

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

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This review highlights some of the research advances in anaphylaxis and hypersensitivity reactions to foods, drugs, and insects and in allergic skin disease that were reported primarily in the *Journal* in 2006. Advances in diagnosis include identification of food proteins to which IgE binding is associated with severe reactions; elucidation of diagnostic relationships of skin prick test wheal size with outcomes of egg, tree nut, and sesame allergy; evaluation of the diagnostic utility of atopy patch testing for food; and the observation that yellow jacket sting outcomes are influenced by species. Mechanistic observations include the following: heating of birch pollen-related foods disrupts IgE binding but not T-cell epitopes; a simple imbalance of T_H1/T_H2 response does not explain variations in clinical expression of peanut allergy; and elucidation of the role of dendritic cells in drug hypersensitivity. With regard to treatment, a rapidly disintegrating epinephrine tablet showed promise for sublingual treatment of anaphylaxis, RNA interference techniques showed promise in creating lower-allergenic foods, and anti-IL-5 showed promise for treatment of eosinophilic esophagitis. Progress in our understanding of the immunology and the etiology of skin barrier dysfunction in atopic dermatitis has also been made. These observations will likely contribute toward optimizing management of these common allergic disorders. (*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 diseases, anaphylaxis, and hypersensitivity to foods, drugs, and insect venom from among over 90 articles on these topics published in the *Journal* in 2006. Some of the key advances are summarized in [Table I](#).

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Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

Received for publication February 8, 2007; accepted for publication February 13, 2007.

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0091-6749/\$32.00

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doi:10.1016/j.jaci.2007.02.013

Abbreviations used

AD: Atopic dermatitis
r: Recombinant

FOOD ALLERGY

Epidemiology

There are very few population-based studies describing the incidence of food allergy in infancy. A whole population birth cohort of 969 infants was established on the Isle of Wight, United Kingdom (September 2001 to August 2002) and followed periodically to age 1 year.¹ The cumulative incidence of parentally reported food hypersensitivity was 25.8%, and 2.2% of those tested (n = 763) were sensitized to at least 1 food. Open or double-blind, placebo-controlled food challenges were offered to confirm most of the suspected reactions. About 1/8 were confirmed, indicating the need to evaluate suspected allergy to avoid a high rate of needless dietary exclusions. Depending on the stringency of criteria applied, the authors estimated that 2.2% to 5.5% of infants have food hypersensitivity during the first year of life. Little is known about the influence of ethnicity on food allergy outcomes. In a population-based cohort of South Asian and white children both in Leicestershire, United Kingdom, South Asian ethnicity was independently associated with food-related wheezing at age 1 to 4 years (odds ratio, 3.8) and 6 to 9 years (odds ratio, 9.1).² Although genetic predisposition is an apparent risk factor, several studies have added insights for the apparent environmental influence on a high and increasing rate of food allergy and atopic disease in Westernized countries. For example, the hygiene hypothesis was supported by observations that atopic disease was less common in schoolchildren following an anthroposophic lifestyle, which includes restrictive use of antibiotics³ and in children living with poor sanitation and increased helminth infection.⁴ Although there has been some suspicion that breast-feeding may contribute to atopic disease, data from a prospective birth cohort of 620 infants from Melbourne, Australia, indicated that early symptoms of atopic disease might prolong the duration of exclusive breast-feeding, underscoring the need to consider reverse causation in studies

