

28. Macy E, Mangat R, Bruchette RJ. Penicillin skin testing in advance of need: multiyear follow-up in 568 test result-negative subjects exposed to oral penicillins. *J Allergy Clin Immunol* 2003;111:1111-5.
29. Bittner A, Greenberger PA. Incidence of resensitization after tolerating penicillin treatment in penicillin-allergic patients. *Allergy Asthma Proc* 2004;25:161-4.
30. Kelkar PS, Li JT-C. Cephalosporin allergy. *N Engl J Med* 2001;345:804-9.
31. Greenberger PA. Utility of penicillin major and minor determinants for identification of allergic reactions to cephalosporins. *J Allergy Clin Immunol* 2005;115(suppl):S182.
32. Romano A, Guenant-Rodriguez R-M, Viola M, Pettinato R, Gueant J-L. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med* 2004;141:16-22.
33. Gruchalla RS. Drug allergy. *J Allergy Clin Immunol* 2003;111(suppl):S548-59.
34. Shear NH, Spielberg SP, Grant DM, Tang BK, Kalow W. Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. *Ann Intern Med* 1986;105:179-84.
35. Strom BL, Schinnar R, Apter AJ, Margolis DJ, Lautenbach E, Hennessy S, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med* 2003;349:1628-35.
36. Greenberger PA. Drug allergy part B: allergic reactions to individual drugs: low molecular weight. In: Grammer LC, Greenberger PA, editors. *Patterson's allergic diseases*. 6th ed. Philadelphia: Lippincott, Williams & Wilkins; 2002. p. 335-59.
37. Gollapudi RR, Teirstein PS, Stevenson DD, Simon RA. Aspirin sensitivity: implications for patients with coronary artery disease. *JAMA* 2004;292:3017-23.
38. Mathison DA, Lumry WR, Stevenson DD, Curd JG. Aspirin in chronic urticaria and/or angioedema: studies of sensitivity and desensitization. *J Allergy Clin Immunol* 1982;69:135.
39. Lam N-S, Yang Y-H, Wang L-C, Lin Y-T, Chiang B-L. Clinical characteristics of childhood erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in Taiwanese children. *J Microbiol Immunol Infect* 2004;37:366-70.
40. Rzyany B, Correia O, Kelly J, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of epileptic therapy: a case-control study. *Lancet* 1999;353:2190-4.
41. Nassif A, Bensussan A, Boumsell L, Deniaud A, Moslehi H, Wolkenstein P, et al. Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. *J Allergy Clin Immunol* 2004;114:1209-15.
42. Viard I, Wehrli P, Bullani R, Schneider P, Holler N, Salomon D, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 1998;282:490-3.
43. Abe R, Shimizu T, Shibaki A, Nakamura H, Watanabe H, Shimizu H. Toxic epidermal necrolysis and Stevens-Johnson syndrome are induced by soluble Fas ligand. *Am J Pathol* 2003;162:1515-20.
44. Bachot N, Revuz J, Roujeau J-C. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol* 2003;139:33-6.
45. Allam J-P, Paus T, Reichel C, Bieber T, Novak N. DRESS syndrome associated with carbamazepine and phenytoin. *Eur J Dermatol* 2004;14:339-42.
46. Tripathi A, Peters NT, Patterson R. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. In: Grammer LC, Greenberger PA, editors. *Patterson's allergic diseases*. 6th ed. Philadelphia: Lippincott, Williams & Wilkins; 2002. p. 289-94.
47. Tripathi A, Ditto AM, Grammer LC, Greenberger PA, McGrath KG, Zeiss CR, et al. Corticosteroid therapy in an additional 13 cases of Stevens-Johnson syndrome: a total series of 67 cases. *Allergy Asthma Proc* 2000;21:101-5.
48. Levine BB, Zolov DM. Prediction of penicillin allergy by immunological tests. *J Allergy* 1969;43:231-44.
49. Saxon A, Adelman DC, Patel A, Hajdu R, Calandra GB. Imipenem cross-reactivity with penicillin in humans. *J Allergy Clin Immunol* 1988;82:213-7.
50. Canaday BR. Anticonvulsant cross-sensitivity. *Am J Health Syst Pharm* 1997;54:2616-7.
51. Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin-converting enzyme inhibitor-associated angioedema. *JAMA* 1997;278:232-3.
52. Slater EE, Merrill DD, Guess HA, Roylance PJ, Cooper WD, Inman WHW, et al. Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition. *JAMA* 1988;260:967-70.
53. Samter M, Beers RF Jr. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Ann Intern Med* 1968;68:975-83.
54. Adkinson NF Jr, Thompson WL, Maddrey WC, Lichtenstein LM. Routine use of penicillin skin testing on an inpatient service. *N Engl J Med* 1971;285:22-4.
55. Stevenson DD, Simon RA. Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. *J Allergy Clin Immunol* 2001;108:47-51.
56. Szczeklik A, Nizankowska E, Bochenek G, Nagraba K, Mejza F, Swierczynska M. Safety of a specific COX-2 inhibitor in aspirin-induced asthma. *Clin Exp Allergy* 2001;31:219-25.
57. Woessner KM, Simon RA, Stevenson DD. Safety of high-dose rofecoxib in patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2004;93:339-44.
58. Quiralte J, Delgado J, Saenz de San Pedro B, Lopez-Pascual E, Nieto MA, Ortega N, et al. Safety of the new selective cyclooxygenase type 2 inhibitors rofecoxib and celecoxib in patients with anaphylactoid reactions to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 2004;93:360-4.
59. Cicardi M, Zingale LC, Bergamaschini L, Agostoni A. Angioedema associated with angiotensin-converting enzyme inhibitor use. *Arch Intern Med* 2004;164:910-3.
60. Greenberger PA, Patterson R. The prevention of immediate generalized reactions to radiocontrast media in high risk patients. *J Allergy Clin Immunol* 1991;87:867-72.

