Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2009

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This review highlights some of the research advances in anaphylaxis and hypersensitivity reactions to foods, drugs, and insects, as well as advances in allergic skin disease that were reported in the *Journal* in 2009. Among key epidemiologic observations, several westernized countries report that more than 1% of children have peanut allergy, and there is some evidence that environmental exposure to peanut is a risk factor. The role of regulatory T cells, complement, platelet-activating factor, and effector cells in the development and expression of food allergy were explored in several murine models and human studies. Delayed anaphylaxis to mammalian meats appears to be related to IgE binding to the carbohydrate moiety galactose-α-1,3-galactose, which also has implications for hypersensitivity to murine mAb therapeutics containing this oligosaccharide. Oral immunotherapy studies continue to show promise for the treatment of food allergy, but determining whether the treatment causes tolerance (cure) or temporary desensitization remains to be explored. Increased baseline serum tryptase levels might inform the risk of venom anaphylaxis and might indicate a risk for mast cell disorders in persons who have experienced such episodes. Reduced structural and immune barrier function contribute to local and systemic allergen sensitization in patients with atopic dermatitis, as well as increased propensity of skin infections in these patients. The use of increased doses of nonsedating antihistamines and potential usefulness of omalizumab for chronic urticaria was highlighted. These exciting advances reported in the *Journal* can improve patient care today and provide insights on how we can improve the diagnosis and treatment of these allergic diseases in the future. (J Allergy Clin Immunol 2010;125:85-97.)

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

Abbreviations used

ACU:	Acquired cold urticaria
AD:	Atopic dermatitis
ADEH:	Atopic dermatitis with history of eczema herpeticum
ADVN:	Atopic Dermatitis Vaccinia Network
AE:	Atopic eczema
α-gal:	Galactose-α-1,3-galactose
APST:	Autologous plasma skin test
APT:	Atopy patch test
ASST:	Autologous serum skin test
CsA:	Cyclosporin A
CU:	Chronic urticaria
DC:	Dendritic cell
DKO:	Double knockout
dsRNA:	Double-stranded RNA
EAC:	Experimental allergic conjunctivitis
EPL:	ϵ-Polylysine
FAHF-2:	Food Allergy Herbal Formula-2
FLG:	Filaggrin
GDM:	Gestational diabetes
HBD:	Human β-defensin
IL-10R2:	IL-10 receptor 2 chain
KIT:	Mast/stem cell growth factor receptor gene
KO:	Knockout
MIF:	Macrophage migration inhibitory factor
NHL:	Non-Hodgkin lymphoma
OFC:	Oral food challenge
OIT:	Oral immunotherapy
OR:	Odds ratio
OVA:	Ovalbumin
PAF:	Platelet-activating factor
PG:	Prostaglandin
SEB:	*Staphylococcal aureus* enterotoxin B
TCI:	Topical calcineurin inhibitor
TCS:	Topical corticosteroid
TLR:	Toll-like receptor
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin
VIT:	Venom immunotherapy
VV:	Vaccinia virus

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This review highlights key advances in allergic skin disease, anaphylaxis, and hypersensitivity to foods, drugs, and insect venom selected primarily from more than 90 articles on these topics published in the *Journal of Allergy and Clinical Immunology* in 2009.

FOOD ALLERGY

Epidemiology and risk factors

Epidemiologic studies on peanut allergy continue to document astoundingly high prevalence rates among children. Ben-Shoshan

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OVA: Ovalbumin
PAF: Platelet-activating factor
PG: Prostaglandin
SEB: *Staphylococcal aureus* enterotoxin B
TCI: Topical calcineurin inhibitor
TCS: Topical corticosteroid
TLR: Toll-like receptor
Treg: Regulatory T
TSLP: Thymic stromal lymphopoietin
VIT: Venom immunotherapy
VV: Vaccinia virus

