with food allergies is the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored "Guidelines for the diagnosis and management of food allergy in the United States."^{1,2} The guidelines were based on a comprehensive independent literature review with evidence grading, which was used by an expert panel. The expert panel received guidance from a coordinating committee of diverse stakeholders and from public comment to provide evidence-based advice and summaries of findings in the areas of epidemiology, natural course, diagnosis, prevention, and treatment. The guidelines are designed not only for allergists/immunologists but also for researchers and practitioners in the areas of pediatrics, family medicine, internal medicine, dermatology, gastroenterology, emergency medicine, pulmonary and critical care medicine, and others. The NIAID is also maintaining a Web site with supporting information (<http://www.niaid.nih.gov/topics/foodallergy/clinical/Pages/default.aspx>). Also of note is a similarly comprehensive guideline focusing on milk allergy developed in a similar fashion through the World Allergy Organization³ and a comprehensive general review of food allergy.⁴ Collectively, these should provide tremendous guidance for improved diagnosis and management.

Epidemiology and risk factors

Three studies used population-based surveys to estimate the prevalence of common food allergies.⁵⁻⁷ In separate studies in the United States⁵ and Canada,⁶ random calling methodologies showed overall rates of self-reported allergies as follows: peanut,

TABLE I. Summary of selected key advances reported in the *Journal* in 2010

Topic	Clinical or basic research concerns	Advances and observations
Food allergy	Epidemiology	• Childhood peanut allergy appears to have increased and exceeds a prevalence of 1%. • Delayed introductions of milk and egg are associated with increased risk of atopic outcomes. • Maternal ingestion of peanut during pregnancy was associated with increased risk of infant peanut sensitization among a cohort of atopic infants.
	Pathophysiology	• Allergen-induced <i>IL4</i> expression was related to milk allergy in the absence of <i>GATA3</i> expression.
	Diagnostic testing	• Binding to Ara h 2 provided the best peanut allergy diagnostic discrimination in a population-based cohort. • Studies of epitope binding provide insights on the prognosis, severity, and phenotypic expression of milk allergy.
	Treatment/management	• Oral immunotherapy shows promise for the treatment of peanut allergy. • A preliminary study of epicutaneous immunotherapy with milk protein shows a trend toward efficacy.
Anaphylaxis	Epidemiology	• A database of >1 million person-years shows increased risk for anaphylaxis among persons with asthma, particularly severe asthma.
Insect venom hypersensitivity	Diagnosis/treatment	• Use of nonglycosylated recombinant allergens for testing improves diagnostic accuracy. • Risks of side effects during vespid venom immunotherapy are related to baseline tryptase levels. • Gene expression profiling differentiated those having effective from ineffective immunotherapy.
Drug allergy	Pathophysiology and treatment	• Identification of plasmacytoid dendritic cells plays a role in drug reactions with eosinophilia and systemic symptoms. • Among those with serious reactions to cephalosporins, 25% had positive results to penicillin.
AD	Mechanisms and treatment	• <i>FLG</i> breakdown products are antimicrobial. • Aside from defects in <i>FLG</i> expression, broad defects of epidermal cornification exist. • Reduced IL-17 production distinguishes hyper-IgE syndrome from AD. • Patients prone to eczema herpeticum are highly atopic and have <i>FLG</i> mutations and <i>TSLP</i> polymorphisms. • Barrier proteins can be increased with topical anti-inflammatory therapy.
Urticaria and angioedema	Diagnosis and treatment	• Identification of FACU as a new form of cold urticaria • Use of high-dose antihistamine and anti-IgE for treatment-refractory cases

0.8% in the United States and 1.0% in Canada; tree nut, 0.6% in the United States and 1.2% in Canada; and sesame, 0.1% for both. The Canadian study⁶ applied various algorithms to determine “probable” allergy, and Slightly lower rates were calculated. They also considered a category of “confirmed” allergies, rates of which were much lower, but were also difficult to determine accurately because of unavailable data that were required for this category. The US study⁵ presented the opportunity to compare survey results over time because the study had been administered in a similar fashion in 1997, 2002, and 2008. The rates of surrogate-reported allergy in children increased significantly for tree nuts (0.6% to 1.2% and finally 2.1%) and peanut (0.4%, 0.8%, and finally 1.4%). Limitations of the studies included decreasing participation rates and self-assessment of allergy.

A study in Singapore and the Philippines⁷ used a similar questionnaire and focused on 4- to 6- and 14- to 16-year-old children. Interestingly, the rates of peanut and tree nut allergy among local inhabitants were on the order of 0.5% and 0.3%, respectively (eg, lower than the US and Canadian estimates). However, the rates among expatriates in Singapore were on the order of 1.2% for each food, which was similar to what was seen in the US and Canadian studies. The Canadian and Asian studies evaluated additional foods. Interestingly, shellfish allergy in children was

reported on the order of 0.5% in Canadians, 0.7% in expatriates, and 4% in the children native to Singapore and the Philippines.