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

Topic	Clinical or basic research concerns	Advances and observations
Anaphylaxis	Diagnosis and management	• A National Institute of Allergy and Infectious Diseases-Food Allergy & Anaphylaxis Network cosponsored panel defines anaphylaxis and suggests diagnostic criteria. • A rapidly disintegrating epinephrine tablet shows promise for sublingual rather than intramuscular administration.
Food allergy	Epidemiology	• Infants supplemented with vitamins A and D in peanut oil were less prone to allergy by age 4 y than those receiving the vitamins in water-soluble form.
	Molecular aspects of food allergy	• Heating disrupts IgE but not T-cell epitopes in birch-related foods. • Identification of IgE binding to lipid transfer proteins in chestnut, apple, and grape may allow more specific diagnosis (severity). • A simple imbalance of T_H1/T_H2 does not explain differences in clinical expression of peanut allergy.
	Diagnostic testing	• The clinical utility of considering skin test wheal size in addition to serum IgE level was reported for egg allergy. • Diagnostic relationships of skin test wheal size to outcomes of tree nut allergy were reported. • The atopy patch test shows modest additional predictive value (used with tests for specific IgE).
	Treatment/management	• Anti-IL-5 shows promise for therapy of eosinophilic esophagitis. • RNA interference techniques show that several tomato allergens can be suppressed. • A study evaluated the persistence of peanut allergen in saliva, allowing for evidence-based patient advice.
Drug allergy	Mechanisms	• Elucidation of the role of dendritic cells in drug hypersensitivity to amoxicillin.
Insect allergy	Diagnosis and treatment	• Patient satisfaction is higher with venom immunotherapy compared with providing epinephrine self-injectors. • There is significant species-specific variation in outcome of yellow jacket stings.
Urticaria	Diagnosis	• Chronic urticaria sera increases basophil CD203c.
	Mechanisms	• Possible role for thrombin in chronic urticaria.
	Treatment	• Reduction of urticaria with anti-IgE treatment.
AD	Mechanisms	• Genetic association with filaggrin null mutations. • Increased IL-31 in AD skin as potential cause of T cell-mediated pruritus. • Propensity for viral skin infections associated with reduced innate immunity.

evaluating risk factors for atopy.⁵ Another concern regarding risk for atopy has been the use of vitamin supplements. Kull et al⁶ followed a birth cohort of 4089 infants to age 4 years and found that subjects supplemented with vitamins A and D in a water-soluble form were roughly twice as likely to have food allergy, allergen sensitization, and asthma compared with those who received the vitamins in peanut oil; the reason for this difference remains unclear, because potentially beneficial fats in the oil as a contribution to the total diet seems unlikely.

Pathophysiology and allergen characterization

Studies that evaluate IgE binding to food allergens and related pollen allergens in well characterized patient populations (eg, relating characteristics of sensitization to outcomes on oral challenge), and studies evaluating IgE binding to food proteins before and after heating or digestion, provide insights that are relevant to diagnosis,

prediction of cross-reactivity, reaction severity, and treatment.⁷⁻¹⁰ For example, Vassilopoulou et al¹¹ showed that lipid transfer protein in grape maintained its biological activity after exposure to simulated gastric and duodenal digestion. IgE responses to these stable proteins may be associated with a higher risk for severe reactions and may indicate that sensitization may be prone to occur from the oral route. Similarly, Fernandez-Rivas et al¹² evaluated allergen sensitization in regard to apple allergy in 389 patients in the Netherlands, Austria, Italy, and Spain. In 3 countries whose patients' apple allergy was typically mild, they found a relationship to birch pollenosis and sensitization to Bet v 1 and its apple homologue, Mal d 1, with an odds ratio of having local oral reactions of 2.8. In Spain, in contrast with the other 3 countries, patients more commonly had severe apple allergy (>35% systemic reactions), and sensitization was related to peach allergy and sensitization to Mal d 3, a nonspecific lipid transfer protein, with an odds ratio of systemic

reactions of 7.76. Another complex food allergen is chestnut, which is often considered an allergic risk for persons with latex allergy. Sanchez-Monge et al¹³ evaluated 12 patients sensitized to chestnut but not to latex and found IgE binding to a 9-kd lipid transfer protein in 91%; allergenic lipid transfer proteins from peach were also reactive, but latex related proteins (avocado class I chitinase and latex hevein) were not. The clinical and diagnostic importance of evaluating binding to specific proteins was further demonstrated by Kondo et al,¹⁴ who described a child who tolerated many types of fish but had anaphylaxis to tuna and marlin; they identified a unique cross-reactive allergen for this child whose serum did not bind the major fish allergen, parvalbumin. Together, these studies show promise for diagnostic tests that could more clearly predict reaction severity and likelihood of cross-reactivity with related foods or other related substances, such as latex.

Dissection of cellular immune responses will likely provide further insights of diagnostic and therapeutic potential. Thottingal et al¹⁵ measured peanut allergen-driven cytokine and chemokine responses in short-term primary culture of PBMCs, paired with ELISAs, in adults with peanut allergy and adults sensitized or not sensitized to peanut who tolerated ingestion of peanut. Individuals with positive skin tests had more frequent or intense IL-5, IL-13 and CCL22 responses than those without, whether or not they had clinical peanut allergy. Surprisingly, the 3 groups were not distinguishable by IFN- γ or CXCL10 responses, which were absent, indicating that a protective T_H1 bias does not explain the distinction in clinical outcomes, whereas a spectrum of T_H2 responses may. In regard to elucidating a direct pathogenic role of T cells in food hypersensitivity, Bohle et al¹⁶ showed, using both *in vitro* systems and clinical oral food challenge studies, that heating birch pollen related food proteins can disrupt IgE binding—for example, extinguish symptoms of oral allergy or pollen-food related syndrome—but that T-cell-binding epitopes remain. These heated birch-related food proteins were capable of stimulating Bet v 1-specific T cells *in vitro*, and the heated foods induced exacerbations of atopic dermatitis (AD).

