

Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2007

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This review highlights some of the research advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects that were reported primarily in the *Journal* in 2007. Advances in diagnosis include possible biomarkers for anaphylaxis, improved understanding of the relevance of food-specific serum IgE tests, identification of possibly discriminatory T-cell responses for drug allergy, and an elucidation of irritant responses for vaccine allergy diagnostic skin tests. Mechanistic studies are discerning T-cell and cytokine responses central to eosinophilic gastroenteropathies and food allergy, including the identification of multiple potential therapeutic targets. Regarding treatment, clinical studies of oral immunotherapy and allergen vaccination strategies show promise, whereas several clinical studies raise questions about whether oral allergen avoidance reduces atopic risks and whether probiotics can prevent or treat atopic disease. The importance of skin barrier dysfunction has been highlighted in the pathogenesis of atopic dermatitis (AD), particularly as it relates to allergen sensitization and eczema severity. Research has also continued to identify immunologic defects that contribute to the propensity of patients with AD to have viral and bacterial infections. New therapeutic approaches to AD, urticaria, and angioedema have been reported, including use of sublingual immunotherapy, anti-IgE, and a kallikrein inhibitor. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

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, primarily from among more than 95 articles on these topics published in the *Journal of Allergy and Clinical Immunology* in 2007. Some of the key advances are summarized in [Table I](#).

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Abbreviations used

AD: Atopic dermatitis
EE: Eosinophilic esophagitis
HAE: Hereditary angioedema
OR: Odds ratio
PAF: Platelet-activating factor

FOOD ALLERGY

Epidemiology, clinical characteristics, and natural course

Obtaining an accurate epidemiologic picture of the burden of food allergy is hampered by a lack of uniform, population-based methodologies that incorporate the gold-standard diagnostic method, a double-blind, placebo-controlled oral food challenge. Through the EuroPrevall initiative, a meta-analysis of 51 studies (883 studies were excluded for various reasons) focusing on allergy to milk, egg, peanut, and seafood showed wide variation in prevalence estimates. For example, self-reported food allergy ranged from 3% to 35%, which likely reflects study limitations of self-report, varied definitions of food allergy, and true population variation.¹ Prevalence studies based on incorporating oral food challenges were few, but considering allergy to “any food” from 6 studies including this methodology, estimates ranged from 1% to 10.8%, with a random-effects model showing an overall approximation of prevalence of approximately 3.5%. While we wrestle with evaluating an apparent increase in food allergy,² we need to be cognizant of methodological issues in various studies, attempt to use standard methods, and be cautious about estimates based on self-report.

Although milk and egg allergy are typically considered transient and likely to resolve by age 3 to 5 years, new reports from a referral center indicate that we might need to revise these tenets. Regarding milk allergy, a retrospective chart review of patients evaluated by Robert A. Wood and colleagues (Johns Hopkins University, Baltimore, Md) since 1993 resulted in identification of 807 children meeting the inclusion criteria for IgE-associated cow’s milk allergy and having sufficient follow-up.³ By using a broad definition of tolerance defined by passing a food challenge or having no reactions for a year with a milk IgE level of less than 3 kIU/L, the study found that milk allergy resolved in 19% by age 4 years, in 42% by age 8 years, in 64% by age 12 years, and in 79% by age 16 years. In a similar study design focusing on egg allergy, in which 881 patients were identified from the practice of 2 faculty members also at Johns Hopkins, and considering that egg tolerance is defined by ingestion of concentrated egg or an egg IgE level of less than 2 kIU/L and no symptoms in 12 months, resolution rates were 11% by age 4 years, 41% by age 8 years, 65% by age 12 years, and 82% by age 16 years.⁴ The authors identified