In another epidemiologic study, Liu et al⁸ took advantage of the serologic testing performed during the National Health and Nutrition Examination Survey in the United States in 2005-2006. Estimations of clinical food allergy risk were based on prior studies correlating clinical outcomes to food-specific IgE concentrations. The rates of clinical food allergy varied by food type and age group and overall showed the following: milk, 0.4%; egg, 0.2%; peanut, 1.3%; and shrimp, 1%. In the children aged 1 to 5 years, clinical allergy to milk, egg, and peanut was estimated at 1.8% each. Although the rates of estimated peanut allergy in these various studies appear spectacularly high, a United Kingdom birth cohort study that included testing and oral food challenges also arrived at a rate nearing 2%.⁹ Evidence for increases in food allergy rates are also possibly reflected in greater numbers of emergency department visits for food-induced anaphylaxis.¹⁰

Adding to the concern of increasing prevalence, there continues to be evidence that food allergies are more persistent than previously appreciated. Savage et al¹¹ reported in a referral practice that soy allergy resolved in 25% by age 4 years, 45% by age 6 years, and only 69% by age 10 years.

It is interesting to speculate on the environmental and genetic influences affecting food allergy prevalence and persistence. In a rostrum article, Vassallo and Camargo¹² propose that vitamin D deficiency might underlie the changing pattern of food allergy through “multiple hits,” including alterations in the intestinal barrier and promotion of sensitizing immune responses.

Although prolonged allergen avoidance in infants at risk for atopy has been suggested as a modality to reduce the risks of food allergy, 2 population-based studies have concluded otherwise for milk and egg allergy. Katz et al¹³ evaluated a cohort of more than 13,000 infants and calculated an odds ratio (OR) of 19.3 (95% CI, 6.0-62.1) for development of IgE-mediated cow's milk allergy among infants exposed after 15 days of age. Koplin et al¹⁴ used a cross-sectional study of 2589 infants and noted that delayed introduction of egg was associated with increased risk of egg allergy. For example, compared with introduction at 4 to 6 months, delaying beyond 12 months carried an adjusted OR of 3.4 (95% CI, 1.8-6.5). These studies, although they carry potential limitations, such as subtle regional influences or reverse causation, add to the notion that oral exposure promotes tolerance and that excessive delays in the introduction of food allergens to the diet might be counterproductive, allowing sensitization to proceed through intermittent oral and environmental exposures.

The implications for allergy prevention argue against prolonged allergen avoidance. However, adding to the complex nature of exposure, a study from the Consortium of Food Allergy Research¹⁵ noted that maternal ingestion of peanut during pregnancy had a positive dose-response association with a risk of the infant having increased peanut-specific IgE antibody levels. The study currently reports on sensitization; however, they will follow the infants, who primarily have had reactions to egg and milk and are avoiding peanut, for progression to clinical peanut allergy. Clearly, the various dietary, environmental, and genetic factors that influence food allergy outcomes pose a challenging puzzle for deriving optimal prevention strategies.

Eosinophilic esophagitis (EoE) is associated with atopy and food allergy and is often responsive to dietary allergen elimination. DeBrosse et al¹⁶ performed an evaluation of pathology specimens and noted that between 1982 and 1999, before diagnoses of EoE at their institution, 30% of children given diagnoses of reflux esophagitis had more than 15 eosinophils per high-powered field, and there was no noted increase in incidence over that time period. Additionally, children with more than 5 eosinophils per high-powered field were noted to be more likely to have additional histologic abnormalities and have persistent eosinophilia, raising questions about broadening the diagnostic criteria for EoE. Additional studies on this disorder indicate a key role of mast cells in the pathophysiology of EoE,^{17,18} of variants of thymic stromal lymphopoietin (TSLP) and its receptor in disease susceptibility,¹⁹ and of FK506-binding protein 5 in responsiveness to steroid treatment.²⁰

Pathophysiology, allergen characterization, and diagnosis

Several insights into the pathophysiology of food allergy were reported. In the Consortium of Food Allergy Research cohort described above,²¹ mononuclear cell allergen stimulation screening was performed with PCR analysis to 7 key markers of immune regulation and T_H1/T_H2 bias. Only allergen-induced *IL4* expression was associated with clinical allergy to milk and sensitization

to milk and peanut. This was noted in the absence of increased *GATA3* mRNA expression, identifying a potential marker but also raising a question about the source of IL-4 not being of T-cell origin. Food processing, specifically heating that results in reactions between reducing sugars and proteins forming advanced glycation end products, might result in foods with increased allergenicity. Ilchmann et al²² observed that heating ovalbumin with glucose enhanced activation of ovalbumin-specific CD4⁺ T cells and increased IL-4 levels. Myeloid dendritic cell uptake of the processed ovalbumin was enhanced, and specific dendritic cell receptors were identified that mediated the process. These observations and others²³ set the stage for additional work to identify characteristics of food proteins that promote allergic responses and might elucidate immune intervention strategies.

