

Food Allergy in Children

Diagnostic Strategies

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Introduction

It is now generally accepted that food allergies affect approx 2% of the population (1-5), with a higher prevalence in infants and younger children compared to older children and adults (1). Fortunately, the list of foods responsible for allergic reaction in children is short and many children are allergic to one or two foods only.

The diagnosis of food allergies can be a difficult exercise in some children. The symptoms attributed to foods may be because of another, unrecognized disease process. Not all adverse reactions to foods are immunologically mediated and diagnostic tests are not available for all immunologically mediated food reactions. The laboratory diagnostic tests that are currently in use are variable in their sensitivity, specificity, and predictive value in identifying a specific food as the cause of the reaction.

The objective of this article is to review the strategies for diagnosing allergic reactions to foods in children. A practical approach to this problem is outlined, followed by an in-depth discussion of the diagnostic methods available.

Clinical Evaluation of Patients (see Fig. 1)

Children with suspected food allergies are evaluated by clinical history, physical examination, followed by specific testing, if indicated. Suspect foods are usually eliminated from the diet for 2 wk. If symp-

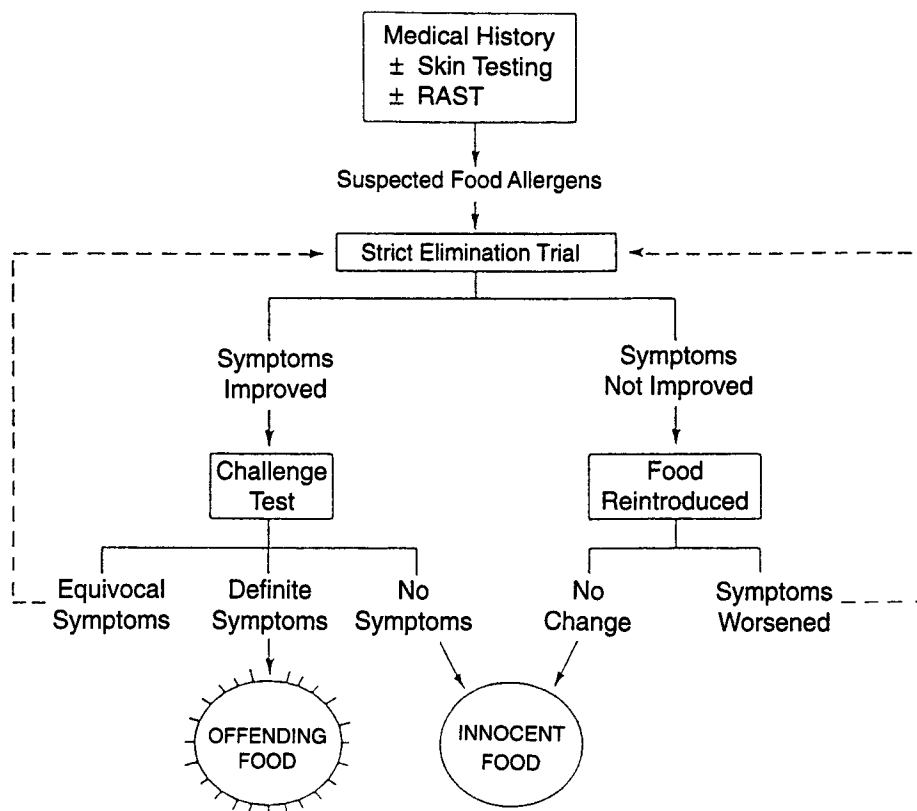


Fig. 1. Flow diagram for clinical evaluation of children with suspected food allergies. From ref. 6.

toms are unchanged, the eliminated foods are unlikely responsible for the reported symptoms and should be reintroduced into the diet. Worsening of symptoms on reintroduction of those foods necessitates another trial of elimination. *It is imperative that any patient with a convincing history of life-threatening anaphylaxis secondary to ingestion of a known food should not undergo an oral food challenge under any circumstance.* When several foods are suspected, after elimination, an oral challenge can be performed in the office setting under observation. If the office challenge reveals positive responses to several foods, appropriate elimination of those foods is advised. Positive challenges to a number of foods in an open fashion should be followed by a double-blind placebo-controlled food challenge (DBPCFC) to eliminate patient, physician, and/or parental biases.