TABLE I. Key advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2007

1. Anaphylaxis/ insect venom	Epidemiology, diagnosis, and management	—There appears to be an increase (Australia) and north-south gradient (United States) to anaphylaxis. —Biomarkers of interest have been identified (eg, basophil CD69, CD203c, and PAF).
2. Food allergy	Epidemiology	—Resolution of egg and milk allergy can occur more slowly than previously reported. —Evaluation of fatalities emphasizes the risks of comorbid asthma, age (teenagers and young adults), lack of prompt epinephrine, and more reports of milk as a trigger. —EE follows a persistent/recurrent course.
	Molecular aspects of food allergy	—Degree of sequence homology to human proteins might determine allergenic potential of animal proteins. —There is a key role for IL-13 in EE.
	Diagnostic testing	—There are similarities in the pathology of asthma airway remodeling and EE. —Clinical and immune characteristics of soy and lupine allergy were identified. —Predictive value of food-specific serum IgE levels varies by age (shown for milk and egg). —Reactions/sensitivity can vary for certain allergens, depending on exposure to digestion.
	Treatment/prevention/ management	—Consumers differentially avoid products with advisory labels (“may contain” vs “in a facility”), but the warnings do not correlate with risks. —Studies question the concept that allergen avoidance in pregnancy/lactation reduces atopy risks. —Studies of probiotics show some treatment or prevention effect for AD, but results are conflicting. —Studies on oral immunotherapy show promise for desensitizing, but results remain unclear regarding prospects of permanent tolerance.
		—Immunization strategies for fruit or vegetable allergies show promise. —Murine models identify targets, such as dendritic cells, and therapies, such as IL-10, IL-12, TGF- β , and a synthetic agonist of Toll-like receptor 9, for treatment.
3. Drug allergy	Triggers, mechanisms, and diagnosis	—Anaphylaxis from omalizumab is reported to often follow an atypical course, and guidelines for monitoring patients after administration are modified. —Insights on pathogenesis of carbamazepine-induced Stevens-Johnson syndrome are determined. —Testing routines for vaccines, chlorhexidine, and platinum salts are described.
4. AD	Mechanisms	—Filaggrin null mutations are associated with the development of AD and increased allergen sensitization and contribute to the atopic march.
	Treatment	—T _H 2 cytokines inhibit filaggrin expression and innate immune response. —Anti-IgE might reduce AD, despite high serum IgE levels. —There is a possible role for sublingual immunotherapy to dust mites.
5. Urticaria and angioedema	Mechanisms and treatment	—Activation of tissue factor pathway in chronic urticaria. —Association of Fc ϵ RI α promoter polymorphisms in chronic urticaria. —Treatment of delayed-pressure urticaria with anti-TNF- α . —Treatment of idiopathic angioedema with anti-IgE. —Role for bradykinin receptor antagonist, kallikrein inhibitor, and stanazolol in HAE.

PAF, Platelet-activating factor.

a reduced chance of achieving tolerance for those with additional atopic diseases and higher concentrations of specific IgE. The slow rate of achieving tolerance reported in these studies is alarming, but the studies emphasize that most of the children became tolerant, and reappraisal is therefore crucial, even into the teenage years. The results likely at least partly reflect selection bias of a referral center but still underscore the need for improved prevention and treatment for foods other than the classically persistent allergies like peanut.

Regarding peanut, new insights on adolescent/adult peanut allergy were reported based on a case series of 35 subjects, 25 with early onset after a few exposures presenting at a median age 3 of years and 10 with late onset at a median age of 25 years among adults with a clear period of previously tolerating peanut.⁵ Those with late onset had lower serum peanut IgE test results than those with early onset and more often had mild oral symptoms that could be related to pollen sensitization, although this was not adequately investigated in the report. One 53-year-old subject with late-onset peanut allergy presents an interesting caution because she had routinely tolerated peanut but had been instructed to avoid it after a positive skin test response was documented.

Three years after strict avoidance, her food challenge resulted in lower airway symptoms, raising a worry that unnecessary avoidance might have resulted in loss of tolerance. Peanut and tree nuts remain a frequent trigger of fatal anaphylaxis, as indicated in 2 case series (25/32 deaths in the United States and 18/48 in the United Kingdom)^{6,7}; these reports also disclose that fatal reactions are associated with lack of timely use of epinephrine, asthma, and being a teenager/young adult. However, these new case series also emphasize that milk is also an important trigger responsible for 10% of the deaths in these reports.