## 9. Food allergy

**Scott H. Sicherer, MD, and Hugh A. Sampson, MD** *New York, NY*

*This activity is available for CME credit. See page 5A for important information.*

**Food allergy, defined as an adverse immune response to food proteins, affects as many as 6% of young children and 3% to 4% of adults. Food-induced allergic reactions are responsible for a variety of symptoms involving the skin, gastrointestinal tract, and respiratory tract and might be caused by IgE-mediated and non-IgE-mediated (cellular) mechanisms. Our understanding of how food allergy represents an abrogation of normal oral tolerance is evolving. Although any food can provoke a reaction, relatively few foods are responsible for the**

**vast majority of significant food-induced allergic reactions: milk, egg, peanuts, tree nuts, fish, and shellfish. A systematic approach to diagnosis includes a careful history, followed by laboratory studies, elimination diets, and often food challenges to confirm a diagnosis. Many food allergens have been characterized at a molecular level, which has increased our understanding of the immunopathogenesis of food allergy and might soon lead to novel diagnostic and therapeutic approaches. Currently, management of food allergies consists**

of educating the patient to avoid ingesting the responsible allergen and to initiate therapy in case of an unintended ingestion. (J Allergy Clin Immunol 2006;117:S470-5.)

**Key words:** Food allergy, food hypersensitivity, oral tolerance, gastrointestinal food hypersensitivity, food allergens, anaphylaxis

Approximately 20% of the population alters their diet for a perceived adverse reaction to food, the cause of which might include a verifiable adverse immune response to a food protein (eg, food allergy), a host-specific metabolic disorder (eg, lactose intolerance), a response to a pharmacologically active (eg, caffeine) or toxic (eg, food poisoning) food component, or nonreproducible adverse reactions, such as food aversions (Table I).<sup>1-4</sup> Food-induced allergic disorders result from immunologic pathways that include activation of effector cells through food-specific IgE antibodies, cell-mediated reactions resulting in subacute or chronic inflammation, or combined pathways. Approximately 6% of young children and 3.7% of adults in the United States have a food allergy.<sup>1,5</sup> In young children the most common causal foods are cow's milk (2.5%), egg (1.3%), peanut (0.8%), wheat (approximately 0.4%), soy (approximately 0.4%), tree nuts (0.2%), fish (0.1%), and shellfish (0.1%). Early childhood allergies to milk, egg, soy, and wheat usually resolve by school age (approximately 80%).<sup>6</sup> Although peanut, tree nut, and seafood allergies are generally considered permanent, 20% of young children with peanut allergy experience resolution by age 5 years (recurrence is also possible).<sup>7,8</sup> Adults are therefore more likely to have allergies to shellfish (2%), peanut (0.6%), tree nuts (0.5%), and fish (0.4%). Reactions to fruits and vegetables are common (approximately 5%) but usually not severe. Allergy to seeds (eg, sesame) is being increasingly reported.<sup>9</sup> Genetic risk factors include a family history of atopic disorders, but environmental factors modulate the expression of food allergy, as evidenced by a recent doubling of the rate of peanut allergy in children.<sup>10</sup>