Exploration of the interaction of humoral immune responses to particular food proteins and epitopes on those proteins can provide insight into diagnosis, natural history, and treatment. Component-resolved diagnosis evaluating binding to specific proteins was explored in several studies. Nicolaou et al⁹ evaluated this strategy for peanut allergy using primarily a population-based cohort and testing with Ara h 1 to 3 and 8; binding to Ara h 2 provided the best discrimination of reactivity. Additional examples of improved diagnostics through component analysis were demonstrated for kiwi²⁴ and shrimp.²⁵ However, Villalta and Asero²⁶ point out limitations of the approaches with regard to birch-related foods. Studies correlating clinical outcomes to serologic results of standard tests continue to reveal slight differences between study populations,²⁷ and it is evident that clinical studies will need to confirm the utility of newer modalities as well.²⁸

A series of studies evaluated IgE binding to specific epitopes on proteins for additional diagnostic or prognostic insights.²⁹⁻³² Ayuso et al³⁰ found that children with shrimp allergy had more intense binding to shrimp proteins and bound a wider diversity of epitopes compared with adults, implying a decrease in sensitization with age and possible waning of the allergy. Several studies evaluated milk allergy.³¹⁻³³ Savilahti et al³² compared the progression of epitope binding of milk proteins in children with resolved or persisting cow's milk allergy. Binding patterns were stable over time for those with persistent allergy, but among those with early recovery, IgG4 epitope binding increased while IgE binding to corresponding epitopes decreased. Different epitope-binding patterns were also noted to differentiate clinical phenotypes of cow's milk allergy³¹: a wider diversity of IgE epitope binding was noted for those with persisting milk allergy and more severe reactions and was more likely to occur in children who could not tolerate extensively heated forms of milk (eg, in muffins) compared with those who could tolerate such foods. In competitive peptide microarray assays, those with persistent milk allergy were fully differentiated from those with resolved allergy or tolerance of extensively heated forms by having high-compared with low-affinity binding, respectively. Additional studies of humoral responses to milk proteins³⁴ implicate a role for immunoglobulin free light chains. Together these studies show a promising start toward more informative diagnostics.

TREATMENT

Current treatment requires avoidance, which is complicated by factors such as confusing labeling on manufactured products or risks of exposure to residual food proteins in vaccines. Ford et al³⁵ evaluated a sample of 401 foods for the presence of milk, egg, or

peanut when those foods had advisory labels (eg, “may contain”) or did not have such warnings. Overall, 5.3% of the products with advisory labels had detectable protein, whereas 1.9% of products with no warnings were contaminated. The latter were primarily accounted for by small companies, and thus was not observed for peanut. Crotty and Taylor³⁶ focused on products with advisory labeling for milk and found high rates of contamination (42%) primarily accounted for by chocolates. Although often the level of allergen is low, there are clearly risks present for sensitive patients.

Another problematic source of allergen exposure is egg through seasonal influenza vaccines. Several studies have highlighted the availability and potential increased safety of vaccines with very low contents of ovalbumin,³⁷⁻³⁹ which could argue for the utility of manufacturers labeling the egg content of vaccines on a lot-by-lot basis. In an editorial and letter by Kelso,^{40,41} an argument is made for liberalizing immunization practices, including eliminating routine skin testing, particularly when the egg content is known. As more studies emerge, evidence-based guidelines will hopefully be developed, but the studies thus far suggest that many more subjects with egg allergy can be safely vaccinated.

Definitive therapies for food allergy are sorely needed. In a study of 23 children with peanut allergy,⁴² oral immunotherapy was instituted with a 7-day rush protocol followed by long-term build-up, aiming for at least 500 mg but possibly 2000 mg of peanut (approximately 500 mg of protein). The study included a final 2-month maintenance phase followed by a 2-week period without treatment and then a final oral food challenge. The rush protocol generally did not result in doses exceeding those tolerated during an initial oral food challenge; 1 child withdrew (anxiety), and only 5 reached the initial goal of 500 mg of peanut. During the build-up phase, additional dropouts occurred (4 because of side effects, 2 because of adherence, and 1 because of infection), and 1 additional subject could never reach 500 mg, leaving 14 of 23 for a final oral food challenge. Of these, 8 reached 500 mg, 5 reached 1000 mg, and 1 reached 2000 mg. At the final food challenge, 11 of 14 tolerated the same or more peanut compared with their daily maintenance dose. Laboratory correlates included an increase in peanut-specific IgG4 and a decrease in IL-2, IL-4, and IL-5 production by PBMCs. Although the results are promising, it appears clear that more studies are needed to identify potentially successful candidates, refine treatment strategies, increase safety, and define whether protocols result in temporary desensitization or more permanent tolerance.