Insights on eosinophilic gastrointestinal disease

Patients with eosinophilic esophagitis (EE) and eosinophilic gastrointestinal disease present diagnostic and therapeutic challenges. Insights about the diseases are improving our ability to manage the disorder and are focusing research efforts. Assa'ad et al⁸ reviewed clinical data on 89 children with EE and showed important epidemiologic and clinical observations, including a predominance of white (94%) male (79%) subjects; symptom onset at a mean age of 3 years with diagnostic endoscopy at 6 years;

predominant presenting symptoms of emesis, pain, and dysphagia; and high rates (>75%) of allergen sensitization. Importantly, the case series indicates that the disease includes eosinophilic inflammation in the gut beyond the esophagus in 77%, and the disease follows a relapsing and recurrent or persistent course for most patients, despite various therapeutic trials. A major concern is fibrosis and stricture formation, and in a study of children with EE ($n = 7$) and reflux ($n = 7$) and healthy control subjects ($n = 7$), Aceves et al⁹ reported that biopsy specimens in children with EE showed comparatively more subepithelial fibrosis, increased TGF- β 1 levels, increased vascular density, and expression of vascular cell adhesion molecule 1. These findings are similar to those of airway remodeling in asthma and might present opportunities for stratifying diagnosis and planning interventions. In a series of elegant experiments using biopsy specimens from patients with EE and transient transfection experiments in esophageal cell lines, Blanchard et al¹⁰ identified a key role for IL-13 in the pathophysiology of the disorder, presenting additional therapeutic targets (this group previously identified a key role for eotaxin 3). Current treatments are clearly inadequate and rely often on steroids and trial elimination diets, sometimes determined with cumbersome and often only modestly informative diagnostic tests for food hypersensitivity.¹¹ In a search for alternative medical therapies, Foroughi et al¹² used omalizumab (anti-IgE mAb) to treat 9 subjects with eosinophilic gastroenteropathies. After a 16-week treatment of 8 doses, symptom scores decreased (70%, $P < .005$), and eosinophil counts decreased in the duodenum (59%, $P = .07$) and gastric antrum (69%, $P = .1$) but not in the esophagus (increase of 25%, $P = .5$). These preliminary results indicate that IgE-associated mechanisms contribute to eosinophilic gastroenteropathies and indicate a potential therapy, although more study is clearly needed. A consensus report and review about diagnosis and management of EE was also published this year.¹³

Pathophysiology, allergen characterization, and diagnosis

Insights that are relevant to diagnosis, prediction of cross-reactivity, reaction severity, and treatment are obtained through studies that evaluate allergen structure¹⁴ and IgE binding to food allergens¹⁵ and related nonfood allergens, such as pollens, in well-characterized patient populations. Jenkins et al¹⁶ compared animal food allergens and human homologues by considering protein families, sequence analysis, and evolutionary relationships. They identified 3 main families (tropomyosins, EF-hand proteins, and caseins) and 14 minor families and noted that sequence identities to human homologues of greater than 62% typically excluded a protein from being an allergen to human subjects, likely because of reduced immunogenicity. They cautioned that creation of modified allergens for immunotherapy of animal protein allergens would need to be evaluated for unintended autoimmune responses.

Regarding plant food allergens, Ballmer-Weber et al¹⁷ performed double-blind, placebo-controlled oral food challenges and serum tests to evaluate 30 subjects with soy allergy in a multicenter study in Europe. Symptoms and threshold doses varied, and statistical modeling indicated that 1% of patients with soy allergy would react with objective symptoms to 37 mg of soy protein. Severity was not well correlated to soy IgE levels or immunoblots, but subjects with pollen-associated soy allergy (positive