Diagnosis

Although the studies described reveal a potential diagnostic utility of evaluating IgE binding to particular food allergen components, additional clinical studies correlating oral food challenge outcomes to results of currently available diagnostic tests provide immediate insight for improved diagnosis. Knight et al¹⁷ showed that among a group of children with low egg white-specific serum IgE (<2.5 kIU/L), where chances of tolerating egg was reasonable, skin test wheal size provided additional diagnostic utility. For example, children who tolerated egg had a median wheal of 3 mm, whereas those who did not had a median wheal of 5 mm. Increasing wheal sizes correlated with failing to tolerate egg, from 14% with a negative skin test failing a challenge to 80% failing when the skin test wheal was 8 mm or larger. Ho et al¹⁸ presented data on sensitivity, specificity, and predictive value of various

tree nut, sesame, and peanut skin test wheal sizes derived from 906 food challenges in 680 children. Several of the nuts (cashew, hazel, walnut) showed a positive predictive value of 1.0 at skin test wheal sizes of 8 mm or higher. Scibilia et al¹⁹ performed double-blind, placebo-controlled food challenges to wheat in adults with suspected wheat allergy and confirmed reactions in 48% of 27 subjects. In addition to showing some variation in reactivity to raw or cooked wheat, they found a very poor correlation of challenge outcome to skin test or serum IgE results, partly attributable to cross-reactivity in subjects with grass pollen allergy, although persons with negative IgE tests also reacted.

Another modality to improve predictions about food allergic reactions that may also identify individuals with food allergy without positive food-specific IgE tests is the atopy patch test. In this test, the food is placed in a Finn chamber on the skin for 48 hours and the results read in the subsequent days. Mehl et al²⁰ presented the results of 1700 such tests in regard to the outcomes of 873 oral food challenges to milk, egg, wheat, or soy in children with suspected food allergy. Although the test showed the best specificity from among serum food-specific IgE and skin prick tests and improved overall sensitivity and specificity of outcome predictions when combined with results from the IgE tests, it added only modest diagnostic information in the context of avoiding an oral food challenge. For example, with combined testing including the atopy patch test, and considering a positive predictive value of 95% to 99% reaction rates to warrant deferring a food challenge, only 0.5% to 14% of study patients would have avoided the food challenge because of the positive patch test. No routine tests have done well in predicting severity of a food-allergic reaction,²¹ although a study by Astier et al²² using recombinant peanut proteins showed that persons polysensitized to recombinant (r) Ara h 2 and either rAra h 1 or rAra h 3 were more likely to have severe reactions than persons monosensitized to rAra h 2.

Treatment

Although there are numerous modalities under investigation to treat food allergy,²³ management currently requires a large dose of education about food avoidance and emergency management.²⁴ A review of reported accidental exposures to peanut from 252 patients at Montreal Children's Hospital indicated that accidental exposures occurred at an annual incidence rate of 14%, lower than most previous reports.²⁵ This good news is likely the result of increased education and awareness. In a study of adolescents with food allergy, a group at special risk for fatal food-induced anaphylaxis, risk-taking behaviors were associated with social circumstances and feelings of isolation.²⁶ The major need identified by the teenagers was third-party education of their peers, which would presumably increase understanding, reduce peer pressure, and present an additional layer of safety. An identified concern of the teens, and a worry for intimate partners of persons with food allergy, is the transfer of food protein in saliva during kissing or sharing utensils or straws. Maloney

et al²⁷ evaluated the time course of the peanut protein Ara h 1 in saliva and determined with 95% confidence that 90% of persons who ingested peanut butter would have no detectable Ara h 1 in their saliva after a peanut-free meal along with a waiting period of several hours. If engineering of less allergenic foods were possible, many of the concerns of food allergy could be allayed. This may someday be a plausible approach, because RNA interference techniques were successfully used to create less allergenic forms of tomato by silencing expression of profilin²⁸ or lipid transfer protein.²⁹

Eosinophilic esophagitis is typically a food-responsive gastrointestinal disease, but food elimination is often an unsatisfactory treatment because numerous foods are commonly implicated, resulting in frustrating dietary trials and socially and nutritionally restrictive treatment diets.³⁰ Stein et al³¹ undertook an open-label phase I/II study of a humanized monoclonal IgG₁ antibody against IL-5 in 4 adults with eosinophilic esophagitis. After 3 monthly infusions, mean esophageal eosinophil counts fell from 46 to 6 per high power field ($P < .001$) and clinical symptoms and quality of life improved, indicating promise for this novel treatment.

