

Review Article

Food allergy: When and how to perform oral food challenges

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In many situations, the diagnosis of food allergy rests simply upon a history of an acute onset of typical symptoms, such as hives and wheezing, following the isolated ingestion of a suspected food, with confirmatory laboratory studies of positive prick skin tests or Radioallergosorbent tests. However, the diagnosis is more complicated when multiple foods are implicated or when chronic diseases, such as asthma or atopic dermatitis, are evaluated. The diagnosis of food allergy and identification of the particular foods responsible is also more difficult when reactions are not mediated by IgE antibody, as is the case with a number of gastrointestinal food allergies. In these latter circumstances, well-devised elimination diets followed by physician-supervised oral food challenges are critical in the identification and proper treatment of these disorders. Because childhood food allergies to common allergenic foods such as milk, egg, wheat and soy are usually outgrown, oral food challenges are also an integral part of the long-term management of these children.

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The accurate diagnosis of food allergic reactions is predicated upon an understanding of the pathophysiology of allergic responses, an understanding of the illnesses related to food allergy, and a grasp of the most common foods resulting in reactions. The public perceives food allergy to be very common, affecting one in five persons (1). Although the prevalence of some of the specific disorders is unknown, food allergy is believed to affect 1.5–2.5% of adults (2) and 6–8% of children (3). The reason for the misperception that food allergy is so common is due to the fact that a large variety of maladies have been related to the common and frequent act of eating. The physician evaluating potentially food-allergic patients must be able to differentiate a variety of adverse food reactions from those that are allergic (immunologic) in nature.

Adverse reactions to foods may be defined as toxic or non-toxic (4). Toxic reactions occur in anyone who ingests a sufficient quantity of the tainted food, regardless of individual sensitivity. Examples of toxic reactions include reactions to histamine in scombroid fish poisoning or to

bacterial toxins in food poisoning. In contrast, non-toxic adverse reactions to food depend on individual susceptibility and are either non-immune-mediated (food intolerance) or immune-mediated (food allergy).

Allergic reactions to food are either IgE-mediated or non-IgE-mediated. The role of IgE antibody in food allergy is well established (5), and symptoms typically involve the skin, respiratory and/or gastrointestinal tract (6). While the pathogenesis of non-IgE-mediated reactions in food allergy is not as clearly defined, T cells and macrophages are likely to play a role. Illnesses due to these non-IgE-mediated immunologic responses to food affect the same organ systems as the IgE-mediated forms (Table 1).

Food allergic reactions account for approximately 20% of the acute urticaria (7), 1–2% of chronic urticaria (8), and approximately one-third of moderate to severe atopic dermatitis in children (9,10). Food allergy does not appear to be a common cause of atopic dermatitis in adults. In contrast to food allergy-related skin disease which is primarily mediated by IgE antibody,

Table 1. Examples of IgE- and non-IgE-mediated food allergic diseases

	IgE-mediated	Non-IgE mediated
Skin	Urticaria Atopic dermatitis	Atopic dermatitis (subset) Dermatitis herpetiformis
Gastrointestinal	Oral allergy syndrome Gut anaphylaxis Eosinophilic gastroenteritis	Enterocolitis syndrome Proctocolitis Eosinophilic gastroenteritis Enteropathy (including celiac) Reflux (subset)
Respiratory	Asthma Rhinitis	Heiner syndrome

food allergic responses of the gastrointestinal tract are primarily non-IgE-mediated. These illnesses include celiac disease, eosinophilic gastroenteritis, proctocolitis and enterocolitis. Characteristics of these illnesses are shown in Table 2. Among food allergies affecting the gut, oral allergy syndrome (11), characterized by oral pruritus caused primarily by fresh fruits and vegetables with proteins cross-reacting with pollens, and a subset of patients with eosinophilic gastroenteritis, have IgE-mediated disease. Food allergy is not a common cause of isolated upper or lower respiratory tract disease in adults (< 1%), but may affect up to 5% of children with asthma (12) and 1–2% of children with allergic rhinitis (13). Food allergy is the most common cause of anaphylaxis (14,15). Food-related, exercise-induced anaphylaxis is one subtype where a combination of exercise with ingestion of a particular food, or more rarely any food, leads to anaphylaxis (16). Food allergy is not confirmed to be a cause for behavioral disorders, migraine or fatigue, although dietary issues and sensitivity to components of foods (e.g. tyramine in migraine, caffeine in behavior) may play a role.

