

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

Scott H. Sicherer, MD,^a and Donald Y. M. Leung, MD, PhD^b *New York, NY, and Denver, Colo*

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 2004. Clinical observations included that gastrointestinal symptoms during anaphylaxis are associated with an increased risk for hypotension; recurrence of peanut allergy can occur for about 8% of children who pass an oral food challenge and is associated with continued avoidance of the food after the challenge; seafood allergy is reported by 2.3% of the US population; and determination of the time to resolution of childhood egg and milk allergy might be predictable by means of serial determination of food-specific IgE levels. The comorbid effects of atopic dermatitis (AD) on asthma and the role of topical calcineurin inhibitors in the therapy of AD were also addressed. Basic and translational research observations indicate that improved diagnosis and therapy might become possible on the basis of reported identification or characterization of allergens such as: lipid transfer proteins and birch pollen-related cross-reactive allergens in plant foods; proteins in scorpion venom that cross-react with proteins from imported fire ant; mosquito saliva proteins responsible for systemic anaphylaxis; and IgE binding to quinolones detectable with an *in vitro* immunoassay. In addition, advances in understanding immune regulation associated with abrogation of oral tolerance in food allergy and of dendritic cell function, modulation of regulatory T cells, and chemokine expression in AD have elucidated possible targets for future intervention. (*J Allergy Clin Immunol* 2005;116:153-63.)

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

Abbreviations used

AD:	Atopic dermatitis
ASST:	Autologous serum skin test
AU:	Autoimmune urticaria
BLG:	β -Lactoglobulin
cAMP:	Cyclic adenosine monophosphate
CCL:	CC chemokine ligand
CIU:	Chronic idiopathic urticaria
CTACK:	Cutaneous T cell-attracting chemokine
CU:	Chronic urticaria
DC:	Dendritic cell
FKN:	Fractalkine
IDEC:	Inflammatory dendritic epidermal cell
LC:	Langerhans cell
nsLTP:	Nonspecific lipid transfer protein
pDC:	Plasmacytoid dendritic cell
PG:	Prostaglandin
TARC:	Thymus and activation-regulated chemokine
Treg:	T regulatory
VAS:	Visual analog scale

This review highlights key advances in allergic skin disease, anaphylaxis, and hypersensitivity to foods, drugs, and insect venom primarily from among more than 50 articles on these topics published in the *Journal of Allergy and Clinical Immunology (JACI)* in 2004. Some of the key advances are summarized in [Table I](#).

ANAPHYLAXIS

There are few studies on the epidemiology of anaphylaxis, particularly regarding children. By using the records of a health maintenance organization participating in the Centers for Disease Control and Prevention's Vaccine Safety Datalink Project, charts of children identified by ICD-9 codes for anaphylaxis and disorders that might have been anaphylaxis were reviewed for the period from 1991 through 1997.¹ By using the most specific codes for anaphylaxis, an incidence rate of 10.5 per 100,000 person-years (95% CI, 8.1-13.3 per 100,000 person-years) was obtained. The authors also noted the following: the highest rate of anaphylaxis was in the 15- to 17-year age group

From ^aThe Elliot and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine, New York, and ^bthe Department of Pediatrics, University of Colorado Health Sciences Center, and the Division of Pediatric Allergy/Immunology, National Jewish Medical and Research Center Denver. Received for publication March 10, 2005; accepted for publication March 10, 2005.

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Reprint requests: Scott H. Sicherer, MD, Division of Allergy/Immunology, Mount Sinai Hospital, Box 1198, One Gustave L. Levy Place, New York, NY 10029-6574. E-mail: scott.sicherer@mssm.edu.

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TABLE 1. Summary of key advances reported in the Journal

Topic	Clinical observations	Basic-translational observations
Anaphylaxis	- Disorder is common but underrecognized, possibly undertreated. - Gastrointestinal symptoms are associated with hypotension.	Modification of peptide vaccines to reduce solubility might reduce potential for anaphylaxis.
Food allergy	- Serum specific IgE can assist in prediction of food challenge outcomes. - Recurrence of peanut allergy is observed in 8%, with risk associated with avoidance after a successful oral food challenge. - Peanut protein is cleaned efficiently from hands and tables with certain common modalities. - Seafood allergy affects 2.3% of the US population.	- Protein microarray immunoassay for peanut indicates IgE binding to diverse epitopes correlates with allergy severity. - Birch-related allergens in peanut and soy are identified and characterized. - nsLTPs are identified and characterized in a variety of plant foods. - Murine models of cow's milk allergy emphasize the role of IL-10 in tolerance and of defective T cell-mediated DC apoptosis. - Immunotherapy with soy for peanut allergy shows efficacy in a murine model.
Drug allergy	Represcription of penicillin to outpatients with a recent allergic reaction to penicillin is common and carries a risk of recurrent reactions.	- A serum immunoassay detects specific IgE to quinolones and identifies cross-reactivity in the class. - Aspirin-sensitive urticaria and asthma share an underlying immune basis.
Insect allergy	Updated Practice Parameter reviews diagnosis and treatment.	- Cross-reactivity is identified between venom of the common scorpion and imported fire ant. - Mosquito salivary proteins responsible for bite anaphylaxis are characterized. - Venom serine proteases are characterized.
Atopic dermatitis	- IgE is not essential for development of AD. - Associated AD can contribute to severity of asthma. - Topical pimecrolimus can reduce skin symptoms of AD within 2 days. - Topical tacrolimus depletes IDEC and cytokine expressing skin T cells.	- TARC, CTACK, and FKN levels correlate with severity of AD. - Superantigens inhibit Treg cell function. - AD is associated with reduced plasmacytoid DCs. - LCs and IDECs contribute to the nature of T-cell infiltrate in AD.
Chronic urticaria	Addition of leukotriene antagonists improves treatment of CU in patients with AU.	Thirty-one percent of children with CU have AU.