ANAPHYLAXIS

There has been a lack of an accepted definition of anaphylaxis, or criteria for diagnosis, 2 deficits that likely hinder research and treatment. A significant advance for the field was a report summarizing a second symposium that was cosponsored by the National Institute of Allergy and Infectious Diseases and the Food Allergy & Anaphylaxis Network in which various stake holders convened and recommended the following definition: "Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."³² The group also offered clinical criteria for diagnosing anaphylaxis that can be validated through future study and identified various research needs. In addition, the Journal offered a review of community management of anaphylaxis authored by F. Estelle R. Simons, MD,³³ and a review of genetic and diagnostic aspects of tryptase in anaphylaxis by George H. Caughey, MD.³⁴ Practical observations about anaphylaxis included a reminder that accidental injection of a digit with epinephrine from an autoinjector may require therapy with warm soaks, topical nitroglycerin, or localized phentolamine injection,³⁵ that in an office-based allergy practice, 0.67% of injection immunotherapy treatments required treatment with epinephrine and 16% of these required more than 1 dose;³⁶ and that serum tryptase could sometimes be elevated for a prolonged period in idiopathic anaphylaxis.³⁷ Unique or rare causes of anaphylaxis were reported, including topical benzocaine,³⁸ the disinfectant solution ortho-phthalaldehyde,³⁹ and prostate-specific antigen in seminal plasma.⁴⁰ In regard to future therapy, a fast-disintegrating tablet to provide sublingual epinephrine was tested in a rabbit model and showed favorable pharmacokinetics compared with intramuscular injection.⁴¹ Considering that fear of needles is a likely reason for underuse of

epinephrine in the community, this novel delivery system may be a promising alternative.

DRUG ALLERGY

In regard to elucidating the mechanisms underlying drug hypersensitivity, Rodriguez-Pena et al⁴² evaluated the role of dendritic cells in subjects who had a delayed-type hypersensitivity reaction to amoxicillin. They found that monocyte-derived dendritic cells cultured with amoxicillin from patients, compared with controls, had increased maturational markers and acquired a higher T-cell stimulatory capacity, presenting both a mechanistic insight and potential diagnostic test. Wu et al⁴³ evaluated mechanisms of drug presentation to T cells and the role for metabolite-specific T cells in cross-sensitization. They performed a lymphocyte transformation test with carbamazepine, oxcarbazepine, and carbamazepine metabolites to develop drug metabolite-specific T-cell clones. They found that lymphocytes and T-cell clones proliferated with carbamazepine, oxcarbazepine, and some carbamazepine metabolites. T cells were stimulated by drug bound directly to MHC. They concluded that some patients with a history of carbamazepine hypersensitivity possess T cells that cross-react with oxcarbazepine, providing a rationale for cross-sensitivity between the 2 drugs. In regard to clinical evaluation of cross-reactivity of penicillins and cephalosporins, Antunez et al⁴⁴ addressed this common clinical issue from the perspective of persons with cephalosporin allergy. They studied 24 patients with IgE mediated cephalosporin allergy, and just 2 patients had a positive skin test result to penicillin determinants; 22 patients with negative results tolerated benzylpenicillin administration, and additional studies showed that the side chain at the R1 position was crucial for immune recognition, rather than the β -lactam structure. They concluded that penicillin could be administered safely to patients allergic to cephalosporins with a negative skin test result to penicillin determinants. As a reminder in regard to drug allergy testing, Co Minh et al⁴⁵ reported that 1.3% of 998 β -lactam skin tests resulted in systemic reactions; historical points indicating risk included anaphylaxis in the clinical history and reaction onset under 1 hour. Finally, of clinical note, a review article by Stevenson and Simon⁴⁶ describes patient selection for aspirin desensitization.