Although, theoretically, any food protein can trigger an allergic response, a small group of foods account for the majority of reactions. The foods most commonly responsible for significant allergic reactions in children are milk, egg, wheat, soy, peanut, tree nuts, fish and shellfish (3,17–19). Allergy to food coloring and preservatives is very rare (< 1%) (20). Allergies to milk, egg, wheat and soy are usually outgrown in early childhood, leaving adults with the more persistent allergies to peanuts, tree nuts, fish and shellfish. The presence of an allergy to one member of a food group does not necessarily indicate that there would be allergic reactions to other members of the food group (21). For example, only 5% with legume allergy react to more than one type of bean (22), 15% with grain allergy react to more than one

grain, about one-third with tree nut allergy (23) react to more than one type of tree nut. Some individuals with fish allergy react to most types of fish while others may react to only one species.

General approach to diagnosis

An evaluation for food allergy is warranted in patients who experience the common clinical manifestations of food allergy. The initial evaluation, beginning with a thorough history and physical examination, must consider a broad differential diagnosis, including metabolic disorders, anatomic abnormalities, malignancy, pancreatic insufficiency and non-immunologic adverse reactions to foods, as well as many other disorders that could lead to similar symptoms. Allergic reactions to substances other than foods (e.g. animal dander, moulds, dust, etc.) must also be considered. Once food allergy is identified as a likely cause of symptoms, confirmation of the diagnosis and identification of the implicated food(s) can proceed. Depending upon the history, this procedure may be limited to testing for IgE antibody to the specific food, or may involve oral food challenge testing.

The history and physical examination

The history and physical examination must review general medical concerns and the atopic disposition. In relation to foods, a careful history should focus upon the symptoms attributed to food ingestion (type, acute versus chronic), the food(s) involved, consistency of reactions, the quantity of food required to elicit symptoms, the timing between ingestion and onset of symptoms, the most recent reaction/patterns of reactivity, and any ancillary associated activity that may play a role (e.g. exercise, alcohol ingestion). The information gathered will be used to determine the best mode of diagnosis or may lead to dismissal of the problem from the history alone. In the case of acute reactions after isolated ingestion of a particular food, such as acute urticaria or anaphylaxis, the history may clearly implicate a particular food and a positive test for specific IgE antibody would be confirmatory. If the ingestion was of mixed foods and the causal food was uncertain (e.g. fruit salad), the history may help to eliminate some of the foods – those frequently ingested without symptoms – and specific tests for IgE may help to further narrow the possibilities.

In chronic disorders such as atopic dermatitis or asthma, it is more difficult to pinpoint causal

Table 2. Characteristics of Non-IgE mediated disease of the gut

Disease	Age onset	Duration	Characteristics
Proctocolitis	Newborn	1 years	Bloody stools, eosinophilic colitis, no systemic symptoms. Cause: milk/soy.
Enterocolitis	Infant	1–2 years	Failure to thrive, shock, lethargy, chronic vomiting, diarrhea. Cause: milk/soy.
Eosinophilic gastroenteritis	Any	Unknown	Eosinophilic infiltrate, possible obstruction, abdominal pain, failure to thrive. Cause: multiple foods
Enteropathy	Any	Unknown	Malabsorption, villus atrophy. Cause: milk/soy.

food(s). The history is helpful, but since these disorders have a waxing and waning course, false associations to food ingestions are common (19). A similar problem arises with gastrointestinal reactions that are often delayed in onset following ingestion of causal foods. Patients may also attribute a host of chronic disorders to food ingestion (arthritis, fatigue, behavioral problems, etc.) and pinpointing particular foods to target becomes difficult. The approach to diagnosis in these chronic disorders usually requires elimination diets and oral food challenges to confirm or refute suspected associations. This is particularly the case for the non-IgE-mediated reactions or those attributed to food dyes/preservatives in which ancillary laboratory testing is not helpful.

