

Food hypersensitivity and atopic dermatitis: Pathophysiology, epidemiology, diagnosis, and management

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Laboratory and clinical investigations over the past two decades have demonstrated that food allergy plays a pathogenic role in a subset of patients, primarily infants and children, with atopic dermatitis (AD). Approximately 40% of infants and young children with moderate to severe AD have food allergy, but identifying this subset of patients and isolating the relevant food allergens requires a high index of suspicion, the use of appropriate laboratory tests, and, in some cases, physician-supervised oral food challenges. Removal of the causal food protein(s) leads to clinical improvement but requires a great deal of education because most of the common causal foods (egg, milk, wheat, soy, peanut, and so forth) are ubiquitous in the food supply, and food elimination diets risk causing nutritional deficits. Fortunately, most food allergies resolve in early childhood, and food allergy is not a common cause for AD in older children and adults. (*J Allergy Clin Immunol* 1999;104:S114-22.)

Key words: Atopic dermatitis, food allergy, oral food challenges

PATHOPHYSIOLOGY OF FOOD ALLERGY IN ATOPIC DERMATITIS

In the early part of this century, Schloss¹ reported several cases of patients who had improvement in their eczematous skin lesions after avoiding specific foods. That report was followed by many others with conflicting findings²⁻⁵ and led to controversy about the role of specific food allergens in atopic dermatitis (AD).⁶ A major argument against the role of IgE antibody mediated allergy in AD has been that the histology of the lesions suggests a classic "type IV," cell-mediated hypersensitivity reaction.⁷ However, studies of the IgE response after allergen-induced mast cell activation have shown that terminal stages of IgE-mediated hypersensitivity reactions are also characterized by infiltration of monocytes and lymphocytes.^{8,9} In addition, the pattern of cytokine expression found in lymphocytes infiltrating acute AD lesions are predominantly those of the T_{H2} type (IL-4, IL-5, and IL-13),^{10,11} which is in contrast to the classic type IV cellular response in which cells express primarily IFN- γ (T_{H1} type).¹² The T_{H2} cytokines promote eosinophil influx and activated eosinophils,¹⁰ and

Abbreviations used

DBPCFC:	double-blind, placebo-controlled oral food challenge
AD:	atopic dermatitis
APC:	antigen presenting cells
HRF:	histamine releasing factors
SBHR:	spontaneous basophil histamine release
CLA:	cutaneous lymphocyte antigen

eosinophil products¹³ are found in lesional skin. Furthermore, these cytokines upregulate high-affinity IgE receptors on antigen presenting cells (APC), including Langerhans cells, and promote synthesis of IgE antibodies. IgE-bearing Langerhans cells are highly efficient at presenting allergen to T cells, activating primarily a T_{H2} profile.¹⁴⁻¹⁶ Thus IgE antibody and the T_{H2} cytokine milieu play a significant role in the pathogenesis of the lesions; the relation of this allergic pathogenesis to specific food allergens has been shown in both laboratory and clinical studies (Table I).

Laboratory investigation

Several lines of laboratory investigation support a role for food-specific IgE antibody in the pathogenesis of AD. Patients with AD generally have elevated concentrations of total¹⁷ and food-specific¹⁸ IgE antibodies. In a series of classic experiments, Walzer et al^{19,20} demonstrated that ingested food antigens penetrated the gastrointestinal barrier and are transported in the circulation to IgE-bearing mast cells in the skin. In these experiments, normal adults were passively sensitized by intradermal injection of serum from a patient with fish allergy. When these subjects subsequently ingested fish, a local wheal developed with flare reaction at the sensitized site. Indeed, in a number of studies in children with food-specific IgE antibody undergoing oral food challenges, positive challenges were accompanied by sharp increases in plasma histamine concentration²¹ and elaboration of eosinophil products,²² and food allergy-induced symptoms were related to activation of plasma eosinophils.²³

Mechanisms involving IgE molecules, in addition to direct allergen activation of cutaneous mast cells, may also be involved in the inflammation of AD. Children with AD who were chronically ingesting foods to which they were allergic were found to have increased "spontaneous" basophil histamine release (SBHR) from peripheral blood basophils in vitro compared with children without food allergy or normal control subjects.²⁴ When these children were placed on the appropriate diet

