

Advances in anaphylaxis and hypersensitivity reactions to foods, drugs, and insect venom

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This review highlights some of the research advances in anaphylaxis and hypersensitivity reactions to foods, drugs, and insect venom that were reported primarily in this Journal from 2001 to 2002. Among the topics highlighted: epinephrine injected intramuscularly into the thigh provides the most efficient absorption profile for adults and children; determination of serum IgE antibody-specific food allergen concentrations and atopy patch tests with foods show promise for enhanced diagnostic accuracy; numerous food allergens are now characterized on the molecular level, allowing for improved diagnostic and treatment modalities; the complex immunologic mechanisms underlying drug hypersensitivity reactions are being elucidated; venom immunotherapy improves quality of life for sufferers, and increased venom immunotherapy doses are useful in recalcitrant cases. (*J Allergy Clin Immunol* 2003;111:S829-34.)

Key words: Anaphylaxis, allergy, hypersensitivity disorders, food, drug, insect venom

Nearly 50 articles concerning clinical anaphylaxis and food, drug, and insect sting hypersensitivity were published in *The Journal of Allergy and Clinical Immunology* from October 2001 to September 2002. This review highlights key advances in these areas reflected primarily by studies in the Journal, with additional pertinent material selected from the literature (Table I).

ANAPHYLAXIS

A previous study by Simons et al¹ showed that intramuscular, compared to subcutaneous, administration of epinephrine provides the most efficient absorption profile in children. During the past year, these researchers extended this observation to adults and additionally determined that the lateral thigh is the preferred site of injection to achieve maximal absorption rates.² This group of researchers also addressed the confusing issue of dosing epinephrine for children. Currently available prepackaged epinephrine for self-administration is available only in doses of 0.15 (EpiPen Jr) and 0.3 mg (EpiPen). As the recommended dose is 0.01 mg/kg, and there are no clear consensus statements for dosing, the physician must select a dose for children along a range of weights. Plasma concentration and physiologic responses

Abbreviations used

CCD:	Cross-reactive carbohydrate determinants
COX:	Cyclooxygenase
DBPCFC:	Double-blind, placebo-controlled oral food challenge
IDHR:	Immune-mediated drug hypersensitivity reaction
LTP:	Lipid transfer protein
PST:	Prick skin test
TEN:	Toxic epidermal necrolysis
VIT:	Venom immunotherapy
VLQ:	Vespid allergy quality of life questionnaire

were determined in children who weigh between 15 and 30 kg, randomized to receive 1 of the 2 available doses.³ Five children with a mean weight of 18 kg received the 0.15 mg dose and achieved a maximum concentration of 2,037 pg/mL at 16 minutes, and 5 children with a mean weight of 25.4 kg received the 0.3 mg dose and achieved a peak concentration of 2,289 pg/mL at 15 minutes. Systolic blood pressure was significantly higher in those who received 0.3 mg (95 mm Hg vs 108 at 30 minutes), but adverse effects were also more common (palpitations, headache, nausea, and 1 patient with a prolonged QT_c). All children experienced pallor, and most had tremors. The authors concluded that the beneficial and adverse pharmacologic affects could not be dissociated, and additional fixed doses would facilitate more precise therapy. The authors further suggested that clinical judgment is necessary to decide between the 2 formulations, taking into consideration numerous factors including weight, clinical history, presence of underlying asthma, and access to emergency services. Prescription of epinephrine to be administered by ampule and syringe could solve these issues; however, Simons et al⁴ also found this approach to be fraught with practical problems. In a nonurgent setting, parents took a mean of 142 seconds to draw up the medication, and half of them were more than 30% off the requested dose. The study concluded that premeasured doses of epinephrine for infants should be developed. For now, the physician must consider a number of factors in deciding how best to dose the medication and, if selected, the ampule/syringe methods would require additional education and practice.