Other in vitro diagnostic techniques are available which may aid in the diagnosis of food allergies. Most of these techniques are currently used in research. In general, these tests are less sensitive than the skin-prick tests and RASTs, and are not available for regular use.

Screening

History and Physical Examination

The offending food(s) may be identified by a careful history. The history must include:

1. The identification of the food or foods suspected of causing reactions;
2. A description of symptoms caused by the food;
3. The time between ingestion and the onset of symptoms;
4. The quantity of food required to induce symptoms;
5. The reproducibility of the symptoms;
6. Presence of other factors (such as exercise) required to initiate the symptoms; and
7. The length of time since the last reaction.

Typically, allergic reactions to foods are immediate and associated with gastrointestinal, respiratory, and/or cutaneous symptoms. In children <1 yr of age, isolated gastrointestinal symptoms may be the only manifestation of an allergic reaction (7). If a child has typical acute allergic symptoms immediately after ingestion of a single food the diagnosis may be easy; however, in general, history can be verified in only 30–40% of cases (8,9). With a chronic condition, such as atopic dermatitis, the identification of foods triggering dermatitis by history alone may be impossible.

The list of foods causing allergic reactions in children is short. In the 1st yr of life, cow's milk protein, eggs, wheat, and soy appear to be more common allergens while peanuts, tree nuts, and fish are more responsible for reactions in older children (7). This is primarily related to the order in which these foods are introduced into the diet. Type I-mediated immunologic reactions usually occur within minutes, or occasionally up to 1 to 2 h after exposure to a specific food allergen. If symptoms take hours or days to develop, food allergy is unlikely.

The presence of other atopic conditions such as atopic dermatitis, asthma, or rhinitis would suggest that the symptoms related to food ingestion may be allergic. Review of the family history for atopy may help identify patients at increased risk of developing food allergies (10).

Physical examination by itself does not diagnose food allergies, but may help to exclude other conditions. Any physical findings which support the diagnosis of other atopic conditions reinforce the probability that food-induced symptoms may be allergic.

Food/Symptom Diary

If the history is vague or there is uncertainty about the effects of diet on the child's symptoms, a food/symptom diary for 2 wk may

focus attention on this relationship (6,11,12). Parents are instructed to record the type and amount of foods ingested and the occurrence and character of adverse reactions. If symptoms are absent or infrequent during the period of recording the diary, an elimination diet will not be successful in defining likely associations between food and the adverse reaction. Diaries may have limited benefit in patients who have chronic daily symptoms because specific foods may be difficult to identify and parents may be very reluctant to record symptoms regularly when they notice no clear relationship to food ingestion. If symptoms are extremely intermittent, parents can record foods eaten in the 24 h prior to the reaction.

The success of the food/symptom diaries also will depend on the diligence of the parent to fill out the diary accurately and completely. If there are strong parental biases, they may show up in the diary records, invalidating the results.

Testing

Skin Tests

Skin testing using extracts of foods suggested by history is an important part of the evaluation of the patient with suspected food allergy. Epicutaneous tests using food extracts in a weight:volume ratio 1:10 to 1:20 (in glycerol) have been demonstrated to test food antigen-specific IgE antibodies in sensitized subjects (13). A positive control (histamine phosphate 1.0 mg/mL) and a negative control (diluent) should be applied at the same time. Skin sites with a wheal diameter 3 mm or larger compared to a negative control 10 min after placement are considered positive. Results of skin tests may vary at different ages (14–16). The mean wheal size of histamine is smaller in infants than in older children and adults and the size of the wheal and flare induced by foods should be compared to the histamine test used as the positive control.

Positive skin tests indicate only the possibility that the patient's symptoms are related to the particular food allergen tested and may not correlate with actual symptoms related to food ingestion. The positive predictive value of skin tests are dependent on the food allergen and the age of the patient. Sampson (9) performed food challenges in children with atopic dermatitis and elevated serum IgE concentrations, who had positive skin tests or a convincing history of an allergic reaction to a food. The positive predictive value of skin tests in this study was 23%. Other investigators (17) reported that 40% of positive skin tests in children with atopic dermatitis were considered clinically significant because of positive food challenges. The positive predictive value of skin tests depended on the food tested (18–20): 61% for eggs,