## PATHOGENESIS

Food allergy might result from a breach in oral tolerance to foods while they are being ingested (class 1 food allergy) or might result from sensitization to allergens apart from their exposure to the gastrointestinal tract, recognized instead during respiratory exposure (class 2 food allergy).<sup>11,12</sup> Class 1 food allergy typically occurs to food proteins that are generally stable to digestion that are encountered by infants or children during a presumed

Abbreviation used  
SPT: Skin prick test

window of immunologic immaturity. In contrast, class 2 food allergy is typically the result of sensitization to labile proteins encountered through the respiratory route, such as pollens resulting in IgE antibodies that recognize homologous epitopes on food proteins of plant origin (eg, pollen-food related syndrome). Murine studies<sup>13</sup> and evidence from human epidemiologic studies<sup>14</sup> indicate that class 1 allergens, such as egg and peanut, might evade oral tolerance by initial sensitizing exposure through the skin.

## Gut barrier

The gastrointestinal mucosal barrier is a complex physical (mucus, epithelial cell tight junctions, acid, and enzymes) and immunologic structure.<sup>12</sup> Abrogation of the barrier might promote food allergy; studies neutralizing stomach pH showed increased ability to promote allergic sensitization.<sup>15</sup> Similarly, developmental immaturity of components of the gut barrier (enzymatic activity and sIgA) might account for the increased prevalence of food allergy in infancy. However, a small amount of ingested food antigens is normally absorbed and transported throughout the body in an immunologically intact form, and oral tolerance prevails.<sup>1,12</sup>

## Oral tolerance induction

Antigen-presenting cells, especially intestinal epithelial cells and dendritic cells, and regulatory T cells play a central role in oral tolerance.<sup>12,16</sup> Five regulatory T cells have been identified in conjunction with intestinal immunity: T<sub>H</sub>3 cells, a population of CD4<sup>+</sup> cells that secrete TGF- $\beta$ ; T<sub>R</sub>1 cells, CD4<sup>+</sup> cells that secrete IL-10; CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells; CD8<sup>+</sup> suppressor T cells; and  $\gamma\delta$  T cells. Intestinal epithelial cells process luminal antigen and present it to T cells on an MHC class II complex but lack a second signal, thus suggesting their potential to play a role in tolerance induction.<sup>12</sup> Dendritic cells residing within the lamina propria and noninflammatory environment of Peyer's patches express IL-10 and IL-4, which favor the generation of tolerance.<sup>12,17</sup> Properties of antigens, dose, and frequency of exposure influence tolerance induction. High-dose tolerance involves deletion of effector T cells, whereas low-dose tolerance is mediated by activation of regulatory T cells with suppressor functions.<sup>12</sup>

Commensal gut flora might also influence the mucosal immune response. Gut flora is largely established in the first 24 hours after birth and is dependent on maternal flora and local environment. Studies feeding lactating mothers and their offspring *Lactobacillus GG* suggest that probiotics might be of benefit in preventing atopic dermatitis,<sup>18</sup> possibly by enhancing a T<sub>H</sub>1 cytokine response (IFN- $\gamma$ ),<sup>19</sup> but whether they will be useful for preventing food allergy remains to be demonstrated.

The Elliot and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine, New York.

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.

0091-6749/\$32.00

© 2006 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2005.05.048

**TABLE I.** Examples of causes of adverse reactions to foods\*

Intolerance (nonallergic hypersensitivity)
Lactose intolerance, galactosemia, alcohol
Pharmacologic
Caffeine (jitteriness), tyramine in aged cheeses (migraine), alcohol, histamine
Toxins
Bacterial food poisoning
Food allergy (see Table II for gastrointestinal disorders)
<i>IgE mediated</i> : urticaria, angioedema, morbilliform rashes, acute rhinoconjunctivitis, acute asthma, anaphylaxis, food-associated exercise-induced anaphylaxis
<i>Not IgE associated</i> : contact dermatitis, dermatitis herpetiformis, celiac disease, Heiner syndrome
<i>Mixed IgE-mediated/non-IgE-mediated</i> : atopic dermatitis, asthma
Masqueraders of food allergy
Auriculotemporal syndrome (facial flush with salivation), gustatory rhinitis, scombroid fish poisoning, anorexia nervosa

\*The revised nomenclature of the World Allergy Organization uses the term "hypersensitivity" to indicate a reproducible symptom or sign to a stimulus tolerated at the same dose by normal persons apart from an immunologic basis (eg, lactose intolerance would be termed "nonallergic hypersensitivity").