to Gly m 4 and Bet v 1) were unlikely to have severe symptoms. Lupine is another allergenic legume that, like soy, can be used as flour, and allergy to lupine might result from cross-reactivity to peanut, other legumes, or *de novo*. Peeters et al¹⁸ evaluated 6 subjects with lupine allergy, 3 of whom had peanut allergy, and identified possible distinguishing patterns of immunoreactivity using immunoblots, although more is needed to define the causal proteins. Although the study was too small to determine eliciting doses, objective symptoms were observed at 300 mg in the participants, and historical reactions were of moderate severity, findings similar to those with peanut allergy. These studies on soy and lupine provide additional insights toward improved diagnosis with IgE-binding profiles. In the meantime, it is important to recognize the appropriate limitations of current tests; for example, in the abovementioned study mild symptoms to soy occurred in 7 of 30 subjects with undetectable soy IgE levels, possibly because of allergy to pollen-related proteins.¹⁷ Additional information relevant to diagnostic test interpretation was reported by Komata et al,¹⁹ who showed that for egg and milk allergy, younger infants reacted to these foods at lower IgE levels than older children. For example, according to probability curves generated in their population of 861 children undergoing food challenge to milk, an IgE level of 3 kIU/L was associated with a 40% risk of reaction in children older than 2 years and an 80% risk for children younger than 1 year. Determination of the severity of a food allergy remains elusive, but Untersmayr et al²⁰ used codfish allergen as a model and showed that an important variable regarding elicitation of reactions is digestion, which can be impeded if stomach acidity is reduced, leading to reactions at lower exposure doses.

Prevention and treatment

A family history of atopy or early evidence of allergy or sensitization in infants²¹ identifies a child at risk for atopic disease and presents a strong opportunity for prevention. Comprehensive programs of dietary allergen and environmental allergen avoidance have shown a positive effect,^{22,23} but the prevention effects of isolated dietary interventions have been a source of constant study, with some mixed results. Several studies in this years' *Journal* have added insights. Matheson et al²⁴ report long-term follow-up from the Tasmanian Asthma study, indicating that at age 7 years, participants who had been exclusively breast-fed and had a history of maternal atopy were less likely to have asthma (odds ratio [OR], 0.8; 95% CI, 0.6-1.0), but by age 14 years, the risk reversed (OR, 1.5; 95% CI, 1-2), and by age 44 years, the participants were even more likely to have asthma (OR, 1.57; 95% CI, 1.2-2.1). The explanation for this effect could be the reduction of early infection, leading to less asthma triggered by infection early in life and later increased atopy caused by immune dysregulation for lack of infection (eg, the hygiene hypothesis). Early asthma was not significantly affected by interventions reported in a 3-year follow-up of the German Infant Nutritional Intervention study.²⁵ This follow-up study showed a continued protective effect of an extensive casein hydrolysate (OR, 0.53; 95% CI, 0.32-0.88) and partial whey hydrolysate (OR, 0.60; 95% CI, 0.37-0.97) in the per-protocol analysis of atopic dermatitis (AD) in high-risk infants not exclusively breast-fed. Regarding the question of maternal exclusion diets during pregnancy, Rowe et al²⁶ followed T-cell and humoral responses in high-risk infants and could not document evidence for prenatal priming. Hourihane et al²⁷ reported peanut allergy outcomes in a cohort of children born after

the United Kingdom government's advice for mothers of high-risk infants to follow maternal avoidance during pregnancy and lactation and avoid introduction of peanut to their children until age 3 years. Very few followed the advice during pregnancy (3.8%); the rate of peanut allergy in the cohort was 1.8%, the highest recorded. Although final numbers were low, the investigators could not determine that following the advice affected outcomes, and although peanut was given to the children at a later age (nearer age 3 years) than in prior years (near age 1 year), this also did not correlate with a protective effect. Another consideration about prevention of allergy is to avoid introducing allergens to infants too soon because of a concern for an immature gastrointestinal and immune response. However, Liem et al²⁸ evaluated a 1995 Manitoba birth cohort (n = 13,980) using an administrative database and could not find an increase in food allergy diagnosis among low-birth-weight or premature infants. A summary of dietary prevention studies was recently published as a clinical report from the American Academy of Pediatrics, presenting a revision from an earlier statement.²⁹