In an editorial, Thyagarajan et al⁴³ point out that peanut oral immunotherapy (OIT) is not yet ready for routine clinical use, citing concerns such as safety, efficacy, and practical considerations. An interesting alternative strategy was reported by Dupont et al,⁴⁴ who used epicutaneous application of milk protein in children with milk allergy as a modality of treatment. In this pilot study that randomized 19 children and applied the therapy for 90 days before a posttreatment oral food challenge, there was a trend toward improvement in the 16 subjects completing the study. Thresholds increased from a cumulative dose of 1.77 to 23 mL of milk ($P = .18$) in treated subjects compared with the placebo group (pre-post of 4.4 and 5.4 mL, respectively). Only 1 treated subject had a reduction in tolerated dose. Milk-specific IgE levels did not change during therapy. The treatment was well tolerated, but larger controlled studies are needed. Additional strategies to improve immunotherapy while maintaining safety are under

investigation.⁴⁵ In a preclinical study a Chinese herbal formula appears to provide protection through a reduction in mast cell and basophil numbers and suppression of IgE-mediated mast cell activation.⁴⁶

ANAPHYLAXIS

An updated practice parameter⁴⁷ emphasizes the importance of the medical history, early administration of epinephrine, and prevention strategies. In a United Kingdom database patients aged 10 to 79 years were evaluated for anaphylaxis through International Classification of Disease, Ninth Revision, classification and record review.⁴⁸ The database included 1,111,124 person-years of data and estimated an anaphylaxis incidence rate of 34.4 per 100,000 person-years. Rates were higher in persons with asthma and increased with severity of asthma (2-fold increased risk for nonsevere asthma and 3.3 relative risk for severe asthma). Anaphylaxis incidence was higher in women compared with that seen in men; drug and food allergies were the most common triggers among known triggers. Coding-based diagnostics carry limitations, but Harduar-Morano et al⁴⁹ validated a coding-based algorithm that appears to capture otherwise missed cases, providing a methodology to improve anaphylaxis rate estimates from International Classification of Disease-coded databases.

Treatment of anaphylaxis requires prompt administration of epinephrine.⁵⁰ Simons⁵¹ reports a recently increasing rate of unintentional injections from autoinjectors; from 1994 to 2007, there were 15,190 reports to US poison control centers, with 60% being after 2002. Although sequelae are rare, the results are a reminder of the need for proper training and education in their use.

Diagnosis of anaphylaxis can be challenging, and symptoms might overlap disorders, such as mastocytosis and the mast cell activation syndrome. Alvarez-Twose et al⁵² evaluated adults with anaphylaxis/mast cell activation symptoms without skin symptoms who had clonal or nonclonal mast cells for the purpose of identifying criteria for bone marrow testing. They found that most of the clonal patients had fulfilled criteria for indolent systemic mastocytosis without skin lesions, and this group showed a higher frequency of male subjects, cardiovascular symptoms, having insect stings as triggers, and baseline tryptase levels, allowing for a multivariate model that could identify clonality before bone marrow. They concluded that a significant percentage of those with clonal mast cell activation disorders can be considered as having indolent systemic mastocytosis without skin symptoms diagnosed at early phases of the disease. Akin et al⁵³ proposed criteria for differentiating mast cell activation “syndrome” from other mast cell disorders.

HYPERSENSITIVITY TO STINGING INSECTS

Several studies address the diagnosis and management of insect venom allergy. Cross-reactive carbohydrate epitopes among insect venoms and pollens reduce the accuracy of diagnostic tests. Mitterman et al⁵⁴ used recombinant nonglycosylated allergens to differentiate patients with pollen and insect allergy and also differentiate subjects reactive to bee and wasp venom. Jin et al⁵⁵ evaluated cross-reactivity between yellow jacket and honeybee hyaluronidase using inhibition studies with cross-reactive carbohydrates and purified honeybee hyaluronidase, as well as phospholipase A1 and antigen 5, and found that the hyaluronidase

was a minor yellow jacket allergen (10% to 15% binding), with most binding having been due to carbohydrate cross-reactivity. Reactivity to antigen 5 and phospholipase detected almost all of those with yellow jacket allergy.

With regard to treatment, Rüeff et al⁵⁶ showed that the risks of side effects during the build-up phase of venom immunotherapy for vespid venom was associated with baseline serum tryptase levels (which was not the case for bee venom, although bee venom immunotherapy was an independent risk). In another study⁵⁷ gene expression profiling was able to distinguish those with or without effective venom immunotherapy; identified genes include those involved in mast cell activation and T-cell differentiation. Additional studies are needed to confirm the findings, explore mechanisms, and assess the potential for clinical utility.