## Food allergens

The major food allergens identified as class 1 allergens are water-soluble glycoproteins 10 to 70 kd in size that are stable to heat, acid, and proteases; examples include proteins in milk (caseins), peanut (vicillins), and egg (ovomucoid) and nonspecific lipid transfer proteins found in apple (Mal d 3) or corn (Zea m 14).<sup>20,21</sup> Birch pollen Bet v 1 is an example of an allergen that can induce sensitization through the respiratory route and result in oral symptoms of pruritis to homologous class 2 allergens in raw apple (Mal d 1) or carrot (Dau c 1). A limited repertoire of related proteins make up the majority of food allergens (eg, the Cupin superfamily, Prolamin superfamily, and the plant defense system pathogenesis-related proteins).<sup>20</sup> A food is comprised of numerous proteins, and immune responses might be directed to particular ones with differing clinical consequences. For example, major class 1 allergens in peanut include Ara h 1, Ara h 2 and Ara h 3, whereas Ara h 8 is a Bet v 1 homologue class 2 peanut allergen that is less likely to be associated with severe clinical reactions.<sup>22</sup> Although many food proteins share regions of homology and cross-reactivity on allergy testing, clinical evidence of cross-reactivity is not as common.<sup>23</sup> Heating of foods might reduce or enhance allergenicity, depending on the protein and circumstances.<sup>21</sup>

## CLINICAL DISORDERS

The disorders can be classified on the basis of inter-related immunologic causes and the organ system or systems affected (Table I). The features of each disorder are described in detail in recent reviews.<sup>1,3,4</sup> Various gastrointestinal food-induced allergic disorders share

symptoms but can be differentiated by patterns of illness and diagnostic tests (Table II).<sup>1,24-26</sup> Additional gastrointestinal symptoms (colic, constipation, and reflux) have sometimes been attributed to food allergy. Food is the most common cause of outpatient anaphylaxis.<sup>27</sup> Common themes associated with fatal food-induced anaphylaxis include the following: reactions to peanut or tree nuts; victims are teenagers or young adults, usually with a known food allergy and asthma; and there is a failure to promptly administer epinephrine.<sup>28,29</sup>

## DIAGNOSIS

The evaluation begins with a thorough history and physical examination to consider a broad differential diagnosis (Table I). The history should determine the possible causal food or foods, quantity ingested, time course of reaction, ancillary factors (exercise, aspirin, and alcohol), and reaction consistency. Reason dictates that a food ingested infrequently is more likely responsible for an acute reaction than one previously tolerated. Symptoms such as urticaria after ingestion of a food are likely caused by a food allergy, whereas chronic symptoms (urticaria and asthma) are less likely attributable solely to food allergy.<sup>4</sup> Certain disorders are commonly associated with food allergy; for example, approximately 35% of young children with moderate-to-severe atopic dermatitis have a food allergy.<sup>30</sup> For chronic disorders, suspicions concerning particular foods are notoriously inaccurate (verified approximately 30% of the time).<sup>31</sup> In some cases confirmation of a diagnosis requires invasive testing, as outlined in Table II, but in most cases the diagnosis rests on determination of food-specific IgE antibodies, results of elimination diets, and responses to oral food challenges.<sup>4</sup>

For IgE-mediated disorders, skin prick tests (SPTs) provide a rapid means to detect sensitization.<sup>31</sup> However, a positive test response does not necessarily prove that the food is causal (specificity of <100%). Negative SPT responses essentially confirm the absence of IgE-mediated allergic reactivity (negative predictive accuracy of >95%). Consideration of the clinical history and disease pathophysiology is required to maximize the utility of test results. For example, a positive SPT response might be considered confirmatory when combined with a recent and clear history of a food-induced allergic reaction to the tested food. The increasing SPT wheal size is roughly correlated with an increasing likelihood of clinical allergy.<sup>32</sup> When evaluating allergy to many fruits and vegetables, commercially prepared extracts are often inadequate because of the lability of the responsible allergen, and therefore the fresh food might be used for testing.<sup>33</sup>