INSECT ALLERGY

Several insights on the epidemiology and treatment of allergic reactions to insect stings were reported from a national survey of 10,000 junior high school students in Israel.⁴⁷ Just more than half had been stung at least once with the following symptoms: 11.5% had a large local reaction (10% of them sought hospital treatment), 6.5% had a mild cutaneous systemic reaction (7.5% sought treatment), and 2.5% had a moderate-to-severe systemic

reaction (but only 14.5% attended a hospital). Although the results may apply primarily to Israel, it seems likely that undertreatment of severe reactions may be common, and a related concern would be undertreatment with venom immunotherapy. In addition to the known efficacy of this therapy, a quality of life study showed a relative preference in patients of venom immunotherapy compared with provision of self-injectable epinephrine.⁴⁸ Several important observations about outcomes of insect stings were reported by Golden et al,⁴⁹ who performed sting challenges by using 2 species of yellow jacket. Objective systemic reactions occurred in 30% of 69 patients stung with *Vespula maculifrons* compared with 8 of 71 patients (11%) stung with *Vespula germanica* ($P = .005$). Systemic reactions were more frequent in patients with a severe history (9/30; 30%) than in those with a mild or moderate history (21/145; 14%; $P = .04$). In only 1 of 111 patients (0.9%) was the reaction to sting challenge more severe than previous reactions. The reaction rate was higher when venom skin tests were positive at $<1.0 \mu\text{g/mL}$ (17/75 = 23%) than when sensitivity was milder (9/100 = 9%; $P = .012$). There were no seasonal differences. These species differences have implications for sting challenges in research and provide insight in predicting responses to future stings. Additional clinical studies underscore the potential for anaphylaxis from the bite of pigeon ticks⁵⁰ and rashes/urticaria or systemic allergic reactions from bedbugs.⁵¹ Last, cloning and expression of the honeybee venom allergen acid phosphatase (Api m 3) should advance diagnostic and therapeutic capabilities in the future.⁵²

CHRONIC URTICARIA

Approximately 40% of patients with chronic idiopathic urticaria have antibodies to the α -subunit of the high-affinity IgE receptor. Until recently, laboratory techniques to detect the autoantibody to Fc ϵ RI α have been technically time-consuming and failed to identify antibodies with histamine releasing properties. Yasnowsky et al,⁵³ however, demonstrated by flow cytometry that sera from patients with chronic idiopathic urticaria and positive autologous serum skin tests significantly up-regulated the basophil activation marker CD203c in an IgG-dependent manner, which correlated with basophil histamine release. This new technique may provide a simpler approach to screen patients for chronic autoimmune urticaria.

Although positive autologous serum skin tests are often attributed to autoantibodies to Fc ϵ RI α or IgE in patients with chronic urticaria, IgG depletion does not always eliminate serum induced wheal and flare reactions. Because thrombin, a serine protease, is known to trigger mast cell degranulation, Asero et al⁵⁴ examined whether plasma of patients with chronic urticaria shows evidence of thrombin generation. Interestingly, these investigators found that intradermal injection of plasma from subjects with chronic urticaria caused wheal and flare reactions more frequently than autologous serum, and there was a

significant relationship between thrombin generation and severity of urticaria at the time of blood sampling.

Patients with severe urticaria have limited treatment options. Boyce⁵⁵ reported the interesting case of a patient who presented with idiopathic cold urticaria complicated by systemic symptoms. A trial of anti-IgE resulted in complete resolution of her urticaria and its associated manifestations. These findings suggest the need for a re-examination of the potential pathogenetic role played by IgE and its high-affinity receptor on mast cells in idiopathic cold urticaria and the potential use of anti-IgE therapy in chronic urticaria.

AD

Atopic dermatitis was a very active area of investigation in 2006. A series of articles explored genetic, immunologic, and environmental factors that give rise to the inflammatory skin response in AD, as well as the clinical management strategies that can be used for effective treatment of this common clinical problem.^{56,57} Genome screens of families with AD have implicated chromosomal regions that overlap with other inflammatory skin diseases.⁵⁸ The findings suggest that epidermal dysfunction manifesting as a compromised skin barrier results in aberrant responses to microbial infection and allergen exposure. Importantly, these studies identified a group of genes that are distinct from atopy genes. One of the major advances in 2006 was the demonstration of a strong association between AD and filaggrin null mutations resulting in defective gene expression of this important skin barrier protein.⁵⁹⁻⁶⁶ Importantly, this mutation is highly associated with allergen sensitization and the subsequent development of asthma. Filaggrin is not found in normal human bronchial mucosa.⁶² Thus, a null mutation in filaggrin would not have a direct consequence on asthma pathogenesis. It is more likely that a defective barrier in AD facilitates the penetration of allergens into the skin and generation of systemic IgE responses. Recent studies also indicate that IL-4 and IL-13 can inhibit filaggrin expression in patients with AD who do not carry filaggrin mutations, suggesting that skin barrier function can be altered by the atopic immune response.⁶³ Aside from filaggrin deficiency, it is likely that other mechanisms exist for the defective skin barrier in AD, including the activation of epidermal proteases and lack of protease inhibitor production.⁶⁴