FOOD HYPERSENSITIVITY

Several studies in the Journal highlighted the practical issues faced by persons with food hypersensitivity in regard to eating in restaurants,⁵ purchasing prepackaged

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TABLE I. Key advances

1. Anaphylaxis. Epinephrine injected intramuscularly into the lateral thigh provides more efficient absorption than the subcutaneous route (or intramuscular injected in the arm).
2. Food hypersensitivity. Studies that correlate clinical outcomes to IgE antibody binding profiles are making it possible to predict: clinically relevant sensitization, the natural course of disease, severity of reactions, and the clinical implications of cross-reactive proteins.
3. Drug hypersensitivity. COX-2 inhibitors are unlikely to cause reactions in NSAID-sensitive patients. Courses of oral penicillin given to skin test-negative patients with a history of prior penicillin allergy are unlikely to elicit resensitization.
4. Insect venom hypersensitivity. Immunotherapy to insect venom significantly improves quality of life for those affected. Higher doses may be needed in patients who are refractory to therapy.

TABLE II. Advances possible through studies that characterize hypersensitivity responses to food proteins at the molecular level

Diagnosis	–Differentiate clinically silent (false positive) from relevant (true positive) sensitization –Differentiate clinically relevant from clinically silent cross-reactivity and predict which foods, never ingested, may be problematic –Predict natural course –Determine likelihood of reactions to cooked versus raw forms of food –Approximate severity of reactions
Therapy	–Allow construction of peptides for immunotherapy vaccines that trigger T-cell responses without binding IgE –Target immunotherapy toward most relevant epitopes –Target therapy toward immune components active in particular hypersensitivity responses

foods (label ambiguities and undeclared allergens),^{6,7} and quandaries faced by the food industry in approaching the question of the amount of allergen contamination that may trigger a reaction.⁸ These studies are an important reminder for clinicians to educate patients about practical considerations of allergen avoidance. They also highlight larger issues that must be addressed by government agencies, the hospitality and food industries. Practical materials to address these issues are available through the Food Allergy and Anaphylaxis Network (www.foodallergy.org, 1-800-929-4040).

Numerous allergenic food proteins have been identified and evaluated on a molecular level.⁹⁻¹⁵ The studies continue to identify seed storage and lipid transfer proteins (LTP) as immunogenic proteins of particular importance for clinical allergy. The advances promised through these studies are summarized in Table II. Hazelnut is an important target food, because the severity of reactions varies and cross-reactivity with pollen proteins confounds diagnostic testing. Through strategies of RAST inhibition and selection of patients with particular reac-

tion profiles with and without birch sensitization, proteins that are specifically associated with significant clinical reactions to hazelnut (a 9 kD LTP¹⁵ and a 40 kD 11 S globulin seed storage protein¹⁶) are distinguishable from less relevant ones. Similarly, for wheat allergy, presence of IgE antibody to omega-5 gliadin carries increased specificity for predicting clinical reactions.¹⁰

In an elegant approach to tease-out the clinical relevance of cross-reactive proteins shared by birch pollen and cherries, Ballmer-Weber and colleagues¹³ evaluated the diagnostic potential of a panel of recombinant cherry allergens. Swiss patients allergic to cherry and exposed to birch pollen, patients with birch allergy who tolerate cherry, Spanish patients with cherry allergy without birch pollen exposure, and nonatopic controls were evaluated with prick skin tests (PST) and serum immunoblot analysis. As expected, nonatopic controls had no binding/positive skin tests. Those with cherry allergy from Switzerland, and those with birch pollen allergy alone, bound primarily to recombinant Pru av 1 and Pru av 4 (related to birch pollen Bet v 1 and Bet v 2), whereas the Spanish patients with cherry allergy bound more extensively to Pru av 3, an LTP. Sensitization to Pru av 3 was positively associated with symptom severity. The study demonstrates that recombinant allergens may improve the diagnostic value of allergy tests.

Determination of the binding profiles of IgE antibodies to particular regions of allergens (epitope analysis) may provide additional diagnostic information. Järvinen and colleagues¹⁴ compared the IgE antibody epitope-binding profiles of children with persistent cow's milk allergy to those who eventually outgrew the allergy (using banked sera from a period of previous reactivity). Decapeptides synthesized according to previously identified IgE-binding epitopes of 5 cow's milk proteins were used to screen the sera, and 5 epitopes were identified that had no binding among the children who achieved tolerance, but were recognized by the majority of those with persistent allergy. The distinction in binding may reflect a differential predilection to produce IgE antibodies toward epitopes that are less influenced by complex conformational protein structures (eg, toward sequential amino acids) in those with persistent allergy.