Serum tests to determine food-specific IgE antibodies (eg, RASTs or, more recently, quantitative measurements of food-specific IgE antibodies, such as the CAP System FEIA or UniCAP [Pharmacia-Upjohn Diagnostics, Uppsala, Sweden] and others) provide another modality to evaluate IgE-mediated food allergy. Increasingly higher

**TABLE II.** Gastrointestinal food allergies

Disorder	Mechanism	Symptoms	Diagnosis
Pollen-food allergy syndrome (oral allergy syndrome)	IgE mediated	Mild pruritus, tingling, and/or angioedema of the lips, palate, tongue or oropharynx; occasional sensation of tightness in the throat and rarely systemic symptoms	Clinical history and positive SPT responses to relevant food proteins (prick-plus-prick method); $\pm$ oral challenge—positive with fresh food, negative with cooked food
Gastrointestinal “anaphylaxis”	IgE mediated	Rapid onset of nausea, abdominal pain, cramps, vomiting, and/or diarrhea; other target organ responses (ie, skin, respiratory tract) often involved	Clinical history and positive SPT responses or RAST results; $\pm$ oral challenge
Allergic eosinophilic esophagitis	IgE mediated and/or cell mediated	Gastroesophageal reflux or excessive spitting-up or emesis, dysphagia, intermittent abdominal pain, irritability, sleep disturbance, failure to respond to conventional reflux medications	Clinical history, SPTs, endoscopy and biopsy, elimination diet and challenge
Allergic eosinophilic gastroenteritis	IgE mediated and/or cell mediated	Recurrent abdominal pain, irritability, early satiety, intermittent vomiting, FTT and/or weight loss, peripheral blood eosinophilia (in 50%)	Clinical history, SPTs, endoscopy and biopsy, elimination diet and challenge
Food protein–induced proctocolitis	Cell mediated	Gross or occult blood in stool; typically thriving; usually presents in first few months of life	Negative SPT responses; elimination of food protein $\rightarrow$ clearing of most bleeding in 72 h; $\pm$ endoscopy and biopsy; challenge induces bleeding within 72 h
Food protein–induced enterocolitis	Cell mediated	Protracted vomiting and diarrhea ( $\pm$ bloody) not infrequently with dehydration; abdominal distention, FTT; vomiting typically delayed 1-3 h after feeding	Negative SPT responses; elimination of food protein $\rightarrow$ clearing of symptoms in 24-72 h, challenge $\rightarrow$ recurrent vomiting within 1-2 h, $\sim$ 15% have hypotension
Food protein–induced enteropathy celiac disease (gluten-sensitive enteropathy)	Cell mediated	Diarrhea or steatorrhea, abdominal distention and flatulence, weight loss or FTT, $\pm$ nausea and vomiting, oral ulcers	Endoscopy and biopsy IgA; elimination diet with resolution of symptoms and food challenge; celiac-IgA anti-gliadin and anti-transglutaminase antibodies

Reprinted from Sampson HA. *J Allergy Clin Immunol*. 2003;111(suppl):S540-S547, with permission from the American Academy of Allergy Asthma & Immunology.  
FTT, Failure to thrive.

concentrations of food-specific IgE correlate with an increasing likelihood of a clinical reaction.<sup>34-39</sup> Table III<sup>35,37,40</sup> provides diagnostic levels of food-specific IgE for a variety of foods based primarily on studies of children in the United States.<sup>35,40</sup> When a patient has a food-specific IgE level exceeding the predictive (diagnostic) values, he or she is more than 95% likely to experience an allergic reaction. Different predictive values are being generated from emerging studies, which might represent nuances of diet, age, disease, and challenge protocols.<sup>38,39</sup> Undetectable serum food-specific IgE levels might be associated with clinical reactions for 10% to 25%.<sup>35</sup> Consequently, if there is a suspicion of possible allergic reactivity, a negative SPT response, physician-supervised food challenge result, or both are necessary to confirm the absence of clinical allergy.

Although not commercially available, determination of specific IgE-binding epitopes on an allergen might provide increased diagnostic utility.<sup>41,42</sup> The specific profiles of epitopes bound might reflect distinctions in binding to areas of an allergen that are dependent on protein folding (conformational epitopes) that are a feature of mild-

transient allergy versus areas that represent linear binding regions that are stable, reflecting severe-persistent allergy. Increasingly, studies are evaluating the utility of the atopy patch test.<sup>43-45</sup> Although the atopy patch test shows promise, there are currently no standardized reagents, methods of application, or interpretation.