The safety of imported fire ant immunotherapy was evaluated in a study of 77 patients in one center that found that risks of a mild systemic reaction were low (0.4% per injection and 9.1% per patient) and best predicted by a mild systemic reaction to skin testing or having a large local reaction.⁵⁸ Increased maintenance dosing was required for 2 of 4 subjects who had loss of consciousness during field stings. Tartibi et al⁵⁹ reported a patient who was refractory to treatment with fire ant immunotherapy and had reactions to the therapy but was protected with omalizumab treatment.

DRUG ALLERGY

The drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms is a reaction that involves reactivation of herpes viruses. Sugita et al⁶⁰ observed that plasmacytoid dendritic cell numbers decreased in the circulation and increased in the skin of affected patients. It remains to be determined whether this shift is the cause or result of viral reactivation and whether the shift predisposes to autoimmunity that is sometimes observed after a reaction. In another study⁶¹ the nature of T-cell responses to sulfonamides was evaluated by using various parent drugs and metabolites. Differential potencies and mechanisms were identified that might provide insights for future drug development or assessment of allergy risk.

In a clinical study Romano et al⁶² evaluated patients with serious reactions to cephalosporins to determine allergy to related drugs. About 25% had positive results to penicillin, 3% to aztreonam, 2% to imipenem, and 1% to meropenem; those with negative results were challenged, and all but 1 (reacting to imipenem with urticaria) tolerated the medication. Two reports indicate that allergy to the clavulanic acid component of amoxicillin/clavulanate products should be considered in the diagnosis of drug reactions to this therapy.^{63,64} Also of clinical note, a protocol for desensitization to buprenorphine is presented,⁶⁵ as well as a general review of drug hypersensitivity diagnosis and management.⁶⁶

ATOPIC DERMATITIS

Mechanisms of barrier dysfunction

Although various candidate gene studies have implicated the involvement of adaptive and innate immune response genes in patients with atopic dermatitis (AD), there has recently been particular interest in skin barrier dysfunction genes (Fig 1).⁶⁷ Loss-of-function mutations in the structural epidermal protein filaggrin (FLG) have been a widely replicated major risk factor for eczema and are providing new insights into disease mechanisms

in patients with AD. The *FLG* gene mutation findings are consistent with the hypothesis that AD results from a genetically transmitted epithelial barrier defect that leads to increased absorption of allergens or enhanced colonization with microbes and ultimately chronic allergic skin inflammation.⁶⁸ Direct evidence for this is supported by the observation that *FLG*-deficient mice spontaneously have AD, and this process is accelerated by application of allergen to the skin.⁶⁹

Given the difficulty in genotyping *FLG*, which is a complex repetitive gene with population-specific mutations, O'Regan et al⁷⁰ have recently sought to determine whether specific Raman micro-spectroscopic natural moisturizing factor (NMF) signatures of the stratum corneum could be used as markers of *FLG* genotype in patients with moderate-to-severe AD. These investigators identified AD subpopulations closely corresponding with *FLG* genotype using Raman spectroscopy. The Raman signature of NMF discriminated between *FLG*-associated AD and non-*FLG*-associated AD. In addition, within the subset of *FLG*-associated AD, NMF distinguished between patients with 1 versus 2 mutations. Raman spectroscopy might permit rapid and highly accurate stratification of *FLG*-associated AD.

Although compelling evidence implicates *FLG* gene mutations in the pathogenesis of AD, it is likely that there are multiple pathways that ultimately lead to eczema. This includes allergic immune responses because T_H2 cytokines themselves can down-regulate *FLG* skin expression.⁷¹

Using genomic profiling of mRNA from the skin of patients with AD and psoriasis compared with normal human skin, Guttman-Yassky et al⁷² reported broad defects of epidermal cornification in patients with AD. Striking differences were identified in epidermal differentiation programs that could be used for precise disease classifications. Although both psoriasis and AD skin lesions displayed regenerative epidermal hyperplasia, keratinocyte terminal differentiation was differentially polarized. In patients with AD, they found selective defects in expression of multiple genes encoding the cornified envelope, with the largest alteration in loricrin (expressed at 2% of the level of normal skin). At the ultrastructural level, the cornified envelope in patients with AD was broadly defective, with highly decreased compaction of corneocytes and reduced intercellular lipids. Hence the entire keratinocyte terminal differentiation program (cytoplasmic compaction, cornification, and lipid release) is defective in patients with AD. Using a novel mass spectrometry-based proteomics approach on skin tape strippings, Broccardo et al^{73,74} also found that patients with AD have unique epidermal protein profiles, some of which are involved in keratinocyte differentiation.