(a high-risk group for fatalities according to previous studies), food was the most common trigger, and there was no increase in the rate of anaphylaxis over the study period. Interestingly, inclusion of likely cases of anaphylaxis that were not included in the primary diagnostic codes increased the incidence estimate from 10.5 to 68.4 per 100,000 person-years, indicating deficiencies either in coding or in recognizing anaphylaxis. Inadequate coding might partly reflect a clinician's diagnosis of anaphylaxis, and a consensus definition of anaphylaxis is under development. Brown² provides an important contribution toward this goal. He reviewed case records of symptoms from 1149 persons (median age, 29 years) with systemic allergic reactions (30% venom allergy, 22% iatrogenic allergy, and 18% food allergy) reporting to an emergency department in a referral hospital in western Australia and performed logistic regression to evaluate associations of each symptom with hypotension and hypoxia. The presence of skin symptoms were not strongly related to the presence of hypotension or cyanosis, but individual

symptoms associated with hypotension (odds ratios of 2.2 or more) included the following: incontinence, collapse, diaphoresis, cyanosis, vomiting, dizziness, dyspnea, and nausea. Symptoms associated with cyanosis included the following: confusion, stridor, dyspnea, hypotension, and wheeze. Importantly, gastrointestinal symptoms, which are likely to be dismissed as not intrinsically dangerous, were associated with severe symptoms. Further studies like this one, extending analysis to specific triggers and various age groups, are needed to improve the recognition and treatment of anaphylaxis.

Insight regarding the treatment of anaphylaxis in the emergency department is lacking. Clark et al³ reviewed 678 charts of persons presenting with food-induced allergic reactions from among 21 emergency departments and found numerous deficiencies and extreme variability in treatment. Although 55% had severe reactions, only 24% received epinephrine, only 16% were prescribed self-injectable epinephrine, and only 12% were referred to an allergist. The results of this study and those of Brown² and

Bohlke et al¹ underscore the need for more research and education regarding anaphylaxis recognition and care.

An advance in the prevention of anaphylaxis to peptide vaccines was reported by Liu et al.⁴ They observed that in murine models and human trials, peptide vaccines for treatment of autoimmune and hypersensitivity disorders, such as those used to treat multiple sclerosis or cat allergy, sometimes cause anaphylaxis. In a murine model they could invariably induce anaphylaxis with a peptide vaccine administered intravenously but only sometimes when the vaccine was administered subcutaneously. Reasoning that the rate of systemic absorption modulates clinical anaphylaxis, they modified B:9-23 peptide, an insulin peptide used in a treatment model of nonobese diabetic mice, through the addition of 2 arginine amino acids in the C-terminus, resulting in a change in the isoelectric point. This modified peptide had reduced solubility for subcutaneous therapy when administered at neutral pH and maintained its ability to induce insulin autoantibodies but induced significantly less anaphylaxis. Although it is not completely known how a decreased rate of absorption reduces the risk of anaphylaxis, the methods tested might have general applicability to improve the safety of peptide vaccines.

FOOD ALLERGY

Several clinical studies provided important insight regarding the prevalence of food allergy, its effect on daily life, and features important to management. By using a random telephone survey of the US population, it was determined that 2.3% of the general population, primarily adults (2.8% of adults), report a seafood allergy that is physician diagnosed, convincing, or both.⁵ The study also showed that reactions were typically recurrent (58%) and severe (50%) and treated with epinephrine in 16% of cases. Not surprisingly, the study showed that adults are less likely to seek evaluations for themselves or to treat their allergy appropriately compared with the diligence of care provided by parents for a child with food allergy. Indeed, caring for a child with food allergy carries a significant burden in regard to day-to-day activities, as indicated by a recently devised instrument to measure quality of life in such families.⁶ Care permeates all food-related activities, including shopping, special occasions, school, and dining out. Among allergenic foods, peanut is the most common and severe trigger in children and accounts for significant stress. One aspect of the stress regards concern for casual exposure to peanut and how to reduce exposures. Perry et al⁷ used an assay to detect the major peanut allergen, Ara h 1, in a variety of common locations and circumstances. They found that after purposeful hand exposure to peanut, no Ara h 1 was detectable when soap and water or commercial wipes were used for cleaning (plain water or sanitizer was not efficient). They also found that tables that were purposefully contaminated with peanut could be cleaned efficiently with common agents, such as water or household cleaners, but not with dishwashing liquid. In a survey of several

schools (one peanut free), Ara h 1 was undetectable on numerous desks and tables and was only detected in very low amounts unlikely to induce a reaction on 1 of 13 water fountains. Lastly, they could not detect peanut in the air near peanut butter or peanuts. These results should help allay some of the concerns families might have about inadvertent exposure to peanut.

An important potential source of inadvertent exposure to milk protein was disclosed by Nowak-Wegrzyn et al,⁸ who followed up on a report of a child with severe milk allergy who reacted with bronchospasm to an Advair Diskus and found that milk protein was detectable in the lactose filler in this and other lactose-containing dry powder inhalers. The researchers note that there is apparent lot-to-lot variability in the contamination of lactose by milk protein in these products and suggest caution in using these for persons with milk allergy.

It is now appreciated that about 20% of young children will experience resolution of their peanut allergy by school age; however, recent studies show that such families might face another stress: recurrence of a peanut allergy. Fleischer et al⁹ followed patients with resolved peanut allergy and found 8% experienced recurrence of allergy. These children had in common the fact that they generally avoided peanut after tolerating it during a food challenge. The important clinical point is that children with resolved peanut allergy should be instructed to eat peanut regularly and have epinephrine available until it is certain they are tolerating the food for a long period. The intriguing corollary is that avoidance of a food to which there is potential allergy (eg, food-specific IgE antibody) might have adverse immune consequences, and this has possible implications for allergy prevention and treatment through dietary avoidance, issues requiring more study.

Primary modalities for the diagnosis of food allergy include measurement of food-specific IgE antibody and oral food challenges. Clinicians, patients, and families must determine when it is appropriate to make a final determination of food allergy by means of oral food challenge when allergy is otherwise not confirmed by test results and history. Information that is helpful for tackling this problem was reported by Perry et al,¹⁰ who reviewed food challenge outcomes for 391 children (median age, 5 years) who underwent 604 food challenges. Children were categorized according to whether they had a clear-cut history of a prior reaction and underwent challenges, usually when their food-specific IgE antibody was about 25% of previously published levels usually associated with clinical reactions.¹¹ They found that for egg and milk, a cutoff level of 2 kUA/L (Pharmacia CAP System FEIA) was associated with a 50% rate of tolerating the challenge. For peanut, the cutoff for a 50% pass rate was also 2 kUA/L, unless there was no clear history of a reaction, in which case the cutoff was 5 kUA/L.