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TABLE I. Relation between food allergy and atopic dermatitis

Laboratory studies

- Allergenic protein able to activate skin mast cells after ingestion
- Presence of elevated food-specific IgE antibodies
- Plasma histamine elevation during positive oral food challenges
- Activation of eosinophils during positive food challenge
- Children allergic to milk with AD have CLA+, milk-reactive T cells
- Langerhans cells bear high-affinity IgE receptors, can present allergen to T cells
- T cells reactive to food allergen cloned from active lesions of AD
- Elevated histamine releasing factors in children when consuming diet with allergenic food
- AD lesions contain eosinophil products
- Increased spontaneous basophil histamine release while ingesting causal food

Clinical studies

- Appropriate dietary elimination results in amelioration of AD
- Double-blind, placebo-controlled oral challenge reproduces skin symptoms
- Hypoallergenic exclusion diets reduce severity and prevalence

excluding the causal food allergens, they had significant clearing of their skin and a significant fall in the SBHR. Peripheral blood mononuclear cells from subjects allergic to certain foods with high SBHR were also found to elaborate cytokines termed histamine releasing factors (HRFs) that could activate basophils from food-sensitive but not food-insensitive, children. It has been established that several isoforms of IgE are secreted,²⁵ and it is postulated that some of these isoforms interact with HRFs. Passive sensitization experiments in vitro with basophils from nonatopic donors and IgE from patients allergic to certain foods revealed that these basophils could be rendered sensitive to HRF.²⁴

Several studies have elucidated the role of food allergen-specific T cells in the inflammatory process underlying AD.²⁶ Food allergen-specific T cells have been cloned from active skin lesions and normal skin of patients with AD.²⁷⁻²⁹ Food allergen-specific IgE antibodies have also been routinely identified from peripheral blood in subjects with relevant food protein-induced AD. In fact, some workers have suggested that food-induced delayed onset of AD (increased rash developing at least 2 to 3 hours after oral challenge) is correlated with in vitro lymphocyte proliferative responses to the implicated food³⁰ or to delayed type hypersensitivity measured by skin patch testing.³¹ However, other workers have noted lymphocyte-proliferative responses in patients with immediate reactions to the relevant food proteins and in nonatopic control subjects.²⁸ The diagnostic use of the test remains marginal because there is considerable overlap in individual responses³²; the clinical utility of patch testing remains to be determined.

The development of AD in relation to food allergy may relate to the homing of allergen-specific T cells to the skin. Cutaneous lymphocyte-associated antigen

% Area
involved

Severity
Score

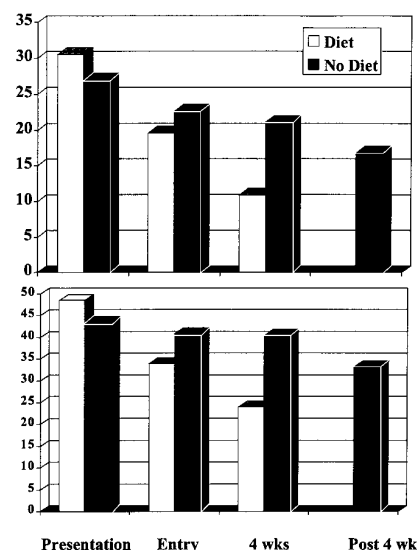


FIG. 1. Results of randomized trial of egg elimination in young children with AD. (Data from Lever R, MacDonald C, Waugh P, Aitchison T. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol* 1998;9:13-9.)

(CLA) is a homing molecule that interacts with E-selectin and directs T cells to the skin. Patients with milk-induced AD were studied and compared with control subjects with milk-induced gastrointestinal reactions without AD and to nonatopic control subjects.²⁷ Casein-reactive T cells from the children with milk-induced AD had significantly higher expression of CLA than *Candida albicans*-reactive T cells from the same patients and either casein or *C albicans*-reactive T cells from the control groups. Taken together, these studies have elucidated the role of allergic responses to food in the pathogenesis of AD.