Tests for specific IgE antibody

In the evaluation of IgE-mediated food allergy, specific tests can help to identify, or exclude, responsible foods. One method to determine the presence of specific IgE antibody is prick-puncture skin testing. While the patient is off anti-histamines, a device, such as a bifurcated needle or lancet, is used to puncture the skin through a glycerinated extract of a food and appropriate positive (histamine) and negative (saline–glycerine) controls. A local weal and flare response indicates the presence of food-specific IgE antibody (a weal diameter 3 mm or greater than a saline control is considered positive (24)). Prick skin tests are most valuable when they are negative since the negative predictive value of the tests is very high (over 95%) (25,26). Unfortunately, the positive predictive value is on the order of only 50% (25,26). Thus, a positive skin test in isolation cannot be considered proof of clinically relevant hypersensitivity. Intra-dermal allergy skin tests with food extracts give an unacceptably high false-positive rate, have been associated with systemic reactions including fatal anaphylactic reactions and should not be used (26).

In vitro tests for specific IgE Radioallergosorbent test (RAST) are also helpful in the

evaluation of IgE-mediated food allergy (27). Unlike skin tests, RASTs can be used while the patient is taking anti-histamines and do not depend on having an area of rash-free skin for testing. 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 and Ho (27) compared the results of double-blind, placebo-controlled food challenges (DBPCFCs) in 196 children with moderate to severe atopic dermatitis to the levels of food-specific IgE antibody obtained using the Pharmacia CAP System FEIA (reported in kU/l). As shown in Table 3, concentrations of food-specific IgE indicating the positive (PPV) and negative (NPV) predictive values for the test were calculated. For egg, milk, peanut and codfish, levels above which clinical reactivity was highly likely ($> 95\%$ PPV) were established. 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 (oral challenges). An oral challenge would be needed to confirm reactivity for children with levels falling below 90 or 95% PPV. It must be kept in mind that the results of this study were based upon children with moderate to severe atopic dermatitis and the values may not apply to other settings (e.g. history of acute anaphylaxis).

In addition to the high false-positive rate of tests for food-specific IgE antibodies, several other issues complicate interpretation of the tests. It is not uncommon for patients to have positive skin tests and RASTs to several members of a botanical family or animal species. As discussed above, this usually represents immunologic cross-reactivity but may not represent clinical reactivity. For example, most peanut-allergic patients will have positive skin tests to at least a few of the other members of the legume family (28). Further testing with oral challenges, if the history does not resolve the issue, would be required. More importantly, the foods to be tested should be carefully selected to include only those suspected to be at issue, in order to avoid false-positive skin

Table 3. Relationship of food-specific IgE concentrations to clinical reactions in children with atopic dermatitis

	> 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		5
Soy	Best PPV = 50% at 65 kU/l		0.9	5
Wheat	Best PPV = 75% at 100 kU/l		2	5
			5	79

Positive predictive value (PPV) and negative predictive value (NPV) of food-specific IgE concentrations (in kU/l using Pharmacia CAP-RAST[®]) for predicting reactions upon oral challenge in children with moderate to severe atopic dermatitis.

tests that inappropriately lead to questions about foods that have been previously tolerated. An additional issue is that the proteins in commercial extracts of some fruits and vegetables are prone to degradation, so fresh extracts of these foods are more reliable (29) and the 'prick-prick' manner of testing may be indicated. Lastly, one should be wary of tests such as measurement of IgG₄ antibody, provocation-neutralization, cytotoxicity, applied kinesiology, among other unproved methods that are not useful (30).