Several studies addressed additional issues regarding oral food challenges. Vlieg-Boerstra et al¹² report the use of a sensory panel to validate masking of foods for challenges; they found 17 of 27 recipes to pass this validation, indicating both the difficulty and potential

biases inherent in this procedure. Perry et al¹³ provide an additional insight to oral food challenge by reviewing the reaction characteristics of 253 positive food challenge results to egg, soy, peanut, wheat, and milk in children. They categorized 28% of the reactions as severe and found no trend of severity with the type of food. In regard to IgE level and severity, only peanut showed a trend (median peanut IgE: 1.3 kUA/L for mild, 2.1 for moderate, and 2.2 for severe reactions). Interestingly, reaction severity did not correlate positively with dose, and more severe reactions were common in persons with reactions at lower doses. All reactions responded to therapy, and no children required hospitalization. The authors emphasize that food challenges are generally safe, probably in part because of the use of gradual progressive dosing, but that severe reactions can occur, even to foods such as milk, wheat, and soy and even at low doses, and therefore proper preparation and supervision is essential.

A major research goal is the creation of tests for better prediction of clinical reactivity, the natural course, and severity of a food allergy. One notion is that decreasing levels of food-specific IgE might signify allergy resolution. Shek et al¹⁴ analyzed the results of food challenge outcomes and food-specific IgE levels for milk and egg in young children over time. In general, they found that the rate of decrease was predictive for development of tolerance, but there was also an effect of age at the time of diagnosis. Stratification into those less than 4 years of age and those more than 4 years of age at the time of the first challenge revealed that the younger age group was more likely to experience clinical tolerance in relation to the rate of decrease in specific IgE levels. The authors calculated mathematic models that could help to predict the timing of resolution of allergy, but studies with larger numbers of children and of children with a wider age range at diagnosis are needed to confirm and extend the study. In regard to the severity of a food allergy, laboratory parameters have traditionally been a poor predictor. Shreffler et al¹⁵ report the use of a microarray immunoassay to assess epitope binding for 213 overlapping 20-residue peptides of the major peanut allergens. In addition to showing the utility of this methodology for rapid evaluation of epitope binding to large numbers of peptides with small serum samples in large numbers of patients, the investigators found a correlation of peanut-specific IgE with high epitope diversity with severity of clinical reactions.

Identification and characterization of food allergens is necessary for improved diagnosis, prediction of allergenicity of novel food proteins, and therapy. Breiteneder and Radauer¹⁶ review a classification of plant food allergens by protein families that provides an important framework for structure-function studies of plant protein allergens. Clinical allergy to plant foods might arise from direct (oral) sensitization, typically toward proteins stable to digestion,¹⁷ and such proteins have an increased likelihood to induce systemic reactions. In addition, sensitization might occur from airborne proteins that share homology with plant proteins; when such proteins are labile, systemic reactions are less likely. Among a number of studies

providing insights into these issues, Mittag et al^{18,19} explored the role of birch-related proteins in peanut and soy allergy. The peanut allergen Ara h 8 shares 46% identity with the birch pollen allergen Bet v 1. By using recombinant (r)Ara h 8, 20 patients with peanut and birch pollen allergy were evaluated for cross-reactivity between birch and peanut.¹⁸ During food challenges to peanut, all patients experienced oral symptoms, and 40% experienced systemic reactions. IgE binding to rAra h 8 was identified in 85% of patients and could be inhibited by Bet v 1. Further studies showed Ara h 8 was labile when subjected to roasting or digestion by pepsin. However, study results could not clearly distinguish those with or without a more severe response to peanut. Similar observations were made in regard to the Bet v 1-homologous soy protein Gly m 4; in a screen of 94 highly Bet v 1-sensitized patients, 71% were sensitized to Gly m 4, and 10% experienced soy allergy.¹⁹ The content of Gly m 4 varied from 0 to 70 ppm in several soy foods tested (highest in dietary soy powders) and was labile to extended heating, adding additional clinical nuances to the spectrum of clinical soy allergy.

Advances were also reported regarding characterization of nonspecific lipid transfer proteins (nsLTPs), 7- to 9-kd monomeric proteins resistant to proteolysis, acid, and heat that are found in fruits, nuts, seeds, and vegetables and account for severe reactions. Scheurer et al²⁰ showed that the nsLTP Pru av 3 from cherry, in contrast to birch pollen-related proteins in cherry, resisted digestion and heating, was stable in skin prick test extracts, and was associated clinically with systemic allergic reactions. Pastorello et al²¹ identified patients with walnut allergy in Milan and identified an nsLTP (Jug r 3) as a major allergen, and Schocker et al²² evaluated subjects with hazelnut allergy in Spain without birch pollen allergy and identified LTP (Cor a 8) as a major allergen. These studies also highlight that patients often react to multiple types of foods that contain nsLTPs, that oral sensitization is likely, and that exposure to homologous pollen proteins is also a possible cause of sensitization.

Several studies have elucidated the immunopathophysiology of food allergy. Dendritic cells (DCs) might act to polarize immune responses, for example, toward T_H2 responses. Working on the observation that DCs might undergo rapid apoptosis after interactions with T cells, thereby downregulating the immune response, Man et al²³ used a murine model of cow's milk allergy to investigate the T cell-mediated apoptosis of myeloid DCs. They showed that systemic and gastrointestinal-derived DCs from allergic mice showed an increased resistance to T cell-mediated apoptosis compared with that seen in control mice, thereby avoiding a regulatory negative feedback loop. They also show that T cell-mediated DC apoptosis is antigen specific and MHC class II dependent. Taken together, these observations support a role for an antigen-specific malfunction in this regulatory pathway in food allergy.