Clinical studies

Clinical studies addressing the role of food allergy in AD have shown that elimination of the relevant food allergen can lead to improvement in skin symptoms, repeat challenge can lead to recrudescence of symptoms, and that disease can be at least partially prevented by prophylactically eliminating the more highly allergenic foods from the diets of infants and breastfeeding mothers.

A number of studies have addressed the therapeutic effect of dietary elimination in the treatment of AD. Atherton et al³³ reported that two thirds of children with AD between the ages of 2 and 8 years showed marked improvement during a double-blind cross-over trial of egg and milk exclusion carried on while in their homes. In this study, there was a high dropout and exclusion rate, environmental and other triggers of AD were not controlled for, and a significant order effect was found, all raising some question about the authors' conclusions. With a similar trial design, Neild et al³⁴ were able to demonstrate improvement in some patients during the

milk and egg exclusion phase, but overall no significant difference was seen in 40 patients completing the cross-over trial. Juto et al³⁵ reported that 7 of 20 infants with eczema had resolution of their rash and 12 of 20 improved on a highly restricted elimination diet. Hill et al³⁶ treated 8 children with severe AD with an elemental formula for 2 weeks followed by the addition of 2 vegetables and 2 fruits for 3 months. All patients experienced improvement in their eczema while on the diet and relapsed within weeks of discontinuing it. Although this supports a role for food allergy in the exacerbation of AD, most of these studies fail to control for other trigger factors, placebo effect, or observer bias.

In a prospective follow-up study³⁷ of 34 patients with AD, 17 children with food allergy who were appropriately diagnosed with the use of double-blind, placebo-controlled oral food challenges (DBPCFCs) and placed on an appropriate allergen elimination diet experienced a marked and significant improvement in their eczematous rash at 1- to 2- and 3- to 4-year follow-up in comparison to 12 control subjects who did not have food allergy and 5 children with food allergy who did not adhere to the diet. In a blinded, prospective study, Lever et al³⁸ performed a randomized, controlled trial of egg elimination in young children with AD and positive RAST to egg (majority under age 2 years) who were examined at a dermatology clinic. At the close of the study, egg allergy was confirmed by oral challenge and 55 children allergic to eggs were ultimately identified. There was a significant decrease in area affected (19.6% to 10.9%, $P = .02$) and symptom scores (33.9 to 24.0, $P = .04$) in the children avoiding eggs compared with control subjects (percent involved 21.9% to 18.9%; symptom score 36.7 to 33.5)(Fig 1).

Oral challenges have been used to demonstrate that repeat challenge with a causal food allergen can induce symptoms of pruritus and rash in children with food allergy-related AD. Because AD often has a waxing and waning course, the importance of performing DBPCFC for determining clinical reactivity was popularized for research and clinical purposes.³⁹ Indeed, Sampson et al^{37,40-42} have published a number of works that used DBPCFCs to identify causal food proteins in AD. In these studies spanning over 17 years, more than 2000 oral food challenges have been performed in more than 600 children, with 40% of the challenges resulting in reactions. Challenges were not performed if there was a history of a recent severe allergic reaction with evidence of IgE antibody to the implicated food. Cutaneous reactions occurred in three fourths of the positive challenges and generally consisted of pruritic, morbiliform, or macular eruptions in the predilection sites for AD. Isolated skin symptoms were seen in only 30% of the reactions; gastrointestinal (50%) and respiratory (45%) reactions also occurred. Most of the reactions occurred within an hour of beginning the oral challenge and required treatment with an antihistamine (50%) and some required epinephrine for respiratory reactions. Reactions to egg, milk, wheat, and soy accounted for almost 75% of the

reactions. Although patients were not challenged until their skin had achieved a stable baseline with mild AD, some patients with repeated reactions during series of daily challenges had increasingly severe AD, further indicating that ingestion of the causal food protein can trigger itching and scratching with recrudescence of typical lesions of AD.