The double-blind, placebo-controlled oral food challenge is the gold standard for the diagnosis of food allergies.<sup>46</sup> A number of reviews have outlined this procedure.<sup>46,47</sup> If the blinded challenge result is negative, it must be confirmed by means of an open and supervised feeding of a typical serving of the food to rule out a false-negative challenge result (approximately 1% to 3%). Open or single-blind oral food challenges are often used to screen for reactions.

## MANAGEMENT

The primary therapy for food allergy is to avoid the causal food or foods. New food-labeling laws effective in January 2006 require simple terms to indicate the presence

**TABLE III.** Predictive values of selected food allergens\*

Food	Mean age 5 y ~50% react†	Mean age 5 y ~95% react‡	Age ≤2 y ~95% react
Egg	2	7	2§
Milk	2	15	5
Peanut	2/5¶	14	–

\*Measured in kIU/L (Pharmacia CAP system FEIA).

†Perry et al.<sup>40</sup>

‡Sampson.<sup>35</sup>

§Boyano Martínez T, García-Ara C, Díaz-Pena JM, Muñoz FM, García Sánchez G, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy* 2001;31:1464-9.

||García-Ara et al.<sup>37</sup>

¶Value is 2 kIU/L for those with and 5 kIU/L for those without a clear history of peanut allergy.

of major food allergens (eg, “milk” instead of “casein”). Patients and caregivers should be encouraged to obtain medical identification jewelry, taught to recognize symptoms, and instructed on using self-injectable epinephrine and activating emergency services. Comprehensive educational materials are available through organizations such as the Food Allergy & Anaphylaxis Network (Fairfax, Va; 1-800-929-4040 or <http://www.foodallergy.org>). Most childhood food allergies resolve,<sup>6</sup> mandating repeated evaluations.<sup>35,48,49</sup>

Various medications can provide relief for certain aspects of food-induced disorders. Antihistamines might partially relieve symptoms of oral allergy syndrome<sup>50</sup> and IgE-mediated skin symptoms. An *in vitro* study showed the ability of activated charcoal to bind peanut proteins,<sup>51</sup> but clinical utility has not been studied, and therefore general use cannot be recommended. Anti-inflammatory therapies might be beneficial for allergic eosinophilic esophagitis—allergic eosinophilic gastroenteritis.<sup>52</sup>

Novel therapies for IgE-mediated food allergy have been reviewed.<sup>53</sup> Injections of anti-IgE antibodies (TNX-901) for treatment of patients with peanut allergy showed an increase in the average amount of peanut tolerated, but 25% of the group showed no improvement.<sup>54</sup> Traditional Chinese herbs showed efficacy in a murine model of peanut-induced anaphylaxis.<sup>55</sup> Standard immunotherapy for pollen-induced rhinitis might improve pollen-food allergy syndrome, although confirmation studies are needed.<sup>56</sup> Immunotherapeutic strategies to avoid IgE binding-activation and promote tolerance include use of engineered proteins that lack IgE-binding sites, small overlapping peptides, engineered chimeric molecules with allergen and Fcγ, and coadministration of T<sub>H</sub>1-promoting adjuvants (CpG and heat-killed bacteria).<sup>53,57,58</sup>

Approaches to delay or prevent allergy through dietary manipulation have been the subject of reviews and consensus statements.<sup>59,60</sup> Studies suggest a beneficial role for exclusive breast-feeding of infants at high risk for atopic disease for the first 3 to 6 months of life and avoidance of supplementation with cow's milk or soy formulas in favor of hypoallergenic formulas if breast-feeding is not possible. There are currently no conclusive studies indicating that manipulation of the mother's diet

during pregnancy or breast-feeding or the restriction of allergenic foods from the infant's diet will prevent the development of food allergy.<sup>14,59</sup> Currently, the American Academy of Pediatrics recommends a conservative approach, including that mothers of high-risk infants avoid allergens, such as peanuts and nuts, during lactation and that major allergens, such as peanuts, nuts, and seafood, be introduced after 3 years of age.<sup>60</sup>

In conclusion, characterization of food allergens at the molecular level and increasing understanding of immune regulatory function should lead to improved diagnostic and therapeutic approaches to food allergy.