Two studies show a role for IL-10 in tolerogenic immune responses toward cow's milk proteins. Tiemessen et al²⁴ compared responses of T-cell clones from children with persistent milk allergy with those of atopic children

who tolerate cow's milk. Cow's milk-stimulated T cells from the children with cow's milk allergy elaborated IL-4 and IL-13 in contrast to activated cells from the atopic children who tolerate cow's milk that produced IL-10 and, to a lesser extent, IFN- γ . In a murine system Frossard et al²⁵ compared mice with anaphylactic responses to the milk protein β -lactoglobulin (BLG) with mice tolerized to BLG. Serum IgG1 and IgE antibody titers and IL-4-producing cell numbers were increased in anaphylactic mice. IL-10 was found in Peyer patch cells from tolerant mice after BLG activation but not in anaphylactic mice. In a further study of the same model system, Frossard et al²⁶ found an increased number of BLG-specific IgA-secreting cells in Peyer patches from tolerant mice compared with those with anaphylaxis. The adoptive transfer of Peyer patch CD3⁺ cells from tolerant mice induced an increased number of IgA-secreting cells preferentially in the Peyer patches of naive recipient mice, and an increase of BLG-induced IL-10 and TGF- β levels was found at IgA production sites. The mice in these studies received specific dose and adjuvant regimens that clearly polarize the immune responses and beg the question of what factors influence the polarized immune response in human subjects. These are vital concerns in regard to prevention and therapy. In regard to therapy, altering the polarized allergic immune response of food allergy is the key. One strategy attempted for peanut allergy was to use soy, a legume with homologous proteins to peanut but perhaps without the potential to trigger allergic responses, as immunotherapy in a murine model.²⁷ The strategy was successful when compared with placebo in reducing anaphylactic responses to peanut challenge. In addition, the cellular response to crude peanut was also downregulated in the soy immunotherapy group, as shown by decreased peanut-specific stimulation indices and a cytokine profile skewed toward a T_H1 response. Strategies to induce a T_H1 cytokine profile in human subjects include exposure to the immunomodulatory properties of bacteria, such as *Lactobacillus* GG. Pohjavuori et al²⁸ evaluated infants with suspected cow's milk allergy and found that secretion of IFN- γ by PBMCs was significantly lower in infants with IgE-associated ($P = .003$) and non-IgE antibody-associated cow's milk allergy ($P = .02$) than in infants without cow's milk allergy. They treated infants with *Lactobacillus* GG, and the level of secreted IFN- γ increased in those with milk allergy ($P = .006$) and in those with IgE-associated dermatitis ($P = .02$) when compared with the untreated group. Frick et al²⁹ reported an approach in atopic dogs with food allergy in which immunotherapy was performed by using a combination of T_H1-promoting bacteria (heat-killed *Listeria monocytogenes*) along with food allergens; they found reduction or elimination of symptoms after food challenges and reduction in specific IgE levels.

DRUG ALLERGY

It is important to evaluate patients with a history of penicillin allergy because many are found to not be aller-

gic, can be prescribed penicillin, and would avoid costly alternative treatments that might carry additional risks. How often are patients with penicillin allergy, particularly outpatients, represcribed penicillin, and how often do such patients have a reaction? Apter et al³⁰ performed a retrospective cohort study using the United Kingdom General Practice Research Database. Only 0.18% of more than 3 million patients who received penicillin had an apparent allergic reaction (75% reported urticaria). Two or more prescriptions for penicillin were given to 2,017,957 patients. Three thousand fourteen (0.15%) patients experienced an allergic-like event after the first prescription, and 57 (1.89%) of those had another event after the second prescription. This absolute rate of reaction after a second course was low but was at least 9 times greater than for those who received a second course after a first course was tolerated. Interestingly, the probability of receiving a second course of penicillin for those who had an apparent reaction was only 20% less than for those without a reaction. The lessons are that in an outpatient population penicillin allergy was not very common (although patients with known allergy before entry in the database would not have been counted), but physicians represcribed the drug surprisingly often to those who had an apparent allergic reaction, indicating that awareness about penicillin allergy needs to be increased and allergist evaluation needs to be encouraged.

In regard to diagnosis, tests for allergy to quinolones have been hampered by false-positive and false-negative skin prick test results. Manfredi et al³¹ reported the results of an assay for specific serum IgE to quinolones. Sera from 55 patients with immediate adverse reactions were tested, and specificity of IgE binding was demonstrated by means of inhibition tests. The test yielded positive results in 30 (54.5%) patients who were tested 1 to 48 months after the reaction had occurred. In addition, clinical and laboratory cross-reactivity between various quinolones was noted, indicating avoidance of all quinolones in a person reactive to one quinolone might be advisable. In regard to T-cell responses to drugs, Depta et al³² transfected the T-cell receptor derived from T-cell clones of a patient with hypersensitivity to sulfamethoxazole into a T-cell receptor-negative mouse T-cell hybridoma and showed that this nonhaptenated molecule could directly stimulate T cells in an MHC-dependant manner through the T-cell receptor. Furthermore, they showed that the transfectants reacted to sulfonamides with a sulfanilamide core structure but not to those without such a structure, possibly allowing for a screening methodology for drug cross-reactivity.

Persons with chronic idiopathic urticaria (CIU) with aspirin sensitivity and those with aspirin-sensitive asthma appear to have 2 distinct clinical entities triggered by the same agent. Mastalerz et al³³ performed aspirin challenge on 74 patients (30 had positive results) with CIU and a history of aspirin sensitivity. Baseline urinary leukotriene (LT) E₄ levels were higher in those with reactions compared with in nonresponders and healthy control subjects and increased further (significantly) after the onset of clinical reaction. Plasma 9 α ,11 β prostaglandin (PG) F₂

levels increased significantly in both aspirin responders and nonresponders. Patients were genotyped for the LTC₄ synthase promoter single nucleotide polymorphism, and in patients who reacted to aspirin, the frequency of the (−444)C allele of LTC₄ synthase was significantly higher than in patients who did not react. The results indicate that persons with CIU with aspirin sensitivity have eicosanoid alterations that are similar to those present in aspirin-induced asthma. Only 3 of the 30 subjects studied had symptoms of both clinical disorders, and therefore more work is needed to understand the determinants of the specific aspirin sensitivity phenotype.