In addition to the above-mentioned studies showing that AD could be ameliorated through elimination of causal food proteins and that reintroduction of the causal proteins elicited symptoms, studies have been undertaken to prevent food allergy and AD through dietary modification. Dietary modification has been attempted during pregnancy, lactation, and early feeding of "at risk" infants. In two series, infants from atopic families whose mothers excluded eggs, milk, and fish from their diets during lactation (prophylaxis group) had significantly less AD and food allergy at 18 months compared with infants whose mothers' diets were unrestricted.^{43,44} Follow-up at 4 years showed that the prophylaxis group had less AD, but there was no difference in food allergy or respiratory allergy.⁴⁴ In a prospective nonrandomized study of 1265 unselected neonates, the effect of solid food introduction was evaluated over a 10-year period.^{45,46} A significant linear relation was found between the number of solid foods introduced into the diet by 4 months of age and subsequent AD, with a 3-fold increase in recurrent eczema at 10 years of age in infants receiving 4 or more solid foods compared with infants receiving no solid foods before 4 months of age. A prospective, nonrandomized study comparing breast-fed infants who first received solid foods at 3 months or 6 months of age revealed reduced AD and food allergy at 1 year of age in the group avoiding solids for the 6-month period⁴⁷ but no significant difference in these parameters at 5 years.⁴⁸ In a study of 105 newborns at risk for atopy, breastfeeding or use of a hypoallergenic formula and delayed introduction of solid foods, along with measures to reduce environmental allergen exposure, resulted in a reduced prevalence of AD (14% vs 31%) compared with control subjects.⁴⁹ Because this series did not randomly assign patients, these studies must be considered suggestive until further randomized trials confirm the findings.

In a randomized study comparing breast feeding to the use of preterm formula in at risk preterm neonates, the breast-fed infants had a reduced prevalence of AD at 18 months of age (16% vs 41%).⁵⁰ In a comprehensive, prospective, randomized allergy prevention trial, Zeiger et al⁵¹⁻⁵⁴ compared the benefits of maternal and infant food allergen avoidance on the prevention of allergic disease in infants at high risk for allergic disease. Breast feeding was encouraged in both prophylaxis and control groups. In the prophylaxis group, the diets of lactating mothers were restricted of eggs, cow milk, and peanut; a casein hydrolysate formula was used for supplementation or weaning, and solid food introduction was delayed. The control infants received cow's milk formula for supplementation and the American Academy of Pediatrics' recommendations for infant feeding were fol-

TABLE II. General approach to evaluation of food allergy in AD

Consider evaluation:
Moderate to severe AD in infant/child
History of AD exacerbated by particular foods
Severe AD in teen/adult
Initial screen:
History, physical
Skin/RAST to implicated foods
Extra suspicion for "history positive" foods
Extra suspicion for common food allergens (milk, eggs, wheat, soy, peanut, tree nuts, fish, shellfish)
Eliminate IgE+ foods from diet (and consider elimination of other highly suspected foods)
No resolution: Food allergy not a cause
Resolution: Food allergy potential cause
Physician-supervised oral food challenges for suspected foods (unless previous severe reaction)
Open, single-blind or double-blind, placebo-controlled challenges
Add back foods as indicated from challenge results
Periodic repeat challenge to monitor resolution of allergy

lowed (peanuts, nuts, and fish are not recommended in the first 2 years). The prevalence of AD and food allergy in the prophylaxis group were reduced significantly during the first 2 years compared with the control group. However, the period prevalence of AD was no longer significantly different beyond 2 years. These investigators concluded that maternal and infant food allergen avoidance reduce food allergy and AD in the first 2 years but failed to modify allergic disease after 2 years of age. As a group, these studies clearly show the link between dietary allergens and the clinical manifestations of AD and the potential for disease modification through dietary intervention.

EPIDEMIOLOGY OF FOOD ALLERGY IN AD

The prevalence of food allergy in patients with AD varies with the age of the patient and severity of AD. By using DBPCFCs, Burks et al⁵⁵ diagnosed food allergy in 33% of 46 children with mild to severe AD from a population enrolled in part from a dermatology clinic (15 patients) and the remainder from referrals to the allergy clinic. In a larger study of 165 children with AD referred to the allergy clinic, Burks et al⁵⁶ diagnosed food allergy in 38.7%. Because many of these patients were referred to an allergist, an ascertainment bias favoring food allergy in these patients with AD was possible. To address this potential bias, Eigenmann et al⁴² evaluated 63 unselected children with moderate to severe AD (median age 2.8 years; range 0.4 to 19.4 years) who were referred to a university dermatologist. These children were evaluated with oral food challenges and 37% were diagnosed with food allergy (95% confidence interval, 25% to 50%). The studies did not stratify patients by severity^{42,55} or demonstrate a direct relation between severity of AD and the presence of food allergy.⁵⁶ However, Guil-