A more active modality to possibly reduce atopic disease is to provide probiotics. Kalliomaki et al³⁰ reported a continued positive effect at age 7 years on AD among the children born to mothers who received *Lactobacillus* GG (43% vs 66%); however, there was no effect on rhinitis or allergen sensitization. Kukkonen et al³¹ used prebiotics and probiotics in a randomized controlled trial in Finland and also showed reduction in AD, although not a strong effect on sensitization, and a Swedish study³² using *Lactobacillus reuteri* showed reduction in IgE-associated AD but not overall eczema. Taylor et al³³ used *Lactobacillus acidophilus* in a controlled prevention trial and did not see a prevention effect but rather increased allergen sensitization at age 1 year. A review by Prescott and Bjorksten³⁴ on this topic indicates that various outcomes can be explained by factors such as the types of treatment, host factors, and microbial burden. Lee et al³⁵ present a study warning that some probiotic preparations might contain cow's milk proteins and suggest this issue be stated in labeling.

Although there are numerous modalities under investigation to treat food allergy,² management currently requires a large dose of education about food avoidance and emergency management. Two studies addressed the use of advisory labeling, one indicating that labeling peculiarities are an important obstacle for consumers with food allergy,³⁶ and the other indicating that consumers tend to ignore advisory labels differentially (eg, expecting that the term "may contain peanut" indicates greater risk than "made in a facility that processes peanut").³⁷ Assay of a sampling of products labeled with advisory warnings showed that peanut was detectable in 7% at clinically relevant amounts, and contrary to the impressions held by consumers, the nature of the warnings did not correlate with risks of detecting peanut protein.

Several studies in murine models have provided insights toward more definitive future therapies. Temblay et al³⁸ demonstrated that dendritic cells from Peyer's patches, but not spleens, of food allergy-susceptible C3H/HeJ mice and not from less susceptible BALB/c mice produced less IL-4—dependent IL-12p70, and IL-4 failed to inhibit IL-10 production by these dendritic cells. These results might indicate that repletion of IL-12 could be a good treatment strategy. Frossard et al³⁹ used *Lactobacillus* species engineered to deliver IL-10 in a prevention strategy that successfully diminished sensitization and reactivity in a murine model of milk allergy. TGF- β is thought to promote tolerance when ingested orally in breast milk, and this theory was tested

in a murine model by Ando et al,⁴⁰ who showed reduced ovalbumin IgE levels, skin test responses, and T-cell reactivity. Zhu et al⁴¹ used a synthetic agonist of Toll-like receptor 9 (immune modulatory oligonucleotide) in the prevention and treatment protocols of orally induced peanut allergy and found reduced T_H2 and increased T_H1 responses, reduced symptom scores, and reduced gastrointestinal inflammation in the treated animals.

Regarding human studies, immunotherapy of pollen allergy can be hypothesized to result in improvements in pollen-related food allergy. Kinaciyan et al⁴² reported on a subset of subjects in a birch pollen sublingual immunotherapy study whose birch nasal provocation scores improved with therapy, but they did not experience improvement in their apple oral allergy symptoms nor did they show serologic responses to birch-related apple proteins. In contrast, Niederberger et al⁴³ undertook vaccination with genetically engineered hypoallergenic derivatives of the major birch allergen Bet v 1 and showed serologic responses to birch homologous food proteins and reported symptom improvement in 7 of 25 treated versus 1 of 19 receiving placebo. Regarding strategies for plant food allergy vaccines, Reese et al⁴⁴ argue that treatment with the food allergen, rather than homologous pollen protein, might be more efficacious, and they evaluated different vaccine strategies that, in murine models and human IgE-binding studies and histamine release assays, favored use of dimers of the mutant major carrot allergen Dau c 1 for increased antigenicity and reduced allergenicity, rather than oligomerization, to attempt to treat carrot allergy. Studies on oral and sublingual immunotherapy with native food allergens are gaining momentum,⁴⁵ and Buchanan⁴⁶ reported preliminary results for egg oral immunotherapy in 7 children undergoing treatment for 24 months. At therapy's end, the children tolerated at least 2 g of egg on oral challenge, and 4 children tolerated the full egg challenge (14.7 g); however, after 3 months off therapy, 2 of these children reacted on rechallenge, indicating that the protocol might have promoted temporary desensitization rather than permanent immunologic tolerance. More studies are ongoing. Finally, traditional Chinese herbal remedies that have shown efficacy in murine models of peanut allergy have begun human trials; this topic was the focus of an elegant review by Xiu-Min Li.⁴⁷