INSECT ALLERGY

Several interesting observations were made in studies that characterized allergens from stinging or biting insects. Venom serine proteases have IgE-binding activity, and the appreciation of their role in stinging insect allergy is evolving. Winningham et al³⁴ characterized serine proteases from honeybee and paper wasp and compared results with bumblebee venom protease. Significant IgE-binding activity was detected, but the framework protein sequences were poorly conserved between protease types, and therefore no significant cross-reactivity was predicted. Nugent et al³⁵ used inhibition IgE immunoblots and skin testing to evaluate cross-reactivity of allergens among patients with scorpion sting or imported fire ant allergy. They had observed that some persons experience acute allergic reactions after a first episode of scorpion sting, and affected persons are in geographic locations where imported fire ants and the common striped scorpion are endemic. Indeed, significant cross-reactivity between the imported fire ant whole-body extract and scorpion venom were observed, implying that persons with imported fire ant allergy are at risk for allergic reactions to scorpion and that persons with scorpion allergy might benefit from immunotherapy with imported fire ant whole-body extracts. In contrast to stinging insects in which venom proteins are relevant, the saliva of biting insects appears to contain the causal allergens. Peng et al³⁶ evaluated sera from 14 persons with acute systemic reactions to mosquito bites and control subjects. Using an indirect ELISA with mosquito salivary preparations from 5 species of mosquito, the investigators found evidence of increased saliva-specific IgE levels in patients compared with in control subjects and no difference in saliva-specific IgG levels. In addition, studies confirmed both species-specific and shared allergens. The authors point out that current commercial assays use mosquito whole-body extract, which is not as sensitive or specific as the assay they use, in which the capture antigen is a mosquito saliva preparation that requires special care to obtain. Recombinant mosquito salivary allergens might allow for better diagnostic testing and perhaps treatment in the future.

The treatment of stinging insect hypersensitivity with allergen immunotherapy represents an important modality for the allergist to modify disease and improve patient

outcomes. The efficacy of venom immunotherapy is well established, and Golden et al³⁷ have added key additional information in regard to the long-term outcomes of sting reactions and of treatment in children. The investigators diagnosed insect sting allergy in 1033 children during the years 1978 through 1985 and were able to obtain results of follow-up for 512 subjects from 1997 through 1999 (a mean follow-up of 18 years). Systemic reactions were less frequent in those treated with immunotherapy (2/64 [3%]) compared with those not treated (19/111 [17%], $P = .007$). The risk reduction was particularly strong for persons who experienced moderate-to-severe reactions and received immunotherapy (5% recurrence) compared with those who were untreated (32% recurrence). The results indicate that an important number of children do not outgrow their venom allergy and that treatment (mean duration of 3.5 years) might impart longstanding protection. The allergist should also be aware that an updated Practice Parameter for the diagnosis and treatment of stinging insect hypersensitivity³⁸ was published this year. The update incorporates studies in the field since the 1999 Practice Parameter, including discussions regarding immunotherapy indications, dosing, and duration and dilemmas associated with patients for whom a sting reaction is evident but initial test results are negative.

ATOPIC DERMATITIS

The natural history, pathogenesis, and treatment of atopic dermatitis (AD) remain important areas of study for investigators who publish in the *JACI*.^{39,40} In 2004, articles focused on disease associations, as well as the role of antigen-presenting cells, keratinocytes, chemokines, and T regulatory (Treg) cells in AD. There was also considerable interest in the clinical and immunologic effects of topical calcineurin inhibitors on AD.

Epidemiology

The extent to which the phenotype of AD is truly atopic has been the subject of much debate. Flohr et al⁴¹ sought to systematically evaluate the evidence for the value of measurement of IgE antibodies in diagnosing AD and whether knowledge of IgE sensitization increases clinical diagnostic and predictive ability. They searched Medline from its inception until September 2003 for studies that measured atopy as either skin prick test positivity or IgE antibody sensitization to environmental allergens in the evaluation of patients with AD. The strength of association between atopy and AD varied significantly between hospital studies (47% to 75%, $n = 14$ studies) and was stronger in hospital than in community populations (7.4% to 78%, $n = 13$ studies). AD severity was positively associated with the number of positive skin prick test responses or IgE antibody levels in 7 of 8 studies that measured both. Two studies found that allergen-specific IgE sensitization in patients with AD is a prognostic marker for allergic airway disease in later life. Atopy-associated AD might also have a worse long-term prognosis than AD that is not

associated with atopy. Although atopy is clearly associated with AD, the role of IgE sensitization in AD requires further study. Longitudinal studies are needed to compare the treatment response and prognosis of IgE-associated and non-IgE-associated AD. Importantly, there is a need for agreement on the extent of allergy testing needed before a patient is declared nonatopic. In this regard patients with so-called intrinsic AD have been reported to have IgE responses to microbial antigens not routinely tested for by most practicing physicians.⁴² In other nonatopic patients, T-cell responses to allergens in the form of atopy patch tests have been observed, suggesting that they can be triggered by aeroallergens through IgE-independent mechanisms.⁴³

Considering the confusion around the term *atopic dermatitis*, because there are patients who appear to have no IgE directed against environmental allergens, the World Allergy Organization has proposed a new terminology that would replace AD.⁴⁴ They suggest use of the term *atopic eczema* to denote skin inflammation dominated by an IgE antibody-associated reaction and the term *nonatopic eczema* where there is no detectable IgE and the dominating cells in skin biopsy specimens are T lymphocytes.