TABLE III. Foods responsible for majority of food-allergic reactions

Infants	Children	Older children/adults
Cow's milk	Cow's milk	Peanut
Eggs	Eggs	Tree nuts
Peanut	Peanut	Fish
Soy	Soy	Shellfish
	Wheat	
	Tree nuts (walnut, cashew, etc)	
	Fish	
	Shellfish	

let and Guillet⁵⁷ evaluated 250 children with AD and noted that increased severity of AD and younger age of patients was directly correlated with the presence of food allergy. Studies in adults with severe AD are very limited and have not shown a significant role for food allergy⁵⁸ or success in reducing symptoms during trials of elimination diets.⁵⁹

DIAGNOSIS

General approach

The diagnosis of food allergy in AD is complicated by several factors: (1) the immediate response to ingestion of causal foods is downregulated with repetitive ingestion, making obvious "cause and effect" relations by history difficult to establish; (2) various environmental factors (other allergens, irritants, infection) may play a role in the waxing and waning course of the rash, obscuring the effect of dietary changes; and, (3) patients have a propensity to generate IgE to multiple allergens, making diagnosis based solely upon laboratory testing impossible. A general approach to the diagnosis of food allergy in patients with AD is presented in Table II.

A complete history is obtained including not only the general medical history but also details concerning the dietary history and any acute reactions (hives, asthma, exacerbation of AD, and so on) to particular ingestion. The taking of this history is aided greatly by including dietary records such as a 3-day diet record completed at home. For breast-fed infants, a maternal dietary history is also obtained. Patients should also bring in labels from packaged foods so that ingredients can be reviewed.

As indicated by the history, selected foods are evaluated by tests for specific IgE. It must be appreciated that most children with AD have positive skin prick test results to several foods, but only about one third of positive skin test results correlate with positive food challenges.^{37,40} Moreover, although virtually any food protein can cause a reaction, only a small number of foods account for more than 90% of reactions⁵⁶ (Table III).^{40,60} In children, the most common foods causing reactions are eggs, milk, peanut, soy, wheat, tree nuts, and fish,^{40,56,60} and in children with AD and food allergy, two thirds are reactive to eggs.⁶¹ In adults, peanut, tree nuts, fish, and shellfish are most frequently implicated in sig-

TABLE IV. Positive predictive value (PPV) and negative predictive value (NPV) of food-specific IgE concentrations (kU/L) for predicting reactions upon oral challenge by using the Pharmacia CAP-RAST System FEIA

	>95% PPV	>90% PPV	>95% NPV	>90% NPV
Egg	6	2	—	0.6
Milk	32	23	0.8	1.0
Peanut	15	9	Best NPV = 85% at <0.35 kU/L	
Fish	20	9.5	0.9	5
Soy	Best PPV = 50% at 65 kU/L		2	5
Wheat	Best PPV = 75% at 100 kU/L		5	79

Results corrected to population prevalence of 10% for food allergy. There was no relation between IgE level and severity.

nificant food-allergic reactions,^{62,63} but, as discussed above, food allergy as a cause for AD in adults is not common. A rational approach is to screen children with moderate to severe AD for allergy to eggs, milk, peanut, soy, wheat, fish, and a tree nut (walnut, cashew) by using prick tests or RAST^{42,56} with additional testing for any other suspected foods. When there is a history suggestive of food-related skin disease and test results for IgE antibody to the food are positive, the first course of action is to completely eliminate all forms of the suspected food from the diet. Further initial testing usually is not needed in cases of severe, acute reactions or if dramatic improvement occurs. However, if symptoms are chronic as is generally the case with AD, and/or if a large number of foods are implicated, it is generally necessary to perform diagnostic oral food challenges. Food additives have been documented to cause flaring of AD but with a much lower prevalence.⁶⁴⁻⁶⁶ Because these reactions are generally not IgE-mediated, diagnosis requires trials of dietary elimination and oral challenge testing.