ANAPHYLAXIS AND INSECT STING

An Australian study of hospital admissions revealed gradual increases within the period from 1993 through 2004 for anaphylaxis (8.8%/year), urticaria (5.7%/year), and angioedema (3%/year).⁴⁸ Increases were strongest for angioedema in older persons and food-induced allergic reactions in children. The authors acknowledge that hospital admission rates do not reflect all anaphylaxis cases but indicate from their data that the results likely reflect an increasing severity or number of reactions and not a change in coding or admissions standards. The reasons for the increase remain obscure. Using a nationwide audit of self-injection epinephrine prescriptions in the United States, Camargo et al⁴⁹ noted a strong geographic gradient, with prescription rates generally higher in northern compared with southern regions in the United States. They hypothesize that reduced sun exposure in the northern regions, with resulting vitamin D insufficiency, might have immunologic consequences resulting in stronger atopic response.

Regarding mechanisms and treatment of anaphylaxis, biomarkers are sorely needed. Gober et al⁵⁰ evaluated basophil

activation markers from 21 subjects with venom allergy undergoing sting challenges (most receiving immunotherapy) and noted that presting basophil CD63 levels were significantly higher in systemic reactors receiving immunotherapy. After stings, the increase in CD69 and CD203c expression was also higher in systemic reactors, and the authors concluded that these might be useful markers for some forms of anaphylaxis. Numerous additional indicators of severity in anaphylaxis were reviewed in a report from PRACTALL (PRACTical ALLergy),⁵¹ and the importance of platelet-activating factor has recently been emphasized.⁵²

Regarding treatment, Carter et al⁵³ present preliminary data on 2 persons with systemic mastocytosis and recurrent anaphylaxis treated with omalizumab; these 2 patients who had experienced 5 and 18 episodes of anaphylaxis in the 2 years before therapy had none during 2 years and 9 months' follow-up, respectively, on therapy. The authors postulate that treatment results in a reduced state of activation of the mast cells. Hare and Ballas⁵⁴ report the efficacy of epinephrine in 2 patients with prolonged anaphylaxis who had cardiac risks initially resulting in avoidance of epinephrine, emphasizing that epinephrine should be considered in these settings and might be effective late in the course. For further insights on mechanisms and clinical treatment, the reader is encouraged to see Fred Finkelman's review of mechanisms of anaphylaxis learned from murine models⁵⁵ and F. Estelle R. Simon's review of recognizing and treating anaphylaxis in infants.⁵⁶

DRUG ALLERGY

Limb et al⁵⁷ present data from 124 cases of anaphylaxis associated with omalizumab that were reported to the United States Food and Drug Administration, to the manufacturer, and in the medical literature. Where recorded, 83% were in female patients, 39% were first-dose reactions, 89% had respiratory compromise, and 14% had hypotension or syncope. One third of the cases had reactions within 30 minutes, one third from 0.5 to 6 hours, and the remainder from hours to 4 days later, and 8% of the patients had a protracted progression of symptoms. These observations of timing (delayed) and pattern (protracted course) are different from typical allergen-induced anaphylaxis, and the authors hypothesize multiple mechanisms, including slow drug absorption. Unfortunately, risk factors could not be identified. A task force report on this topic⁵⁸ recommended increased observation times (eg, 2 hours for the first 3 doses and 30 minutes for subsequent doses), careful health monitoring, and patient education among other recommendations. Pilette⁵⁹ additionally reported a convincing case of serum sickness induced by omalizumab.