AD is considered to be one of the first manifestations in the atopic march.⁴⁵ However, few prospective studies on AD and its association with childhood asthma exist. Illi et al⁴⁶ prospectively investigated the natural course of AD to determine factors influencing its prognosis and to analyze the relationship of AD with childhood asthma. The Multicenter Allergy Study, a German birth cohort, followed 1314 children from birth to age 7 years. The cumulative prevalence of AD in the first 2 years of life was 21.5%. Of these children with early AD, 43.2% were in complete remission by age 3 years, 38.3% had an intermittent pattern of disease, and 18.7% had symptoms of AD every year. Early AD without these cofactors constituted no increased risk of subsequent wheeze or bronchial hyperreactivity. The prognosis of AD was mostly determined by the severity and the presence of atopic sensitization. Early AD was associated with asthma at school age, but in many of these asthmatic children, wheezing manifested before or with the onset of AD. Interestingly, children with AD and wheeze had a marked loss of lung function, suggesting a distinct phenotype that associated AD might contribute to more severe asthma.

Cellular immune mechanisms

AD is a biphasic inflammatory skin disease characterized acutely by overexpression of T_H2 cytokines and then switching to a T_H1-dominated phase in chronic skin lesions. Thus far, the small number of FcεRI-bearing Langerhans cells (LCs) and inflammatory dendritic epidermal cells (IDECs) in the epidermis of patients with AD has hampered a functional analysis of these DCs. Novak et al⁴⁷ studied FcεRI-mediated mechanisms of LCs and IDECs using a novel *in vitro* model. They found that FcεRI-activated LCs-DCs release chemokines that increase the migratory capacity of precursor cells of IDECs and naive T cells *in vitro*. Furthermore, FcεRI-

activated IDECs-DCs prime naive T cells into IFN-γ-producing T cells and release IL-12 and IL-18, which together might contribute to a switch of the initial T_H2-type immune response to a response of the T_H1 type *in vivo*. This study provides evidence that FcεRI-activated LCs-DCs and IDECs-DCs contribute distinctly to the outcome of T-cell responses and might have implications for the biphasic nature of AD.

Plasmacytoid dendritic cells (pDCs), which are instrumental in the defense of viral infections, are present in reduced amounts in the skin of patients with AD, which is characterized by a high susceptibility to viral infections. Novak et al⁴⁸ explored phenotypical and functional characteristics of pDCs in the peripheral blood of patients with AD and healthy individuals. pDCs in patients with AD, compared with in healthy subjects, expressed high amounts of IgE-occupied FcεRI. Furthermore, FcεRI aggregation on pDCs impaired the surface expression of MHC I and II, induced the production of IL-10, and enhanced the apoptosis of pDCs. Importantly, FcεRI-preactivated pDCs produced less IFN-α and IFN-β after stimulation with CpG motifs and enhanced the outcome of immune responses of the T_H2 type. These data indicate that FcεRI-bearing pDCs from patients with AD have different characteristics compared with pDCs of healthy individuals and might contribute to the enhanced susceptibility of patients with AD to viral infections.

Keratinocytes participate in the initiation and amplification of AD-induced skin inflammation. Histamine can be released from both resident skin cells and infiltrating leukocytes during inflammatory skin response. Little information is available on the effects of histamine on keratinocytes. To examine the presence of functional H1 receptors on human keratinocytes and the capacity of histamine to modulate the expression of inflammatory molecules in these cells, Giustizieri et al⁴⁹ analyzed primary cultures of resting and cytokine-activated keratinocytes from healthy subjects for histamine H1-receptor expression and the production of inflammatory mediators after exposure to histamine receptor agonists and antagonists. Cultured keratinocytes constitutively expressed H1-receptor mRNA and protein, and this was not influenced by IFN-γ, TNF-α, or IL-4. H1, but not H2, agonists induced calcium fluxes in keratinocytes. Treatment of keratinocytes with histamine (10⁻⁷ to 10⁻⁴ mol/L) or β-histidine increased the IFN-γ-induced expression of membrane intercellular adhesion molecule 1 and MHC class I, but not MHC class II, molecules. Moreover, H1 stimulation promoted basal CC chemokine ligand (CCL) 5/RANTES and GM-CSF secretion and augmented IFN-γ-induced release of the chemokines CCL2/monocyte chemoattractant protein 1, CCL5/RANTES, CCL20/macrophage inflammatory protein 3α, and CXC chemokine ligand 10/IFN-induced protein of 10 kd, as well as GM-CSF. Treatment with the H1 antihistamine levocetirizine, but not with the H2 antihistamine cimetidine, abolished histamine-dependent expression of all of the investigated proinflammatory molecules in a dose-dependent manner. Levocetirizine at higher doses also reduced

intercellular adhesion molecule 1, CCL5/RANTES, and GM-CSF release induced solely by IFN- γ . These data suggest that histamine exerts proinflammatory effects on keratinocytes through the H1 receptor, and these effects are efficiently inhibited by levocetirizine.

CD4⁺CD25⁺ Treg cells are thought to play an important role in controlling allergic inflammatory responses.⁵⁰ Interestingly, patients with XLAAD/IPEX (X-linked autoimmunity-allergic dysregulation syndrome/immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) disease⁵¹ specifically lack naturally occurring CD4⁺CD25⁺ Treg cells because of a mutation in the FoxP3 gene and have severe eczema, increased IgE levels, and eosinophilia. However, little is known about environmental factors that might alter Treg cell function. Because staphylococcal superantigens are known to amplify inflammatory skin reactions in AD, Ou et al⁵² studied the effects of a prototypic superantigen, staphylococcal enterotoxin B, on Treg cell function. CD4⁺CD25⁺ naturally occurring Treg cells in patients with AD were found to have normal function (ie, they were anergic and able to suppress T effector cell proliferation). However, after staphylococcal enterotoxin B stimulation, CD4⁺CD25⁺ Treg cells were no longer anergic, and they lost their immunosuppressive activity. These data suggest a novel mechanism by which superantigens can augment T-cell activation in patients with AD.

Role of chemokines

T-cell trafficking to the skin of patients with AD is mediated by specific chemokines and their receptors.⁵³ Hijnen et al⁵⁴ investigated the participation of the chemokines thymus and activation-regulated chemokine (TARC) and cutaneous T cell-attracting chemokine (CTACK) in 455 patients with allergic diseases. Both TARC and CTACK serum levels in patients with AD were significantly higher than those in healthy control subjects and patients with allergic respiratory disease. Furthermore, serum TARC and CTACK levels significantly correlated with disease activity in patients with AD. Serum TARC levels paralleled clinical improvement in patients treated with cyclosporin A. Immunoreactive TARC was found in infiltrating cells and endothelial cells of the dermis but not in epidermal cells. These studies indicate that serum TARC level is an objective parameter for disease severity specific for AD and might be a promising tool for treatment monitoring.