Skin and in vitro testing

There are several methods to detect food-specific IgE. Prick skin testing is performed by using a device such as a bifurcated needle or lance to puncture the skin through a glycerinated extract of food with appropriate positive (histamine) and negative (saline-glycerine) controls. A local wheal and flare response indicates the presence of food-specific IgE antibody. Results are evaluated at 15 minutes and wheals of 3 mm or larger are considered positive. Skin prick tests are most informative when they are negative because the negative predictive value of the tests is very high (>95%).^{67,68} Unfortunately, the positive predictive value is on the order of 30% to 50%.^{67,68} Thus a positive skin test result in isolation cannot be considered proof of clinically relevant food hypersensitivity, whereas a negative test virtually rules out IgE-mediated food allergy to the food in question. Intradermal allergy skin tests with food extracts give an unacceptably high false-positive rate and a greater risk for adverse reactions

to testing and should not be used.⁶⁸ The protein in commercial extracts of some fruits and vegetables are prone to degradation, so fresh extracts of these foods are more reliable.⁶⁹

Although slightly less sensitive than skin prick tests, in vitro tests for specific IgE antibodies (RAST) are practical in the screening of food allergy in most office settings. Like skin tests, a negative result is very reliable in ruling out an IgE-mediated reaction to a particular food, but a positive result has low specificity. A study by Sampson et al⁷⁰ compared the results of DBPCFCs in 196 patients with the levels of food-specific IgE antibody obtained by using the Pharmacia CAP System FEIA (reported in kU/L). As shown in Table IV, concentrations of food-specific IgE indicating the positive predictive values (PPV) and negative predictive values (NPV) for the test were calculated (corrected for a population prevalence of 10%). For eggs, milk, peanut, and codfish, levels above which clinical reactivity was highly likely (>95% PPV) were obtained. Thus patients with concentrations of food-specific IgE above these values would be likely to react upon ingestion of the food and would not necessarily need further evaluation. An oral challenge would be needed to confirm reactivity for children with levels falling below the 90% or 95% PPV. Tests such as measurement of IgG₄ antibody, provocation-neutralization, cytotoxicity, applied kinesiology, among other unproven methods are not useful.⁷¹

In addition to interpreting the tests for specific IgE in the context of the history and physical examination, several other specific issues must be considered. For example, patients frequently have positive skin tests and RASTs to several members of a botanical family or animal species, indicating immunologic cross-reactivity, but very few patients have symptomatic intrabotanical or intraspecies cross-reactivity. Legume cross-reactivity was evaluated in 69 children with AD by use of skin prick tests, RASTs, and Western blot analyses.^{72,73} Extensive immunologic cross-reactivity was demonstrated in many patients. However, only 2 patients were symptomatic to more than one legume when challenged orally. Both patients had a history of severe allergic reactions to peanut and mild reactions to a soy challenge. Similar studies with cereal grains showed significant IgE antibody cross-reactivity but little (about 20%) clinical cross-reactivity.⁷⁴ In our experience, about 50% of children allergic to eggs have IgE antibodies to chicken meat, but few (about 5%) have clinical reactivity. Similarly, about 50% of children who are allergic to milk have a positive skin prick test or RAST to beef but only about 10% exhibit clinical symptoms. Because of increased severity of reactions and greater possibility of misidentifying similar foods, consideration should be given to eliminating certain food families such as shellfish, fish,^{75,76} and tree nuts,⁷⁷ once an allergy to one type of these foods is identified. However, the practice of avoiding all foods within a botanical family when one member is suspected of provoking allergic symptoms generally appears to be unwarranted.