Food elimination diets

There are three types of elimination diets: elimination of one or several foods suspected to be causing symptoms, elimination of all but a defined group of 'allowed' foods (oligo-antigenic diet), and an elemental diet consisting of a hydrolyzed formula or an amino acid-based formula. The type of elimination diet used will depend upon the clinical scenario being evaluated and the results of tests for IgE antibody. The first type of diet involves the elimination of one or several foods. This may be the obvious course of action when an isolated food ingestion (e.g. peanut) causes a sudden acute reaction and there is a positive test for IgE to the food. This would also represent a therapeutic intervention. However, eliminating one or a few suspected foods from the diet when the diagnosis is not so clear (asthma, atopic dermatitis, chronic urticaria) may be a crucial step in determining whether food is causal in the disease process. If symptoms persist, the eliminated food(s) is (are) excluded as a cause of symptoms. The length of trial depends upon the type of symptoms, but 1–6 weeks is usually the range required.

The second type of elimination diet consists of eliminating a large number of foods suspected to cause a chronic problem (usually including those that are common causes of food-allergic reactions as described above) and giving a list of 'allowed foods'. This 'oligo-antigenic' diet is useful for evaluation of chronic disorders when a larger

number of foods are suspected. In most cases, this is the situation with atopic dermatitis or chronic urticaria. An example of such a diet may be one that allows lamb, rice (all forms), cooked apple, broccoli, asparagus, spinach, lettuce, sweet potato, salt, sugar, vinegar and olive oil. Individualization for this type of elimination diet is almost always needed. The advantage of this diet is that a nutritionally balanced, palatable diet is maintained while most possible causal foods are removed. The primary disadvantage is that, if symptoms persist, the cause could still be attributed to foods left in the diet.

The third type of elimination diet is an elemental diet in which calories are obtained from a hydrolyzed formula or, preferably, from an amino-acid based formula. Meat-based formulas have also been suggested (31). A variation is to include a few foods likely to be tolerated (but, again, this adds the possibility that persistent symptoms are caused by these foods). This diet is extremely difficult to maintain in patients beyond infancy. In extreme cases, nasogastric feeding of the amino-acid based formula can be achieved, although some patients can tolerate the taste of these formulas with the use of flavoring agents provided by the manufacturers. This diet may be required when the diets mentioned above fail to resolve symptoms, but suspicion for food-related illness remains high. It is also required in disorders associated with multiple food allergies such as allergic eosinophilic gastroenteritis (AEG). With AEG, prolonged elimination, 3–6 weeks, is typically needed to achieve resolution of symptoms (32).

In any of these diets, specific information must be carefully reviewed to ensure adherence to the diet. It is common for families to make errors. In a milk-free diet, for example, patients must be instructed not only to avoid all milk products, but also to read ingredient labels for key words, which may indicate the presence of cow's milk protein. Terms such as casein, whey and lactalbumin, for example, signify the presence of cow's milk protein (Table 4). When vague terms such as

Table 4. Examples of words/ingredients on food labels indicating common allergens in the USA

Food	Ingredients
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, chocolate, caramel flavoring, high protein flour, margarine, Simplese [®]
Egg	Albumin, egg (white, yolk, dried, powdered, solids), egg substitute, eggnog, globulin, livetin, lysozyme, mayonnaise, meringue, ovalbumin, ovomucin, ovomucoid, Simplese [®]
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 heat flour, spelt
MAY contain wheat	Gelatinized 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, chilli, chocolate candy, egg rolls, hydrolyzed plant protein, hydrolyzed vegetable protein, marzipan, nougat

‘high protein flavor’ or ‘natural flavorings’ are used, it may be necessary to call the manufacturer to determine whether a particular protein, such as milk, is an ingredient. Patients 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.

Contamination with the food protein being eliminated is also an issue. For example, a spatula 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 chocolate candies without peanuts are processed on the same equipment used for making peanut-containing candy, 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 as a ‘secret ingredient’ in sauces. Lay organizations such as the Food Allergy Network (Fairfax, Virginia, USA; <http://www.foodallergy.org>) assist families and physicians in the difficult task of eliminating the allergenic foods. When multiple foods are eliminated from the diet, it is prudent to enlist the aid of a dietitian in formulating a nutritionally balanced diet.