Fractalkine (FKN) induces activation and adhesion of leukocytes expressing its receptor, CX(3)CR1. Echigo et al⁵⁵ sought to assess FKN and CX(3)CR1 expression in the skin, serum soluble (sFKN) levels, and CX(3)CR1 expression on blood leukocytes in patients with AD. FKN was found to be strongly expressed on endothelial cells in skin lesions of patients with AD and psoriasis but not in normal skin. FKN mRNA levels in AD lesional skin increased to an extent similar to that of TARC and macrophage-derived chemokine mRNA levels. CX(3)CR1-expressing cells in the affected skin of patients with AD or psoriasis were also increased compared with

those in normal skin. Serum sFKN levels were increased in patients with AD but not in patients with psoriasis relative to levels in healthy control subjects. Serum sFKN levels were associated with disease severity and decreased with the improvement of skin lesions in patients with AD. These results suggest FKN plays a role in the trafficking of CX(3)CR1(+) leukocytes in skin inflammation caused by AD.

The chemokine CCL27 attracts skin-homing T cells. Therefore understanding mechanisms underlying its regulation is important. Kanda et al⁵⁶ examined the *in vitro* effects of PGE₂ on CCL27 production in human keratinocytes. TNF- α increased CCL27 secretion and mRNA levels in parallel to NF- κ B activity in keratinocytes. NF- κ B p50 or p65 antisense oligonucleotides suppressed TNF- α -induced CCL27 production, indicating the requirement of NF- κ B for CCL27 production. PGE₂, EP2, or EP3 agonists reduced TNF- α -induced CCL27 secretion and mRNA levels in parallel to NF- κ B activity and CCL2, CCL5, CXCL8, and CXCL10 mRNA levels. Either EP3-specific or dual EP1-EP2 antagonist partially blocked the inhibitory effects of PGE₂ on CCL27 production and NF- κ B activity, and the addition of both completely abrogated the inhibition, whereas EP1 or EP4 antagonists were ineffective. Intracellular Ca²⁺ chelator BAPTA/AM or cyclic adenosine monophosphate (cAMP)-dependent protein kinase inhibitor H-89 partially blocked the inhibitory effects of PGE₂ on CCL27 production and NF- κ B activity, and the addition of both completely abrogated the inhibition. PGE₂ or EP3 agonist increased intracellular Ca²⁺ concentrations. PGE₂ or EP2 agonist increased intracellular cAMP concentrations. These results indicate that PGE₂ might suppress CCL27 production by inhibiting NF- κ B activity through EP2-mediated cAMP and EP3-mediated Ca²⁺ signals and thereby terminate T cell-mediated skin inflammation by inhibiting CCL27 production.

Treatment

Topical calcineurin inhibitors have been demonstrated to be effective in the treatment of AD.⁵⁷ However, data on the efficacy of pimecrolimus cream 1% within the first days of treatment are scarce, and as in previous studies, the first postbaseline assessment was performed only after 1 week. Kaufmann et al⁵⁸ sought to investigate the onset of action of pimecrolimus cream 1% in infants with mild to very severe AD. They used pimecrolimus cream 1% (n = 129) or vehicle cream (n = 66) administered in a double-blind manner for 4 weeks and then open-label pimecrolimus cream 1% for 12 weeks, with a 4-week follow-up period. Pimecrolimus cream 1%, compared with vehicle control, significantly reduced the mean Eczema Area and Severity Index at 4 weeks. The reduction in the Eczema Area and Severity Index with pimecrolimus cream 1% was significant by day 4. Significant improvements in caregivers' assessments of pruritus and sleep loss were observed with pimecrolimus cream 1% by day 2 and day 3 compared with vehicle. Responses to pimecrolimus cream 1% were sustained during the open-label phase, and pimecrolimus cream 1% was well tolerated. Symptoms of AD returned gradually after discontinuation. Thus

pimecrolimus cream 1% was well tolerated and effective in patients with mild to very severe AD, with rapid onset of action and no disease rebound after discontinuation.

The mechanism by which topical calcineurin inhibitors reduce skin inflammation in AD is not completely understood. Simon et al⁵⁹ examined the cellular infiltrate in skin lesions of 10 patients with AD and characterized the cytokine pattern expressed by the infiltrating cells before and after short-term topical therapy with tacrolimus 1% ointment. In this study all patients showed a significant improvement after tacrolimus therapy of their skin lesions associated with a marked regression of spongiosis, acanthosis, and density of the cellular infiltrate in the dermis. The latter was a result of reduced infiltration of T cells, B cells, and eosinophils. Moreover, the expression of the T_H2 cytokines IL-5, IL-10, and IL-13 in CD4⁺ T cells was reduced after therapy. Interestingly, tacrolimus therapy was also associated with a reduction of CD8⁺ T cells expressing the T_H1 cytokine IFN- γ . Thus this study demonstrated that topical tacrolimus treatment has anti-inflammatory effects on AD skin, as indicated by reduced infiltration of cytokine-expressing inflammatory cells.

Schuller et al⁶⁰ also examined whether tacrolimus ointment induces apoptosis of LCs or IDECs in AD lesions. Epidermal single-cell suspensions were prepared from AD lesions of 9 tacrolimus-treated and 5 hydrocortisone butyrate-treated patients before and after 1 week of treatment. Cell numbers, apoptosis rate, and immunophenotype were assessed by using a standardized FACS technique with terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling, Annexin V, and 3-color immunophenotyping. Tacrolimus and steroid ointment induced a selective depletion of IDECs from the epidermis and reduced the expression of the costimulatory molecules CD80 and CD86. Tacrolimus ointment did not increase the rate of apoptotic DCs, whereas steroid ointment did. Thus tacrolimus ointment selectively depletes IDECs and alters the immunophenotype of epidermal DCs in AD lesions, but there is no evidence for tacrolimus-induced DC apoptosis in this phenomenon.