Immune response

Although there is a significant association of *FLG* mutations in patients with AD, it is important to note that these gene mutations can occur in healthy subjects or other diseases that do not lead to AD. Therefore environmental and immune factors also likely play a critical role in determining the final AD clinical phenotype. Infection is a common trigger of skin disease in patients with AD, as reviewed by Boguniewicz and Leung.⁷⁵ In the case of *Staphylococcus aureus*, virulence factors play a critical role in driving skin inflammation and immune activation.⁷⁶⁻⁷⁹ These staphylococcal products activate several critical cytokines, including TSLP, that alter dendritic cell responses to skew

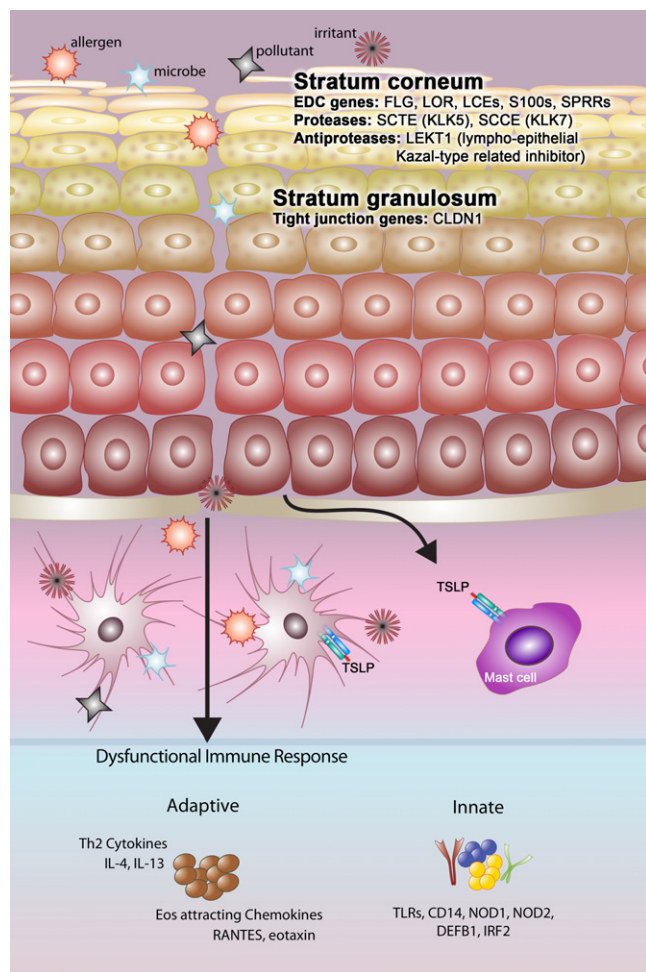


FIG 1. *DEFB1*, Defensin beta-1; *EDC*, epidermal differentiation complex; *Eos*, eosinophils; *IRF2*, interferon regulatory factor 2; *LOR*, loricrin; *NOD*, nucleotide-binding oligomerization domain; TLRs, Toll-like receptors.

T-cell differentiation toward T_H2 cells and influence the chemokine expression that is critical for cell infiltration and migration.⁸⁰⁻⁸² Interestingly, *FLG* breakdown products have also been found to control the growth of *S aureus*, suggesting that structural proteins can play a role in host defense against microbial invasion.⁸³

Recently, there has been a surge of research assessing mechanisms underlying the increased propensity of patients toward viral infections. As part of the National Institutes of Health/NIAID's Atopic Dermatitis Vaccinia Network, Beck et al⁸⁴ recently contrasted the phenotype and laboratory biomarkers in patients with AD with a history of eczema herpeticum (ADEH+) compared with those seen in patients with AD without eczema herpeticum (EH). These investigators found that patients with ADEH+ had more severe skin disease and biomarkers (higher circulating eosinophil counts and serum IgE levels, allergen sensitization, thymus and activation-regulated chemokine levels, and cutaneous T cell-attracting chemokine levels) than patients with AD without EH. Cutaneous infections with *S aureus* or molluscum contagiosum virus were also more common in patients with ADEH+. Consistent with the observation that patients with ADEH+ are more atopic, *FLG* mutations and *TSLP* polymorphisms have been found to confer an increased risk of the ADEH+

phenotype.^{85,86} In a gene-profiling study of skin biopsy specimens to vaccinia virus, Grigoryev et al⁸⁷ found differences in the transcriptional response to vaccinia virus between patients with AD compared with that seen in patients with psoriasis or healthy subjects. This unique molecular signature in AD skin included genes involved in the innate immune response and wound healing.

Advances continue to be made in understanding the pathobiology of cytokines in patients with AD. There is particular interest in TSLP, which has recently been found to be induced in the epidermis after mechanical stimulation⁸⁸ and to play a role in activation of T_H2 cytokine-secreting invariant natural killer cells, numbers of which are increased in AD skin.⁸⁹ There has also been considerable interest in the contribution of IL-32 to keratinocyte apoptosis in patients with AD,⁹⁰ as well as the role of T_H17 and T_H22 cells.^{91,92} After varicella vaccination, children with AD have been found to have normal T-cell responses.⁹³

Management and natural history

Management of AD begins with making an accurate diagnosis. Hyper-IgE syndrome can often be confused with AD because both conditions are associated with eczema and increased serum IgE levels. During the past year, Schimke et al⁹⁴ reviewed clinical and immunologic findings to differentiate hyper-IgE syndrome from AD. Key clinical findings, such as *Staphylococcus aureus* abscesses, recurrent pneumonia, increased serum IgE levels, and eczema in combination with low T_H17 cell numbers, were found to be predictive of patients with hyper-IgE syndrome with signal transducer and activator of transcription 3 (*STAT3*) mutations.