Food challenges

General considerations

Oral food challenges are performed by feeding the patient the suspected food under physician observation. There are several settings in which physician-supervised oral food challenges are

required for diagnosis of food-allergic disease. In general, when several foods are under consideration as a cause of symptoms, tests for specific IgE are positive and elimination resulted in resolution of symptoms, then oral challenge testing for each food eliminated would be indicated to allow expansion of the diet. For acute anaphylactic-type reactions without evidence of food-specific IgE for a food highly suspected to have caused a significant reaction, a physician-supervised challenge would be indicated to safely re-introduce the food (in cases of a false-negative skin/RAST test). If suspicion concerning particular food(s) remains high despite elimination without resolution of symptoms, challenge(s) may be needed to settle the issue. If tests for specific IgE are not relevant to the illness, challenges may be the only means of diagnosis. Oral challenges are also an integral part of following patients likely to lose their clinical reactivity to the food in question. Since skin tests may remain positive for years following the achievement of clinical tolerance to a particular food, oral food challenges are often the only means to determine whether the allergy has been ‘outgrown’.

There are settings in which oral challenges may be optional or contra-indicated. Severe anaphylaxis to an isolated ingestion, with a positive test for specific IgE antibody to the causal food, is one clear example of a relative contra-indication for oral challenge (although this is also individualized since follow-up challenge for determination of resolution of allergy may be appropriate in some settings). If the food being eliminated is not a major part of the diet (e.g. kiwi fruit), then challenge is not usually warranted. If several

members of a food family are being eliminated, but the food family is not a major part of the diet (e.g. tree nuts), these same rules may apply.

Challenge type and setting

When it is decided that an oral food challenge is needed, the first step is to discuss, in detail, the procedure and its risks and benefits with the family/patient. The next step is to consider whether the test can be performed at home or needs to be under direct physician supervision. There are many specific issues that must be considered in this particular decision. In general, whenever there is an even remote potential for an acute and/or severe reaction, physician supervision is mandatory. This decision for a supervised challenge includes, but is not limited to, a history of prior significant reactions and/or positive tests for IgE to the food in question. In considering this issue, a distinction should also be made between 'challenging' a food and 'adding a food back to the diet'. For example, if many foods were eliminated for a chronic, non-IgE-mediated disease and acute reactions are not an issue, adding the previously tolerated food back to the diet at home is not a 'challenge' and would not be suspected to cause an acute, severe reaction. In a similar manner, a chronic disease that did respond to elimination, but was not severe and not IgE-mediated (abdominal pain, headaches, behavioral issues), may be challenged by adding one food at a time back into the diet for 5 days for each food at home while monitoring for recurrence of symptoms.

For oral food challenges performed under physician supervision, several issues must be taken into consideration. Oral challenges can elicit severe, anaphylactic reactions, so the physician must be comfortable with this potential for reaction and be prepared with emergency medications and equipment to promptly treat such a reaction. Medications to have immediately available, in pre-measured doses based upon weight, include epinephrine, anti-histamines, corticosteroids, inhaled β -agonists, type-2 histamine blockers (cimetidine), activated charcoal and intravenous fluid (volume expanders such as normal saline or colloids). Performing the challenge in a hospital setting may be necessary if the challenge is considered 'high risk' (positive test for IgE, previous severe reaction, asthmatic patient). In high-risk challenges, it may be prudent to have intravenous access prior to commencing challenges. Patients avoid the suspected food(s) for at least 2 weeks, anti-histamines are discontinued according to their

elimination half-life, and asthma medications are reduced as much as possible prior to undertaking the challenge. The patients should be examined carefully prior to challenge to confirm that they are not already having chronic symptoms and to determine their 'baseline'. For some diseases (e.g. severe atopic dermatitis), hospitalization may be necessary to treat acute disease and establish a stable baseline prior to challenges.