Several studies also show that improved diagnostic accuracy can be achieved with currently available methods.^{17,18} For example, Rancé and colleagues¹⁸ evaluated PSTs using a raw and a commercial peanut extract and determined the concentrations of serum peanut-specific IgE antibodies (CAP System FEIA, Pharmacia & Upjohn Diagnostics) among 363 children evaluated with double-blind, placebo-controlled food challenges (DBPCFC) to peanut. They found that if the largest diameter of the raw extract was 16 mm or greater, or if IgE antibody concentration was more than 57 kU/L, there was 100% positive predictive value for a reaction. They observed no reactions when the largest wheal diameters using raw peanut extracts was less than 3 mm (as long as the serum peanut-specific IgE concentration was simultaneously below 57 kU/L). Commercial peanut extract had comparatively poor

TABLE III. Characterization of the inflammatory response in food hypersensitivity disorders affecting the gastrointestinal tract

Authors	Study population	Tissue	Finding
Lin et al ²²	Adults with isolated gut reactions, no detectable IgE to causal foods	Duodenal biopsies	Increased IL4+ cells, eosinophils, and IgE-bearing cells, reduced interferon gamma-positive cells
Beyer et al ²³	Children with allergic eosinophilic gastroenteritis and/or food protein induced enteropathy syndrome	Duodenal biopsies	Th-2 cytokines were elaborated by milk-specific T-cells following in vitro stimulation with cow's milk.
Straumann et al ²⁴	Adults with eosinophilic esophagitis	Esophagus	Increased eosinophils, mast cells, IL-5 and TNF-alpha expression (that were not reflected in parallel study of peripheral blood).
Schade et al ²⁵	Infants with cow's milk allergy	Peripheral blood	Milk-specific T-cell clones showed increased IL-2 receptor alpha, and CD 30 (marker of activation); decreased CD 26 (dipeptidyl-peptidase IV, a marker of TH-1 inflammation)
Chung et al ²⁶	Infants with food-protein-induced enterocolitis syndrome	Duodenal biopsies	Increased TNF alpha, reduced TGF-beta receptor; (TGF-beta is a cytokine associated with improved gut permeability and oral tolerance)

predictive accuracy. An emerging methodology to diagnose food allergy, particularly reactions that may be delayed (with or without IgE antibody), is the atopy patch test.^{19,20} In this method, a slurry of the diluted food is used in a Finn chamber and evaluated in a manner similar to patch tests for contact allergens. More studies are needed to define the role of this methodology, but additional diagnostic information appears to be attainable, particularly for delayed reactions and symptoms attributable to wheat.

The immunopathophysiologic basis of food hypersensitivity is being unraveled. Beyer and colleagues²¹ found that T-cell expression of cutaneous lymphocyte antigen, a skin homing receptor, was upregulated after in vitro stimulation of peripheral blood mononuclear cells with milk in individuals with milk-responsive urticaria and atopic dermatitis, but not in those with isolated gastrointestinal reactions. This discovery partly explains target organ specificity of reactions. Comparatively less is understood about hypersensitivity reactions that occur without evidence of IgE antibody (most commonly manifested as isolated gastrointestinal reactions to foods). Numerous studies elucidated the role of Th-2-induced inflammation in these disorders, as summarized in Table III.²²⁻²⁶

Novel approaches to therapy of food allergy are under investigation,²⁷ including vaccination with modified proteins, use of immunostimulatory sequences, gene therapy, and anti-IgE antibodies. Li et al²⁸ showed that a Chinese herbal remedy (FAHF-1) protected peanut-sensitized mice from anaphylactic reactions and actually reversed an established IgE-mediated peanut allergy. The search for the component(s) responsible for this effect is underway. New animal models of food hypersensitivity may speed discoveries of novel therapies.²⁹

DRUG HYPERSENSITIVITY

The Health and Environmental Sciences Institute Task Force published a report on the research needs for the prevention and management of immune-mediated drug hypersensitivity reactions (IDHR).³⁰ The report recognized that IDHRs account for up to 230,000 hospital admissions in the United States, with a price tag of up to \$600 million annually, but that there are numerous gaps in our knowledge about mechanisms, and insufficient diagnostic and treatment methods. A review by Dr Gruchalla³¹ also acknowledged the gaps in our knowledge, but highlighted new mechanistic information and practical approaches to patients with IDHRs. A comprehensive practice parameter that reviews the approach to clinical issues in drug hypersensitivity was published in 1999.³² Several studies in the past year have also addressed diagnostic issues, elucidated basic mechanisms, and provided insights for approaching clinical problems.