Factors that might affect the clinical course of AD are important to consider during the management of these patients. Peters et al⁹⁵ evaluated whether early-life factors, family history of atopic diseases, and job history were predictive of the incidence, recurrence, and persistence of AD. High socioeconomic status, female sex, asthma symptoms and a positive skin prick test response at baseline, parental history of rhinitis/AD, and having worked in a high-risk job were significant predictors for the course of disease. The authors concluded that genetic factors, early allergen sensitization, and having worked in a high-risk job seem to be more important for disease development in late adolescence than other early-life exposures.

Pincus et al⁹⁶ explored the hypothesis that prenatal maternal hormonal levels, which are involved in developmental programming of the fetus, could play a role in determining the course of AD later in life. Low levels of maternal progesterone (which can occur in response to stress) increased the risk of AD in girls during later life. Although confirmation of this association is needed, the authors speculated that progesterone supplementation might be of benefit in preventing AD in such subjects.

Silverberg et al⁹⁷ assessed whether wild-type varicella zoster virus (WTVZV) infections in childhood protects against AD. A single episode of WTVZV infection in childhood was associated with a decreased OR for AD. When using intervals for age corresponding to bimodal distribution of age of WTVZV infection, the effects of WTVZV infection were significant when occurring at ages 0 to 8 years but not at ages 8 to 18 years. WTVZV infection was also associated with decreased odds of moderate or severe AD. Children with WTVZV infection, compared with vaccine, who eventually had AD required fewer pediatrician's office sick visits for management of AD. The

authors concluded that WTVZV infection in childhood protected for up to 10 years of age against AD, delayed onset of AD symptoms, and decreased AD severity and office visits.

Once AD is diagnosed, management of this skin disease requires a multipronged approach, including skin barrier repair, avoidance of allergens, control of infection, and anti-inflammatory therapy. Several recent studies have demonstrated that T_H2 responses can reduce skin barrier proteins,⁷¹ suggesting that immunomodulatory or immunosuppressive therapy can enhance the barrier. Jensen et al⁹⁸ investigated the effect of 2 common anti-inflammatory treatments, a calcineurin inhibitor and a corticosteroid, on the skin barrier. Stratum corneum hydration and transepidermal water loss improved in both groups. Dye penetration, a marker of barrier permeability, was also reduced with both drugs. Electron microscopic evaluation of barrier structure displayed ordered stratum corneum lipid layers in pimecrolimus-treated skin but inconsistent extracellular lipid bilayers after betamethasone treatment. Betamethasone was superior in reducing clinical symptoms and epidermal proliferation; however, it led to epidermal thinning. This study supports the notion that topical steroid is useful for gaining rapid control of acute AD exacerbations. Topical calcineurin inhibitors, however, might be more suitable for long-term treatment of AD and continued barrier repair.

Concerns have been raised about whether topical immunosuppressants might enhance the occurrence of lymphoma among patients with AD. Arellano et al⁹⁹ assessed the risk of lymphoma associated with AD and use of topical corticosteroids (TCSs) or topical calcineurin inhibitors (TCIs) in a database allowing medical record validation. They conducted a nested case-control study using the United Kingdom-based The Health Improvement Network database. In the study population of 3,500,194 subjects, they reported that AD was associated with an increased lymphoma risk (OR, 1.83). They did not find any cases of lymphoma in TCI users; however, the number of patients exposed to TCIs was insufficient to study any possible association between lymphoma and these drugs. TCS use was associated with an increased lymphoma risk (OR, 1.46). The risk increase was dependent on TCS potency (OR for high-potency TCS, 1.80). The increased risk involved both Hodgkin disease and non-Hodgkin lymphoma, especially non-Hodgkin lymphoma with skin involvement (OR for high-potency TCSs, 26.24). Their results suggest an association between lymphoma, especially skin lymphoma, and use of TCSs. The risk increased with duration of exposure and the potency of the TCS.

There continues to be controversy over the role of probiotics in the treatment or prevention of AD.¹⁰⁰ Grüber et al,¹⁰¹ however, recently assessed the effect of supplementation of an infant and follow-on formula with prebiotic and immunoactive oligosaccharides on the occurrence of AD. Healthy term infants from 5 European countries with low atopy risk were recruited before the age of 8 weeks, either having started with formula feeding or being on full breast-feeding (breast-feeding group). Formula-fed infants were randomized to feeding with a regular formula containing a specific mixture of neutral oligosaccharides and pectin-derived acidic oligosaccharides (prebiotic formula group) or regular formula without oligosaccharides (control formula group). The rate of AD was significantly decreased in the prebiotic group versus the control group. These data suggested formula supplementation with a specific mixture of oligosaccharides was effective in reducing the occurrence of early AD in low-atopy-risk infants.