TABLE V. Examples of words used on food labels

MILK: artificial butter flavor, butter, butter fat, buttermilk, casein, caseinates (sodium, calcium, etc), cheese, cream, cottage cheese, curds, custard, Half & Half, hydrolysates (casein, milk, whey), lactalbumin, lactose, milk (derivatives, protein, solids, malted, condensed, evaporated, dry, whole, low-fat, non-fat, skim), nougat, pudding, rennet casein, sour cream, sour cream solids, sour milk solids, whey (delactosed, demineralized, protein concentrate), yogurt. MAY contain milk: brown sugar flavoring, natural flavoring, chocholate, caramel flavoring, high protein flour, margarine, Simplesse.
EGG: albumin, egg (white, yolk, dried, powdered, solids), egg substitute, eggnog, globulin, livetin, lysozyme, mayonnaise, maringue, ovalbumin, ovomucin, ovomucoid, Simplesse.
WHEAT: bread crumbs, bran, cereal extract, cracker meal, enriched flour, farina, gluten, graham flour, high gluten flour, high protein flour, malt, vital gluten, wheat bran, wheat germ, wheat gluten, wheat starch, whole wheat flour, spelt. MAY contain wheat: geatinized starch, hydrolyzed vegetable protein, modified food starch, modified starch, natural flavoring, soy sauce, starch, vegetable gum, vegetable starch.
SOY: hydrolyzed vegetable protein, miso, shoyu sauce, soy (flour, grits, nuts, milk, sprouts), soybean (granules, curd), soy protein (concentrate, isolate), soy sauce, textured vegetable protein (TVP), tofu. MAY contain soy: hydrolyzed plant protein, hydrolyzed soy protein, hydrolyzed vegetable protein, natural flavoring, vegetable broth, vegetable gum, vegetable starch.
PEANUT: cold pressed peanut oil, ground nuts, mixed nuts, Nu-Nuts artificial nuts, peanut, peanut butter, peanut flour. MAY contain peanut: African, Chinese, Thai and other ethnic dishes, baked goods (pastries, cookies, etc), candy, chili, chocholate candy, egg rolls, hydrolyzed plant protein, hydrolyzed vegetable protein, marzipan, nougat.

Oral food challenges

When there is suspicion of food-induced AD and improvement with appropriate dietary elimination, oral challenge with particular foods may become necessary to determine reactivity. Oral challenges are also needed to evaluate resolution of the allergy. Oral challenges usually should not be performed when there is a clear, recent history of food-induced airway reactivity or if there was a history of a severe reaction in the face of a positive test for IgE antibody to the implicated food. The practice of instructing patients to perform home challenges should not be undertaken because potentially severe reactions can result.⁷⁸ DBPCFCs are considered the gold standard for diagnosing food allergy.^{60,67,79} The procedure is labor intensive but can be modified to an office setting.⁷⁹ Patients avoid the suspected food(s) for at least 2 weeks, antihistamines are discontinued according to their elimination half-life, and asthma medications are reduced as much as possible. Children with moderate to severe AD may require several days of in-hospital topical skin care including hydrating baths, moisturizers, and topical steroids,⁸⁰ and, in some cases, antibiotics⁸¹ to establish a clear baseline before challenges. Intravenous access is necessary in some cases before challenges. Medical supervision and immediate access to emergency medications, including epinephrine, antihistamines, steroids, inhaled β -agonists, and equipment for cardiopulmonary resuscitation are required because reactions can potentially be severe. The authors generally perform two challenges each day, one containing the test food antigen and one containing placebo. The taste of the food is camouflaged so the patient is unaware of the contents of the challenge substance. Over a 60-to 90-minute period, up to 10 g of dehydrated powdered food is administered in 100 to 150 mL of liquid such as juice, blenderized food, or infant formula. The initial challenge dose is generally 100 to 500 mg and is increased in a step-wise fashion at 10- to 15-minute intervals until the entire 10 g is con-

sumed or a reaction occurs. If the history indicates that the implicated food must be ingested for a prolonged time period until skin reactions occur, the DBPCFC can be adjusted to evaluate this history. Each challenge is evaluated and scored using a standardized symptom sheet.⁸² Negative challenges are always confirmed with open feedings of larger, meal-sized portions of the food. Patients are also observed for delayed reactions. If allergy to only a few foods is suspected, single-blind or open challenges may be used to screen for reactivity. These challenges, of course, are subject to observer and patient biases and may overestimate true reactivity.