The possibility of predicting adverse drug reactions through HLA typing was investigated by Mallal and colleagues.³³ The authors found a strong association of hypersensitivity to the HIV-1 reverse-transcriptase inhibitor, abacavir, to the 57.1 ancestral haplotype HLA-B*5701, HLA DR7, and HLA-DQ3, such that there was a positive predictive value of 100% and negative predictive value of 97% in the presence of this haplotype. Screening based on this observation would reduce reactions to this drug from 9% to 2.5% with no patient inappropriately denied treatment. Unfortunately, the limitations of such studies were highlighted by a later replication study showing much poorer predictive value in another population.³⁴

Several studies have illuminated the molecular mechanisms of drug hypersensitivity. In a brief report, Kudva-Patel and colleagues³⁵ describe a child with X-linked agammaglobulinemia who experienced a maculopapular rash after therapy with ceftriaxone, and then a somewhat more acute reaction consisting of flushing and hyperthermia to an additional dose. The child had no B cells or detectable IgE and negative skin tests to penicillin reagents and ceftriaxone, but further studies revealed a positive patch test to ceftriaxone and infiltration of the test site with CD4-, CD7-, and CD45RO-positive mononuclear cells, indicating that morbilliform and maculopapular rashes occur in the absence of IgE and are T-cell mediated.

The importance of, and mechanisms underlying, T-cell-mediated reactions to drugs were a theme of recent studies. Nassif and colleagues³⁶ evaluated cells in the blister fluid of a patient with toxic epidermal necrolysis (TEN) induced by cotrimoxazole. The death of keratinocytes in TEN is considered to result from Fas/Fas ligand interactions, but the initial trigger is unknown. This group demonstrated a predominance of CD8+, DR+, CLA+, and CD56+ T-lymphocytes that were perforin positive and exhibited cytotoxicity to autologous cells only in the presence of cotrimoxazole and certain metabolites. Posadas and colleagues³⁷ examined expression of TNF-alpha, perforin, granzyme B, and Fas ligand in mononuclear cells from peripheral blood and blister fluid of subjects with delayed skin reactions to drugs: maculopapular exanthema, desquamative exanthema, Stevens-Johnson syndrome, and TEN. They documented, in acute lesions, a large increase in TNF-alpha (9-fold), perforin (6-fold), and granzyme B (7-fold) in patients compared with control subjects and found a high association between cytotoxic markers and disease severity ($P < .001$). Fas ligand was expressed by the cells only in TEN and Stevens-Johnson syndrome. Like the study by Nassif, the results indicate a cytotoxic mechanism, not just Fas-Fas ligand-mediated apoptosis, might be occurring and that T cells play an essential role.

The tremendous complexity of the T-cell response in IDHRs was demonstrated by Hashizume and colleagues who generated phenobarbital-specific T-cell clones and lines from peripheral blood mononuclear cells of patients with phenobarbital hypersensitivity and various degrees of cutaneous and extracutaneous involvement.³⁸ They found that most of the clones and lines exhibited a Th-2 phenotype, but those with Th-1 or Th-0 phenotype also constituted minor populations. T-cell receptor V-beta repertoire was diverse. Together, these studies show the importance of diagnostic and therapeutic strategies aimed toward T-cell responses in IDHR.

Insights for several common clinical questions regarding IDHRs were also realized. For example, there is concern that the selective cyclooxygenase-2 (COX-2) inhibitors could pose problems for NSAID-sensitive patients. However, this seems not to be the case, because a study published in the *Journal* over a year ago of 60 aspirin-sensitive asthmatic patients,³⁹ and several more studies this past year in patients with cutaneous (243 patients) or respiratory (40

patients) reactions to NSAIDs, showed that only a single patient developed mild urticaria.⁴⁰⁻⁴² A case report indicating a significant reaction to both rofecoxib and celecoxib in an NSAID-sensitive patient with urticaria adds a note of caution,⁴³ but the drugs seem generally safe for most NSAID-sensitive patients.