In regard to elucidating the mechanisms underlying drug hypersensitivity, Lerch et al⁶⁰ evaluated skin tests (intradermal/patch) and T-cell responses to iodinated contrast media to elucidate the triggers and potential cross-reactivity of agents that cause delayed-type hypersensitivity reactions. They found that iodide ions are not a cause but that based on proliferation assays, there was broad cross-reactivity to contrast media (12 tested), although there was some variation that might allow *in vitro* identification of agents with less reactivity (eg, reactivity might differ when comparing iohexol and iobitridol). Insights into the pathogenesis of Stevens-Johnson syndrome were presented by Yang et al,⁶¹ who hypothesized that the association of this disorder with *HLA-B*1502* likely represents a pathophysiologic link. They showed, by using carbamazepine as a model trigger, that likely noncovalent interactions of drug, peptides, and HLA-B molecules of

antigen-presenting cells and T-cell receptors trigger drug-induced responses leading to cell death, which contrasts with the theory that a haptenation of drug is responsible. Wu et al⁶² identified that in persons with carbamazepine-induced skin eruptions, drug-specific reactive T cells were identifiable many years after a reaction. Ueta et al⁶³ evaluated *IL4R* polymorphisms in a case-control association study in Japanese individuals and found an association that is distinct from those associated with atopic disease; the authors postulate, based on triggers of Stevens-Johnson syndrome and observed features of inflammation, that *IL4R* might be linked with innate immunity. These 3 studies will likely pave the way toward a better understanding of non-IgE-associated reactions to drugs. Several studies of practical consequence present data that show important information about irritant responses when skin testing for allergy to common vaccines,⁶⁴ safety of nabumetone and meloxicam for persons with intolerance of non-steroidal anti-inflammatory drugs,⁶⁵ and evaluation of IgE-associated allergy to chlorhexidine⁶⁶ and platinum salts.⁶⁷

ATOPIC DERMATITIS

Recent studies indicate that epidermal barrier dysfunction drives skin inflammation and allergen sensitization in AD.⁶⁸ Initial observations demonstrating that loss-of-function null mutations in the filaggrin gene are associated with development of AD have now been replicated in multiple studies.⁶⁹⁻⁷² Importantly, the filaggrin gene, which is located within the epidermal different complex on chromosome 1q21, is associated with allergen sensitization; early-onset eczema, which has a more severe phenotype; and eczema-associated asthma. Because filaggrin is not found in the lung,⁷³ these data suggest that allergen absorption through the skin leads to high systemic IgE levels to food and inhalant allergens with progression of the atopic march through systemic allergen sensitization or priming of allergic effector cells. Filaggrin null mutations have also been reported to be associated with increased asthma severity in children and young adults.⁷⁴ However, filaggrin null mutations do not occur in the absence of eczema (ie, it is not an asthma gene).⁷⁵

Genetic mutations are not the only pathway that can lead to skin barrier dysfunction. A study by Howell et al⁷⁶ demonstrated low filaggrin expression, even in patients without filaggrin gene mutations. In that report it was found that T_H2 cytokines could downregulate the filaggrin gene and protein expression by skin keratinocytes. This is consistent with previous studies that demonstrate topical anti-inflammatory treatment can improve skin barrier function. The observation that T_H2 responses can downregulate filaggrin expression and the association of filaggrin gene mutations with severe AD is consistent with a recent finding that severe refractory AD is often associated with allergen sensitization.⁷⁷ Reefer et al⁷⁸ found that patients with low IgE allergen sensitization had decreased eczema severity.

Patients with AD are known to have defects in their innate immune response that predispose them to microbial infections.⁷⁹ Studies reported in the *Journal* have demonstrated that allergen-driven T_H2 responses can result in disseminated vaccinia infection, which might explain their propensity to eczema vaccinatum.⁸⁰ A deficiency in production of human β -defensin and macrophage inflammatory protein 3 α in atopic skin inflammation might contribute to disseminated viral infection.^{81,82} These data highlight the importance of understanding mechanisms underlying the skin atopic immune response. In this regard

studies during the past year have demonstrated that chemokine responses and differences in inflammatory dendritic cells distinguish AD from other inflammatory skin conditions.^{83,84}