During the past year, there have also been several new treatments proposed for chronic AD. In a pilot study

Kasperkiewicz et al¹⁰² studied the effects of immunoadsorption in 12 patients with treatment-refractory severe AD and high serum IgE levels. After 13 weeks of treatment, there was a significant reduction in pruritus and eczema severity, as well as a reduction in skin-bound IgE levels and decreased skin-infiltrating inflammatory cell numbers. Further studies are needed to understand the mechanisms of action of immunoabsorption in AD.

Using a murine model of AD, Hatano et al¹⁰³ evaluated the efficacy of activators of peroxisome proliferator-activated receptors (PPARs) α , β/δ , and γ and liver X receptor. Their data suggested that topical applications of certain activators/ligands of PPAR α , PPAR β/δ , and liver X receptor reduced skin inflammation and improved skin barrier function. This new class of drugs could therefore be useful for the treatment of AD.

URTICARIA AND ANGIOEDEMA

Gandhi et al¹⁰⁴ described 3 unrelated families with a new hereditary disease of cold urticaria called familial atypical cold urticaria (FACU). Thirty-five subjects were described with FACU (family A, 17; family B, 8; and family C, 10), displaying an autosomal dominant pattern of inheritance. All tested subjects had negative cold stimulation time test results. Completed questionnaires revealed that all affected subjects had lifelong symptoms that began in early childhood with pruritus, erythema, urticaria, and angioedema after cold exposure. Triggers included cold atmosphere, aquatic activities, handling cold objects, and ingestion of cold foods or beverages. Skin biopsy specimens demonstrated a mast cell infiltrate with the appearance of degranulation after cold challenge. The authors concluded that FACU is a new cold-induced inherited disease that is different than acquired cold urticaria in its natural history, atmospheric cold elicitation, severity of systemic reactions, and cold stimulation time test results.

H_1 -antihistamines are used as first-line treatment of chronic urticaria, but many patients do not get satisfactory relief with recommended doses. Eighty tertiary referral patients with chronic urticaria were randomized for double-blind treatment with levocetirizine or desloratadine to determine whether increased antihistamine doses can bring relief to patients who do not respond to standard doses of antihistamines.¹⁰⁵ Treatment started at the conventional daily dose of 5 mg and then increased weekly to 10 mg, 20 mg, or 20 mg of the opposite drug if relief of symptoms was incomplete. Increasing antihistamine doses reduced urticaria and improved quality of life but did not increase somnolence. Analysis of the effect of treatment on discomfort caused by urticaria showed great individual heterogeneity of antihistamine responsiveness: approximately 15% of patients were good responders, approximately 10% were nonresponders, and approximately 75% were responders to higher than conventional antihistamine doses. These authors concluded that increasing the dosage of levocetirizine and desloratadine up to 4-fold improves symptoms of chronic urticaria without compromising safety in approximately three quarters of patients with difficult-to-treat chronic urticaria. In a separate study Siebenhaar et al¹⁰⁶ reported that increased dosing of desloratadine decreased wheal volume and improved cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria using a randomized, placebo-controlled, crossover study design.

For patients who do not respond to antihistamine therapy, alternative treatments have been sought. Low-dose cyclosporine has been reported to be a good option for severe chronic urticaria.¹⁰⁷ Several groups have also described favorable experiences in the use of anti-IgE (omalizumab) or anti-CD20 (rituximab) for the treatment of chronic urticaria refractory to other forms of therapy.¹⁰⁸⁻¹¹⁰ Randomized, placebo-controlled trials with these humanized mAbs in larger populations of patients with chronic urticaria are needed to confirm these promising observations. An interesting study has found that patients with chronic urticaria have reduced vitamin D levels.¹¹¹ This raises the interesting possibility that oral supplementation with vitamin D could be used as adjunctive therapy for this often difficult-to-treat condition because vitamin D has been suggested to have steroid-sparing effects in asthmatic patients.¹¹²

CONCLUSIONS AND SUMMARY

In the year since our last review,¹¹³ numerous exciting advances have been reported in the *Journal*. In particular, basic and clinical-translational studies are bringing us closer to improving the diagnosis and treatment of food allergies primarily through component-resolved diagnostics and epitope analysis. Studies of oral immunotherapy are encouraging, but more needs to be done to characterize risks and efficacy because there are clear limitations. Advances have also been made in our understanding of the mechanism and treatment of allergic skin diseases (Table I). These advances present information that can be implemented immediately to improve patient care.

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