The acute inflammatory response in AD skin is facilitated by IgE receptor-bearing Langerhans cells that are armed with IgE to allergens that promote allergen capture, and the activation of T_H2 memory T cells.⁶⁵ AD skin inflammation develops as the result of a complex immune and inflammatory response driven by the release of pro-inflammatory cytokines and chemokines from multiple resident cell types including keratinocytes, Langerhans cells, monocyte/macrophages, and the cutaneous vascular system.⁶⁶⁻⁶⁸ Hyperresponsive T_H2 cells with enhanced nuclear factor- κ B activation also contribute to enhanced skin inflammation in animal models of AD.⁶⁹

During the past year, there was considerable interest in the identification of IL-31 in human AD skin, because it is a novel T_H2-derived cytokine known to cause severe pruritus and eczema in animal models. Interestingly, IL-31 is primarily expressed in skin-homing T_H2 cells and its production is markedly increased by staphylococcal superantigens.⁷⁰⁻⁷² Unlike asthma, it was found that CD1d-restricted natural killer T cells were not required for allergic skin inflammation.⁷³ CCL4 was also found to be an important chemokine associated with the infiltration of eosinophils into atopic skin inflammatory responses.⁷⁴

The important role that the host innate immune system plays as the first line of defense against microbes was recently reviewed.^{75,76} This concept was reinforced in a report by Howell et al,⁷⁷ demonstrating that patients with AD with eczema herpeticum have significantly lower expression of antimicrobial peptides generated from their keratinocytes than patients with uncomplicated AD. As well, reports of AD association with polymorphisms of the *NOD1* gene, which encodes cytosolic pathogen recognition receptor, suggest an important role for microbes in the pathogenesis of AD.⁷⁸ A recent report did not find an association of Toll-like receptor polymorphisms with AD.⁷⁹ However, Toll-like receptor 2 polymorphisms may define a subgroup with more severe AD.⁸⁰

Atopic dermatitis has a significant effect on patients despite the availability of effective treatments.⁸¹ Thus, strategies are needed to help patients gain disease control. Several articles in the Journal addressed issues relating to the treatment of patients with AD. Kelsay et al⁸² addressed the challenges confronting clinicians managing sleep disturbance in patients with AD and reviewed treatment options that exist. Boguniewicz et al⁸³ examined the role of fungi in AD and the management of severe eczema. Bussmann et al⁸⁴ also examined whether existing data support the use of allergen-specific immunotherapy as a therapeutic option for patients with AD, outlining the need for better controlled trials.

Finally, Williams and Flohr⁸⁵ used data from epidemiologic studies to challenge several prevailing concepts. They argued that although atopy is associated with AD, its etiologic importance may be modest. This is consistent with the concept that a defective skin barrier function may be a primary process in causing AD. Atopy is more likely related to severity of illness. Their data argued against a simple inverse relationship between infections and AD risk—a link that might be expected if the hygiene hypothesis is valid, but which is likely more complex and critically dependent on timing and type of infectious exposure.

CONCLUSION

In the year since our last review,⁸⁶ numerous exciting advances have been reported in the Journal. Clinical studies present us with interesting epidemiologic observations that will require further investigation toward preventing allergies, and also show us ways to provide advice to improve care for our patients now. Clinical and translational

studies have elucidated modalities for improved diagnosis of food allergies using existing technologies such as skin tests, and present good prospects for improved diagnosis and treatment in the future, aiming toward a component-resolved diagnostic strategy and immunomodulatory therapies. Studies have also revealed potential imminent improvements in treatment of anaphylaxis and eosinophilic esophagitis. Translational and basic research work continues to elucidate mechanisms of the allergic response to various triggers to refine future treatment strategies. 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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