Several interesting articles have highlighted novel therapies in AD. These include the use of low-dose anti-IgE therapy, even in patients with high serum IgE levels.⁸⁵ In this study changes in IgE/IgG mRNA levels were observed in B cells without effect on serum IgE levels, suggesting a novel mechanism of action for this antiallergic drug. AD is often associated with dust mite sensitization. Pajno et al⁸⁶ therefore carried out a randomized, double-blind, placebo-controlled study examining the effectiveness of sublingual immunotherapy with dust mites on children with AD. They found that sublingual immunotherapy to dust mites reduces the severity of skin disease and medication use in children with mild-to-moderate AD. Because AD is often the first step in the atopic march, there has been considerable interest in whether treatment of AD can reduce asthma severity. A preliminary communication by Virtanen et al suggested that treatment of AD with topical tacrolimus might improve bronchial hyperreactivity.⁸⁷

Outcome measurements are a prerequisite for evidence-based practice. Schmitt et al⁸⁸ carried out a systemic review to determine the best outcome measurements for AD. They reported that 3 measurements (the Severity Scoring of Atopic Dermatitis index, the Eczema Area and Severity Index, and the Patient-Oriented Eczema Measure) had the greatest validity in the current literature.

URTICARIA AND ANGIOEDEMA

Although chronic urticaria is often regarded as autoimmune in nature, only 25% to 50% of sera from patients with chronic urticaria contain autoantibodies to the high-affinity IgE receptor FcεRI or IgE. This suggests other factors contribute to the clinical expression of this condition. Recently, Asero et al⁸⁹ observed that if autologous plasma rather than autologous serum is used to perform the skin testing for autoantibodies, the proportion of patients showing a skin response increases to 95%. In the past year, they followed up this observation, demonstrating that the extrinsic pathway of the clotting cascade is activated in chronic urticaria and disease severity was associated with activation of the coagulation pathway.⁹⁰ Other factors that were reported to contribute to chronic urticaria include FcεRIα promoter polymorphisms that increase the expression of FcεRIα on mast cells⁹¹ and the expression of basophil Src-homology 2-containing inositol phosphatases that control FcεRIα-mediated histamine release.⁹²

The management of chronic urticaria includes control of pruritus. Interestingly, the histamine H4 receptor was found to be more involved in pruritic responses than the histamine H1 receptor,⁹³ suggesting that H4 receptor antagonists might be more beneficial in treating chronic pruritic diseases, such as chronic urticaria or AD. Delayed-pressure urticaria is associated with an inflammatory cell infiltrate, suggesting a potential role for TNF-α in this condition. An interesting case report documented rapid and successful treatment of delayed-pressure urticaria with a TNF-α inhibitor.⁹⁴ Further studies are needed to confirm this observation. Idiopathic angioedema can be a challenging condition to treat because antihistamines can have little effect on its course. Sands et al⁹⁵ reported 3 cases of refractory idiopathic angioedema that resolved on treatment with anti-IgE therapy, suggesting a role for IgE in idiopathic angioedema.

Hereditary angioedema (HAE) is an autosomal dominant disorder caused by C1 inhibitor gene mutation. Stanazolol is

effective in the control of HAE attacks and has recently been shown to be safe, even in patients treated long-term with this attenuated androgen.⁹⁶ Novel therapies for HAE have also been developed. A controlled clinical trial reported by Schneider et al⁹⁷ found that ecallantide, an inhibitor of plasma kallikrein, significantly improved HAE symptoms compared with placebo. This provides strong support for the role of the kallikrein-kinin cascade and its end product, bradykinin, in the pathophysiology of HAE. Consistent with this trial, Bork et al⁹⁸ reported in an uncontrolled pilot study that treatment with a bradykinin receptor 2 antagonist, icatibant, reduced acute edema attacks caused by HAE.

CONCLUSIONS AND SUMMARY

In the year since our last review,⁹⁹ numerous exciting advances have been reported in the *Journal*. Clinical observations have raised concerns about an increase and persistence of atopic diseases, but basic, clinical, and translational research studies reported in the past year have identified several potential strategies that can improve diagnosis, treatment, and possibly prevention. The importance of skin barrier dysfunction has been highlighted in the pathogenesis of AD, particularly as it related to allergen sensitization and eczema severity. Research has also continued to identify immunologic defects, which contribute to the propensity of patients with AD to have viral and bacterial infection. These advances present information that is immediately helpful to improve patient care and set the stage for further discoveries likely to improve diagnosis and management.

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