A clinical question addressed by Solensky and colleagues is whether administration of penicillin to persons with a history of reactions, but no current evidence of sensitization, can induce resensitization.⁴⁴ Fifty-three adults with a history consistent with IgE-mediated reactions to penicillin, but with negative skin test results, were challenged with 3 successive 10-day courses of penicillin V potassium. Forty-six patients completed the protocol and all tolerated the 3 courses of penicillin and maintained negative skin tests (resensitization rate, 0%; 95% confidence interval, up to 2.1%). This study result is limited to oral courses of penicillin in adults, many of whom had distant histories of reactions (the paper reviews additional studies in children and in persons receiving parenteral penicillin, both revealing a higher rate of resensitization), but it is helpful in indicating that repeated testing is generally not necessary in the context studied.

INSECT VENOM ALLERGY

The efficacy of insect venom immunotherapy (VIT) is well established, but some patients continue to react to stings despite therapy with standard doses (100 µg). Ruëff et al⁴⁵ identified patients who remained reactive to a sting challenge while treated with 100 µg monthly and treated them with 150 or 200 µg. Only 2 of 10 patients on 150 µg and 2 of 30 receiving 200 µg reacted to re-sting challenge. Three of the 4 patients who still reacted achieved protection after further dose increases. Interestingly, baseline serum tryptase was elevated in 28% of 32 subjects tested, indicating that a search for mastocytosis should be considered in patients refractory to VIT at standard doses.

The impact of VIT on quality of life was assessed by researchers from the Netherlands and Canada who developed and validated a health-related quality of life questionnaire for allergy to stinging insect venom, the VespID Allergy Quality-of-Life Questionnaire (VQLQ).⁴⁶ The instrument was used to compare patients treated with yellow jacket VIT to those receiving no VIT, just self-injectable epinephrine (by randomization if the patients consented) over 1 year.⁴⁷ Seventy-four patients agreed to be randomized (36 received VIT). The mean change in VQLQ score in the group randomized to VIT was 1.07 (95% confidence interval [CI], 0.68-1.46), compared with reduced scores in the group randomized to no VIT (-0.43; 95% CI, -0.71 to -0.16, $P < .001$). The study shows that VIT provides clinically important improvement in quality of life for 2 of every 3 patients treated.

An interesting observation concerning venom diagnostic testing was made by Hemmer and colleagues.⁴⁸ Cross-reactivity through shared hyaluronidase epitopes and true double sensitization have been assumed to

account for cosensitization (eg, approximately 50% copositive on serum IgE antibody tests) to honeybee and yellow jacket venom. IgE antibodies against cross-reactive carbohydrate determinants (CCD), however, may underlie this observation. Inhibition experiments were performed with pollen and food proteins and a derived neoglycoprotein containing allergenic carbohydrate determinants that are similar to those known for venom. Inhibition was noted in 2 of 14 single-positive honeybee venom sera, 2 of 16 single-positive yellow jacket venom sera, and 33 (80.5%) of 41 double-positive sera ($P < .00001$). The data suggest that carbohydrate-specific IgE is a major cause for the double positivity to honeybee and yellow jacket venom seen in patients with *Hymenoptera* allergy. It will be interesting to determine the proportion of positive tests to venom that are solely the result of IgE directed initially to CCD of plant origin (these antibodies appear to have low clinical relevance). The study result indicates that in the search for improved diagnostic tests, CCDs must be taken into careful consideration.

CONCLUSION

It is amazing to ponder the large number of practical, and yet unanswered, clinical questions facing the allergist-immunologist regarding the management of anaphylaxis and hypersensitivity reactions to foods, drugs, and insect venom. Thankfully, excellent clinical research, a portion of which has been highlighted here, continues to answer these questions. Importantly, we are also reaping the benefits that emerge from unraveling the immunopathophysiologic basis of these disorders, with improved diagnostic and therapeutic methods on the horizon. It is exciting to consider that the application of newer laboratory techniques, such as microarray technologies, the use of HLA tetramers, and others are likely to speed advances in the coming years and bring the clinical applications of these results to fruition in an expedient manner.

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