et al[1] followed up on a 2000-2002 cross-sectional prevalence study evaluating peanut allergy in 2005-2007 among kindergarten to grade 3 schoolchildren in Montreal, Quebec, Canada. The study applied allergy tests, including double-blind, placebo-controlled oral food challenges (OFCs) when possible. Among 5,161 families responding to the survey (64.2% response rate), after adjustment for missing data, an estimated 1.62% of the cohort (95% CI, 1.31% to 1.98%) had peanut allergy compared with 1.34% (95% CI, 1.08% to 1.64%) 5 years earlier (P = not significant). In a retrospective study of peanut allergy based on specialist referral and evaluations in the Australian Capital Territory, the estimated minimum incidence of peanut allergy in children by age 6 years born in 2004 was 1.15% compared with an estimate of 0.73% for those born in 2001.[2] The search for reasons behind the increase in atopy and food allergy remains an active area of study, with little evidence that maternal dietary allergen avoidance can reduce risk.[3] One theory is that delayed introduction of peanut averts an opportunity for development of oral tolerance while allowing potentially sensitizing, noningestion environmental exposure to proceed.

Fox et al[4] performed a questionnaire-based, case-control study evaluating maternal and household peanut consumption among 133 children with peanut allergy, 150 nonallergic children, and 160 children with egg but not peanut allergy. Although there was no difference in peanut consumption among the infants, household peanut consumption was significantly greater in the children with peanut allergy (18.8 g) compared with that in the children with egg allergy (1.9 g) or nonallergic control subjects (6.9 g). They found no relationship to maternal peanut ingestion but noted a dose-response risk relationship in household (environmental) exposure to peanut. The authors further postulate that early oral exposure might have been protective for those with environmental exposure. Finally, Visness et al[5] noted from the US National Health and Nutrition Examination Survey (2005-2006) an increased risk of food allergen sensitization (milk, egg, peanut, and shrimp) among participants with obesity (odds ratio [OR], 1.59; 95% CI, 1.28-1.98). The observation raises interesting questions about the relationship of the obesity epidemic to the apparent increase in food allergy and how systemic inflammation noted in obesity might influence an allergic outcome.

Pathophysiology, allergen characterization, and diagnosis

Several insights on the pathophysiology and expression of food allergy were reported from murine models. Working on the hypothesis that exposure to *Staphylococcus aureus* enterotoxin B (SEB) is associated with atopic disease and addressing some shortcomings in murine food allergy models that rely on LPS-hyporesponsive strains, Ganeshan et al[6] used orally administered SEB, with peanut and ovalbumin (OVA) showing T_H2-polarized responses (increased allergen-specific IgE and IgG1 levels), clinical reactions on rechallenge, and eosinophilia (circulating and intestinal). In a series of experiments using this model, it was noted that SEB impaired expression of TGF-β and regulatory T (Treg) cells, and in dose-ranging sensitization studies SEB promoted responses to peanut antigens by impairing low-dose tolerance. In murine models of oral antigen–induced diarrhea, in which initial sensitization is performed by means of intraperitoneal injection followed by repeated oral feeding of OVA, Brandt et al[7] evaluated the relative roles of IL-4 and IL-13. They found that IL-13 supplements the ability of IL-4 to induce allergic diarrhea by contributing to the oral sensitization phase rather than the effector phase and that blockade of both IL-4 and IL-13 after establishment of allergic diarrhea was only partially effective at reducing diarrhea. Yamada et al[8] used a similar model of allergic diarrhea and showed that antigen-inducible regulatory $CD8^+$ T cells could prevent sensitized mice from having allergic diarrhea through both IL-10–dependant and IL-10–independent mechanisms. The above-cited models include sensitization-inducing allergen-specific IgE and IgG1.

Khodoun et al[9] explored whether peanut could induce anaphylaxis without prior sensitization in mice pretreated with β-adrenergic receptor antagonists and IL-4 to increase sensitivity. They noted dose-dependent shock after intravenous injection of peanut extract and conducted a series of experiments to elucidate the mechanisms. They concluded that peanut extract contributed to shock through activation of complement with generation of C3a stimulating macrophages, mast cells, and basophils to produce platelet-activating factor (PAF) and histamine.