MANAGEMENT

In addition to medical management of AD (eg, therapy with hydration, moisturizers, topical corticosteroids, antibiotics, environmental avoidance of allergen and irritants), the mainstay of treatment for food allergy is dietary elimination of the offending food(s). The elimination of food proteins is a difficult task, and incomplete elimination of an incriminated food can lead to confusing results during trials of dietary elimination. In a milk-free diet, for example, patients must be instructed to not only avoid all milk products but also to read ingredient labels for key words that may indicate the presence of cow's milk protein. Terms such as casein, whey, lactalbumin, caramel color, and nougat may, for example, signify the presence of cow's milk protein. When vague terms such as "high protein flavor" or "natural flavorings" are used, it may be necessary to contact the manufacturer to determine if a particular protein, such as milk caseinate, is an ingredient. Examples of words used in food labeling are shown in Table V. Patients and parents must also be made aware that the food protein, as opposed to sugar or fat, is the ingredient being eliminated. For example, lactose-free milk contains cow's milk protein and many egg substitutes contain chicken egg proteins. Conversely, peanut oil and soy oil generally do not contain allergenic food

protein unless the processing method is one in which the protein is not completely eliminated (as with cold pressed or "extruded" oil).⁸³ When patients have been doing well for a period on the appropriate diet, flares of AD attributable to food are much more likely to represent an accidental ingestion of a previously identified but hidden common food allergen (eg, milk, egg) rather than a reaction to a new food. This is because elimination of a particular food can be more difficult than expected. For example, a utensil used to serve cookies both with and without peanut butter can contaminate the peanut-free cookie with enough protein to cause a reaction. Similarly, when a food without cow's milk or peanuts is processed on the same commercial equipment used for making cow's milk- or peanut-containing food, contamination can occur. Hidden ingredients can also cause a problem. For example, egg white may be used to glaze pretzels or peanut butter may be used to seal the ends of egg rolls. The Food Allergy Network, Fairfax, Va (800-929-4040) is a lay organization that provides educational materials to assist families, physicians, and schools in the difficult task of eliminating allergenic foods and in approaching the treatment of accidental ingestions. When multiple foods are eliminated from the diet, it is prudent to enlist the aid of a dietitian in formulating a nutritionally balanced diet.

In addition to elimination of the offending food, an emergency plan must be in place to treat severe reactions (respiratory reactions, anaphylaxis) caused by accidental ingestion. Patients with previous, severe, acute reactions to food ingestion or those with underlying asthma⁸⁴ are at particular risk, although anyone may, theoretically, experience a severe allergic reaction. Allergy to peanut, tree nuts, fish, and shellfish^{63,77,84-87} are responsible for the majority of severe, acute reactions. Injectable epinephrine and oral antihistamine should be readily available to treat patients at risk for severe reactions. The prompt administration of epinephrine at the first signs of a severe reaction must be emphasized because delayed administration of epinephrine has been associated with reports of fatal and near-fatal food allergic reactions.⁸⁴ Caregivers must be taught the indications for the use, method of administration of these medications and the need to seek immediate medical attention in the event of a reaction.

NATURAL HISTORY

Most children outgrow their allergies to milk, eggs, wheat, and soy,⁸⁸ and this usually corresponds to the resolution or improvement of their AD. However, patients allergic to peanut, tree nuts, fish, and shellfish are much less likely to lose their clinical reactivity,^{62,63,85,89-91} and these sensitivities may persist into adulthood. Approximately one third of children with AD and food allergy "lost" (or "outgrew") their clinical reactivity over 1 to 3 years with strict adherence to dietary elimination, which was believed to have aided in a more timely recovery.³⁷ Elevated concentrations of food-specific IgE may indi-

cate a lower likelihood of developing tolerance in the subsequent few years.^{92,93} However, skin prick test results do not correlate with loss of clinical reactivity and remain positive for years after the food had been reintroduced into the diet.³⁷ Thus it is recommended that patients be rechallenged intermittently (eg, eggs every 2 to 3 years; milk, soy, wheat every 1 to 2 years; foods other than peanut, nuts, fish, and shellfish every 1 to 2 years) to determine whether their food allergy persists, so that restriction diets may be discontinued as soon as possible. Although food allergy and AD may resolve, these infants and children are, unfortunately, likely to have other allergic sensitivities and atopic diseases. Asthma and respiratory allergies develop in approximately 90% of children with AD and egg-specific IgE antibody.^{94,94}

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