## REFERENCES

- Sampson HA. Update on food allergy. *J Allergy Clin Immunol* 2004; 113:805-19.
- Sampson HA. Food allergy. Part 1: immunopathogenesis and clinical disorders. *J Allergy Clin Immunol* 1999;103:717-28.
- Sicherer SH. Food allergy. *Lancet* 2002;360:701-10.
- Sicherer SH, Teuber S. Current approach to the diagnosis and management of adverse reactions to foods. *J Allergy Clin Immunol* 2004;114:1146-50.
- Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. *J Allergy Clin Immunol* 2004;114:159-65.
- Wood RA. The natural history of food allergy. *Pediatrics* 2003;111: 1631-7.
- Hourihane JO, Roberts SA, Warner JO. Resolution of peanut allergy: case-control study. *BMJ* 1998;316:1271-5.
- Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: resolution and the possibility of recurrence. *J Allergy Clin Immunol* 2003;112:183-9.
- Derby CJ, Gowland MH, Hourihane JO. Sesame allergy in Britain: a questionnaire survey of members of the Anaphylaxis Campaign. *Pediatr Allergy Immunol* 2005;16:171-5.
- Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 2003;112:1203-7.
- Breiteneder H, Ebner C. Molecular and biochemical classification of plant-derived food allergens. *J Allergy Clin Immunol* 2000;106:27-36.
- Chehade M, Mayer L. Oral tolerance and its relation to food hypersensitivities. *J Allergy Clin Immunol* 2005;115:3-12.
- Hsieh KY, Tsai CC, Wu CH, Lin RH. Epicutaneous exposure to protein antigen and food allergy. *Clin Exp Allergy* 2003;33:1067-75.
- Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003;348: 977-85.
- Untersmayr E, Bakos N, Scholl I, Kundi M, Roth-Walter F, Szalai K, et al. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. *FASEB J* 2005;19:656-8.
- Mowat AM. Anatomical basis of tolerance and immunity to intestinal antigens. *Nat Rev Immunol* 2003;3:331-41.
- Frossard CP, Tropia L, Hauser C, Eigenmann PA. Lymphocytes in Peyer patches regulate clinical tolerance in a murine model of food allergy. *J Allergy Clin Immunol* 2004;113:958-64.
- Kalliomaki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003;361:1869-71.
- Pohjavuori E, Viljanen M, Korpela R, Kuitunen M, Tiittanen M, Vaarala O, et al. Lactobacillus GG effect in increasing IFN-gamma production in infants with cow's milk allergy. *J Allergy Clin Immunol* 2004;114:131-6.
- Breiteneder H, Radauer C. A classification of plant food allergens. *J Allergy Clin Immunol* 2004;113:821-30.
- Breiteneder H, Mills EN. Molecular properties of food allergens. *J Allergy Clin Immunol* 2005;115:14-23.
- Mittag D, Akkerdaas J, Ballmer-Weber BK, Vogel L, Wensing M, Becker WM, et al. Ara h 8, a Bet v 1-homologous allergen from peanut,