Challenges can be done 'openly' with the patient ingesting the food, 'single-blind' with the food masked and the patient unaware whether they are receiving the test food, or, as double-blind, placebo-controlled oral food challenges (DBPCFCs) where neither patient nor physician knows which challenges contain the food being tested. In all of these challenges, the food is given in gradually increasing amounts that may be individualized both in dose and timing depending on the patient's history. For most IgE-mediated reactions, we give 8–10 g of the dry food or 100 ml of wet food (double amount for meat/fish) at 10–15 min intervals over about 90 min (9,33) (Table 5), followed by a larger, meal size portion of food a few hours later. However, researchers and clinicians have used a variety of other challenge regimens (lower starting doses, doubling doses, etc.) with good success (18,34). Some workers have performed screening challenges by placing the food extract on the lower lip for 2 min (labial food challenge) and observing for local or systemic reactions in the ensuing 30 min (18,35,36). The development of a contiguous rash of the cheek and chin, edema of the lip with conjunctivitis or rhinitis, or a systemic reaction is considered a positive test (18). Negative labial food challenges are generally followed by an oral food challenge.

During oral food challenges, symptoms are recorded and frequent assessments are made for symptoms affecting the skin, gastrointestinal tract, and/or respiratory tract (Table 6). With children, early indications of a reaction can include subtle signs such as moving the tongue in the mouth to rub an itchy palate, or ear pulling due to referred pruritus. Children may become suddenly quiet or assume a fetal position as a prodrome to more objective symptoms. Children with atopic dermatitis may develop a maculopapular rash in predilection areas of eczema. Objective monitoring may be performed with peak flow or pulmonary function tests, as indicated. Challenges are terminated when a reaction becomes apparent, and emergency medications are given, as needed. Generally, anti-histamines are given at the earliest sign of a reaction, with epinephrine and other treatments

Table 5. Oral food challenge protocol (example)

Stage	Procedure
1	No food 2 h prior, IV as indicated, emergency medication drawn up
2	Divide 8–10 g of dry, or 100 cc of liquid challenge into 6 doses
3	Doses given in increasing increments at 10–20 min intervals (consider a 'taste' to start if high risk): 1%, 4%, 10%, 20%, 20%, 20%, 25%

given if there is progression of symptoms or any potentially life-threatening symptoms (Table 6). If the history indicates delayed reactions or reactions after prolonged ingestion, adjustments can be made to make the challenge more closely resemble the suspected course for reactions.

Open oral food challenges can be very helpful, particularly in eliminating the food as a potential cause of symptoms. The challenge takes no significant preparation and the patient can be asked to bring the food with them to the office. These are best performed when it is not very likely that symptoms will develop and there is little psychologic interplay that could bias results. Thus, open challenge would be perfect for confirming a skin test-negative food as safe in the setting of a potential reaction that was not severe (unless the family/patient was strongly convinced it was causal). Similarly, objective positive responses (hives, reduced pulmonary function) in reliable patients are helpful. When an open challenge is suspected to be falsely positive, a follow-up DBPCFC is needed.

DBPCFCs are considered the 'gold standard' for diagnosing food allergy (6,25,37). The procedure is labor-intensive but can be modified to an office setting (37). Graded doses of either a challenge food or a 'placebo' food are administered. The food is hidden either in another food or in opaque capsules. Vehicles used for masking taste and odor may include fruit juices, baby foods, cereals, infant formulas, ground beef, strong flavors (mint, fish), etc. and are only limited by the imagination and care not to include foods to which allergic reactivity is present. Depending upon the particular disorder, timing of administration can be adjusted. For IgE-mediated reactions, two challenges may be performed each day with 4 h between challenges (one is placebo, one is active, so one food is tested each day). The practice of interspersing placebo and active food proteins during a single challenge (e.g. random ordering of sequential doses that may or may not contain the causal protein) should be discouraged as it may be difficult to determine whether a reaction shortly after a particular dose, possibly a placebo dose, was actually a delayed response from an active dose

Table 6. Signs and symptoms of reactions

Organ system	Life-threatening	Not life-threatening
Respiratory	Throat tightness Wheezing Shortness of breath Repetitive coughing Hypoxia/cyanosis	Nasal congestion Rhinitis Cough
Gastrointestinal	Obstructive tongue edema	Nausea Vomiting Diarrhea Abdominal pain Itchy mouth/ear canal Lip edema
Skin		Flushing Pruritus Urticaria Angioedema Morbilliform rash
Cardiovascular	Hypotension Shock Syncope Arrhythmia Chest pain	
Other	'Impending doom'	Conjunctival injection/itch

administered previously. The aid of a 'third party' is needed to prepare the challenges, and a 'coin flip' can be used to randomize the order of administration. When multiple foods are suspected, single-blind challenges may be used to screen for reactivity. Negative challenges are always confirmed with open feeding of a larger, meal-sized portion of the food, also under physician supervision.