CHRONIC URTICARIA

The cause of chronic urticaria (CU) in childhood often remains unrecognized. Recently, in adults it has been shown that approximately 40% of patients with CU have autoimmune urticaria (AU). Brunetti et al⁶¹ examined the prevalence and possible risk factors for AU in children with CU. Ninety-three consecutive children with CU were evaluated for AU by means of autologous serum skin tests (ASSTs) and serum-induced basophil histamine release (HR-urticaria tests). All other known causes of CU were excluded as appropriate. A cause for CU was identified in 44 (47%) children, whereas 49 (53%) remained idiopathic. ASSTs and HR-urticaria tests had positive results in 22 (45%) of 49 and 16 (52%) of 31 children with idiopathic CU compared with 1 (2%) of 44 and 5 (24%) of 21 with CU of a known cause, respectively ($P < .00001$ and

$P = .09$, respectively). Thus prevalence of AU in childhood was 31%. These results demonstrate for the first time that children have the same ability as adults to produce functionally active autoantibodies directed against IgE or IgE receptor and that AU occurs in children in as many as 31% of cases.

Because leukotrienes have potent local effects on cutaneous vasculature, leukotriene antagonists might be effective in the treatment of CU. A double-blind, placebo-controlled trial comparing 10 mg of cetirizine daily in combination with 20 mg of zafirlukast twice a day versus 10 mg of cetirizine daily and placebo was conducted to determine whether subjects with CU benefit from add-on therapy with a leukotriene-modifying agent.⁶² At baseline, all subjects were skin tested to autologous serum to assess for the potential presence of Fc ϵ R1 or IgE autoantibodies. Subjects meeting the initial entry criteria were treated with 10 mg of cetirizine daily and placebo twice daily for 1 week. Those patients with persistent hives were randomized to receive 10 mg of cetirizine daily and 20 mg of zafirlukast twice a day or 10 mg of cetirizine daily and placebo. At each successive weekly visit, physician and patient treatment effectiveness score and visual analog scale (VAS) ratings were recorded. Combination therapy with zafirlukast demonstrated a modest but significantly greater improvement compared with cetirizine monotherapy in physician- and patient-recorded VAS ratings at visit 4 and across treatment visits 4 through 6 ($P < .05$ unless stated otherwise). Subjects with positive ASST results receiving combination therapy compared with subjects with negative ASST results exhibited a significant improvement in patient-recorded VAS ratings. Subgroup analysis of subjects with positive ASST results receiving combination therapy versus monotherapy showed improvement in physician-recorded treatment effectiveness score. There were no significant results for patients with negative ASST results. The results of this study indicate that only patients with autoimmune (positive ASST results) CU refractory to H1 antagonist monotherapy might benefit from the addition of the LTD₄ receptor antagonist zafirlukast to their treatment regimen. These results also suggest that routine screening of patients with CU with the ASST might be useful in formulating therapeutic algorithms in the management of CU.

H1-receptor antagonists are considered to be particularly effective in reducing pruritus, and they are therefore recommended as first-line treatment in patients with CIU. Recently, antileukotriene receptors have been used in patients with CIU, either administered as monotherapy or combined with H1-receptor antagonists. Di Lorenzo et al⁶³ compared the clinical efficacy of 5 mg of desloratadine administered once daily either as monotherapy or combined with a leukotriene antagonist, 10 mg of montelukast daily, and 10 mg of montelukast administered daily as monotherapy for the treatment of patients affected by CIU with placebo. One hundred sixty patients aged 18 to 69 years (mean $\pm$ SD, 43.9 $\pm$ 13.4 years) with a history of moderate CIU were selected. A randomized, double-blind, double-dummy, placebo-controlled, parallel-group study

design was used. Patients were treated with 5 mg of desloratadine once daily (n = 40), 10 mg of montelukast once daily (n = 40), 5 mg of desloratadine (n = 40) in the morning plus montelukast in the evening, or matched placebo (n = 40). Assessment of treatment efficacy was based on scores of daily cutaneous symptoms evaluated reflectively and instantaneously. Only the group treated with desloratadine as monotherapy or as combined therapy concluded the whole study. Twenty-seven of the 40 patients in the montelukast group and 35 of the 40 patients in the placebo group discontinued the treatment. As reflective evaluation, all groups showed significant differences compared with the placebo group in terms of total symptom score, number of hives, and size of the largest hive. In addition to the pruritus, only the groups treated with desloratadine as monotherapy or combined therapy showed significant differences compared with those receiving placebo, whereas there were no differences between the montelukast and placebo groups. Finally, no differences were found between the desloratadine group and the desloratadine plus montelukast group. The instantaneous evaluation demonstrated similar results regarding the desloratadine group and the desloratadine plus montelukast group versus the placebo group, whereas there were no significant differences between the group treated with montelukast alone and the placebo group for pruritus and size of the largest hive. No differences were found between the group treated with desloratadine alone and the desloratadine plus montelukast group. The results of this comparative study demonstrate that desloratadine is highly effective for the treatment of patients affected by CIU. In addition, the regular combined therapy of desloratadine plus montelukast does not seem to offer a substantial advantage with respect to desloratadine as monotherapy in patients affected by moderate CIU. These studies are consistent with the above Bagenstose study⁶² because a distinction was not made between AU and idiopathic CU.

CONCLUSIONS

Laboratory-based investigations reported in the Journal in 2004 have advanced our understanding of the molecular and cellular events underlying allergic responses to foods, drugs, and insects and the inflammatory responses underlying AD. In particular, elucidation of inflammatory pathways and the effect of exposure to allergens and immunomodulatory molecules from microbes might provide key opportunities for treatment and prevention. Clinical observations reported in 2004, such as the presence of milk protein in lactose used in dry powder inhalers, the possible recurrence of peanut allergy, and the utility of topical calcineurin inhibitors for AD and of leukotriene antagonists for autoimmune CU, have an immediate influence on clinical practice. Finally, results of a number of epidemiologic studies of anaphylaxis and food and drug allergies underscore the need for our specialty to continue to address the education of physicians and patients about the care of these disorders.

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