- is a major allergen in patients with combined birch pollen and peanut allergy. *J Allergy Clin Immunol* 2004;114:1410-7.
23. Sicherer SH. Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol* 2001;108:881-90.
  24. Sampson HA, Sicherer SH, Birnbaum AH. AGA technical review on the evaluation of food allergy in gastrointestinal disorders. *Gastroenterology* 2001;120:1026-40.
  25. Sampson HA, Anderson JA. Summary and recommendations: classification of gastrointestinal manifestations due to immunologic reactions to foods in infants and young children. *J Pediatr Gastroenterol Nutr* 2000;30(suppl):S87-94.
  26. Bischoff S, Crowe SE. Gastrointestinal food allergy: new insights into pathophysiology and clinical perspectives. *Gastroenterology* 2005;128:1089-113.
  27. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol* 1999;104:452-6.
  28. Sampson HA, Mendelson LM, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-4.
  29. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191-3.
  30. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;101:E8.
  31. Sampson HA. Food allergy. Part 2: diagnosis and management. *J Allergy Clin Immunol* 1999;103:981-9.
  32. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000;30:1541-6.
  33. Ortolani C, Spano M, Pastorello EA, Ansaloni R, Magri GC. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol* 1989;83:683-90.
  34. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444-51.
  35. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891-6.
  36. Boyano-Martinez T, Garcia-Ara C, Diaz-Pena JM, Martin-Esteban M. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. *J Allergy Clin Immunol* 2002;110:304-9.
  37. Garcia-Ara C, Boyano-Martinez T, Diaz-Pena JM, Martin-Munoz F, Reche-Frutos M, Martin-Esteban M. Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant. *J Allergy Clin Immunol* 2001;107:185-90.
  38. Osterballe M, Bindslev-Jensen C. Threshold levels in food challenge and specific IgE in patients with egg allergy: is there a relationship? *J Allergy Clin Immunol* 2003;112:196-201.
  39. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy* 2005;35:268-73.
  40. Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. *J Allergy Clin Immunol* 2004;114:144-9.
  41. Beyer K. Characterization of allergenic food proteins for improved diagnostic methods. *Curr Opin Allergy Clin Immunol* 2003;3:189-97.
  42. Shreffler WG, Beyer K, Chu TH, Burks AW, Sampson HA. Microarray immunoassay: association of clinical history, in vitro IgE function, and heterogeneity of allergenic peanut epitopes. *J Allergy Clin Immunol* 2004;113:776-82.
  43. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 2002;109:363-8.
  44. De Boissieu D, Wagué JC, Dupont C. The atopy patch tests for detection of cow's milk allergy with digestive symptoms. *J Pediatr* 2003;142:203-5.
  45. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996;97:9-15.
  46. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, et al. Standardization of food challenges in patients with immediate reactions to foods—position paper from the European Academy of Allergology and Clinical Immunology. *Allergy* 2004;59:690-7.
  47. Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, Sachs M, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988;82:986-97.
  48. Perry TT, Matsui EC, Conover-Walker MK, Wood RA. Risk of oral food challenges. *J Allergy Clin Immunol* 2004;114:1164-8.
  49. Shek LP, Soderstrom L, Ahlstedt S, Beyer K, Sampson HA. Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy. *J Allergy Clin Immunol* 2004;114:387-91.
  50. Bindslev-Jensen C, Vibits A, Stahl Skov P, Weeke B. Oral allergy syndrome; the effect of astemizole. *Allergy* 1991;46:610-3.
  51. Vadas P, Perelman B. Activated charcoal forms non-IgE binding complexes with peanut proteins. *J Allergy Clin Immunol* 2003;112:175-9.
  52. Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol* 2004;113:11-28.
  53. Nowak-Węgrzyn A, Sampson HA. Food allergy therapy. *Immunol Allergy Clin North Am* 2004;24:705-25.
  54. Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, et al. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003;348:986-93.
  55. Li XM, Zhang TF, Huang CK, Srivastava K, Teper AA, Zhang L, et al. Food Allergy Herbal Formula-1 (FAHF-1) blocks peanut-induced anaphylaxis in a murine model. *J Allergy Clin Immunol* 2001;108:639-46.
  56. Bolhaar ST, Tiemessen MM, Zuidmeer L, van Leeuwen A, Hoffmann-Sommergruber K, Bruijnzeel-Koomen CA, et al. Efficacy of birch-pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double-blind food challenges. *Clin Exp Allergy* 2004;34:761-9.
  57. Frick OL, Teuber SS, Buchanan BB, Morigasaki S, Umetsu DT. Allergen immunotherapy with heat-killed *Listeria monocytogenes* alleviates peanut and food-induced anaphylaxis in dogs. *Allergy* 2005;60:243-50.
  58. Zhu D, Kopley CL, Zhang K, Terada T, Yamada T, Saxon A. A chimeric human-cat fusion protein blocks cat-induced allergy. *Nat Med* 2005;11:446-9.
  59. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part III: critical review of published peer-reviewed observational and interventional studies and final recommendations. *Pediatr Allergy Immunol* 2004;15:291-307.
  60. American Academy of Pediatrics Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics* 2000;106:346-9.

## 10. Atopic dermatitis

Mark Boguniewicz, MD, and Donald Y. M. Leung, MD, PhD Denver, Colo

This activity is available for CME credit. See page 5A for important information.

Atopic dermatitis is a common chronic inflammatory skin disease often preceding the development of asthma and allergic disorders, such as food allergy or allergic rhinoconjunctivitis. Pathophysiology involves a complex series of interactions

between resident and infiltrating cells orchestrated by proinflammatory cytokines and chemokines. A deficiency of antimicrobial peptides might contribute to the propensity for colonization or infection by microbial organisms seen in atopic