The successful administration of oral food challenges to young children requires a great deal of preparation, ingenuity, and often patience. It is not uncommon for a young child to become stubborn and refuse to ingest the challenge food. Prior planning with the family to choose vehicles for masking that are likely to be accepted by the child is helpful (e.g. milk protein hidden in soy frozen dessert products). Having additional challenge vehicles, for example liquid and solid forms of the challenge substance, readily at hand may prevent delays. Allowing the use of well-cleansed utensils and dinner ware that are familiar to the patient (e.g. a favorite cup or plate) makes the challenge appear more natural. Diversions such as toys, games or videotapes are helpful. Since splattered or drooled food can elicit a local skin reaction from direct skin contact (but not necessarily from ingestion), it is helpful to have wet napkins on hand.

Special considerations

It is more difficult to diagnose non-IgE-mediated reactions (e.g. AEG, enterocolitis, etc.) and to

pinpoint specific causative foods since there are no specific laboratory tests for these illnesses. In some cases, a biopsy may be needed (e.g. AEG) to establish a diagnosis. Elimination diets with gradual re-introduction of foods and supervised oral food challenges are often needed to identify the causal foods. For AEG, the re-introduction of foods at home (if there is no evidence of IgE to the particular food and no history of sudden reactions) with one new food added at 5–7 day intervals is a reasonable approach.

Food protein-induced enterocolitis syndrome (FPIES) is a special case of severe, non-IgE mediated allergy (38,39). FPIES describes a symptom complex of poor growth and profuse vomiting and diarrhea with or without microscopic blood in the stool that is usually diagnosed in infancy (39,40). The most common causal proteins are cow's milk and soy; rarely, other foods such as rice, egg, fish and poultry are responsible. When severe, particularly with re-feeding after a period of elimination, these symptoms may lead to lethargy, dehydration and hypotension, and may be complicated by acidosis (40–42). Food challenges for this non-IgE-mediated syndrome are typically performed with 0.15–0.6 g/kg of the causal protein, and reactions of profuse vomiting and diarrhea typically begin 2–6 h after the ingestion and are accompanied by a rise in the absolute neutrophil count of over 3500 cells/mm³ (3). Because of these characteristics and the potential for shock, intravenous access must be obtained in advance and the challenge is best performed in a hospital setting.

When the history of a food-allergic reaction credibly suggests that the onset of symptoms are delayed by hours or days following ingestion, the challenge can be adjusted to correspond to these characteristics. However, the recreation of this time course may require challenges to be performed during prolonged hospital stays. If patients are sent home after feeding, it may be impossible to determine whether their late-onset symptoms are due to the food given or to other exposures. For example, atopic dermatitis or asthma could flare from environmental exposures in the home. To some extent, double-blind challenges may help to prevent false-positive results.

Another difficulty in diagnosis occurs when food additives (coloring and flavoring agents and preservatives) are implicated in reactions. Certain additives have been documented to cause the same types of reactions as those caused by IgE-mediated responses (asthma, urticaria, atopic dermatitis, etc.) but with a much lower prevalence

(20,43,44). Since these reactions are generally not IgE-mediated, diagnosis requires trials of elimination and oral challenge testing. The same can be said for symptoms not likely to be associated with food allergy (behavior, etc.).

In summary, oral food challenges are a fundamental tool in managing food-allergic patients. In many cases, oral challenges can be carried out in the office setting, but 'high-risk' challenges may require a more controlled hospital setting.

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