Table 1
Usefulness of Skin Tests for Selected Foods Studied^a

Food ^b	Predictive accuracy ^c	Predictive accuracy		
		>3 yr	<3 yr	Total group
Eggs, <i>n</i> = 168	v	0.40	0.80	0.75
	g	0.96	0.91	0.95
Peanuts, <i>n</i> = 167	v	0.45	0.72	0.49
	g	1.00	1.00	1.00
Milk, <i>n</i> = 206	v	0.81	0.80	0.64
	g	0.83	0.83	0.89
Nuts, <i>n</i> = 64	v	0.43	0.50	0.45
	g	1.00	1.00	1.00
Wheat, <i>n</i> = 64	v	0.17	0.39	0.27
	g	1.00	1.00	1.00
Fish, <i>n</i> = 64 ^d	v	0.17	1.00	0.25
	g	1.00	1.00	1.00

^aFrom ref. 19.

^bn, number of food challenges; v, positive predictive accuracy; g, negative predictive accuracy.

^cThe following formulas were used to calculate predictive accuracy: $v = sP / sP + [(1 - f)(1 - P)]$ and $g = f(1 - P) / f(1 - P) + (1 - s)P$, where *s*, sensitivity; *f*, specificity; *P*, prevalence (number of confirmed reactions divided by total number of challenges); data not shown for these values.

^dFish and shellfish.

44% for peanuts, 50% for milk, 75% for wheat, 30% for soy, and 25% for fish (20). Negative predictive values ranged from 82% for eggs to 100% for soy, fish, and peanuts. Overall, the positive predictive values for foods were higher in children <3 yr than children >3 yr (19) (see Table 1).

Recently infants who were evaluated for possible food-induced allergic symptoms elicited by a number of foods were skin tested or had RAST to eggs prior to their first ingestion of eggs (21). Subsequent DBPCFC were performed with eggs in the skin test positive and negative groups. The sensitivity of the skin-prick test was 92% and the specificity of the positive skin-prick test was 57%. The positive predictive value of the skin-prick test was 61%, while the negative predictive value was 91%. This study is one of the first to attempt to document the ability of skin tests to predict an adverse reaction in children with food-related symptoms prior to overt exposure to the food allergen. It is not clear if this is unique to eggs, or would be common to other foods. Further studies are needed involving other commonly encountered food allergens prior to their introduction into the diet.

In general, skin tests to foods have an excellent negative predictive value, but there are some exceptions to this rule. IgE-mediated sensitiv-

ity to some fruits and vegetables may not be effectively evaluated by commercially compared reagents because the antigen is labile (22–24). Negative tests may also occur when the reaction is immunologically mediated but not IgE mediated (e.g., cow's milk or soy enterocolitis syndrome), the target organ is locally sensitized (IgE present on mast cells in target organ, for example, the gastrointestinal tract, and not present on mast cells in the skin). Use of antihistamines prior to testing will blunt or negate the cutaneous response. Skin testing shortly after the occurrence of a severe reaction (anaphylaxis) may be falsely negative because of temporary anergy (25). Other causes of false-negative tests include poor technique and use of antigen extracts which have lost their potency. In children <1 yr of age, negative skin tests should be viewed carefully (26). The presence of positive skin tests are highly suggestive that foods are producing symptoms, but skin tests have a lower negative predictive accuracy in this age group compared to older children.

A positive skin-prick test to a food eaten individually, which has caused an anaphylactic reaction, should be considered diagnostic. Subsequent food challenge is contraindicated and could be life threatening. Often children who previously had food allergies to some foods (e.g., milk, wheat, and soy) can tolerate those foods after avoidance for 1 to 2 yr, despite persistently positive skin tests.

Intradermal testing can be more sensitive but less specific in skin-prick testing. No patient with a positive intradermal test and a concomitant negative skin-prick test to a food subsequently had a positive oral challenge to that food (18,27). Intradermal skin testing carries an increased risk of systemic reactions, with deaths reported in highly sensitive patients. Intradermal testing to foods is therefore not warranted.

Serum IgE

Many children with IgE-mediated food allergies have elevated serum IgE concentrations. Bock et al. (7) studied 68 children with a history of adverse reactions to foods. Of those children who reacted to a challenge with the suspected food, 93% had an elevated serum IgE concentration. In another study of 47 children, all but 2 under the age of 3 yr with a clinical diagnosis of food allergy had an elevated serum IgE concentration (28). The sensitivity of serum IgE determinations for the diagnosis of food allergy in this study was 94% and specificity was 80%. Thus an elevated serum IgE level in children may support a more thorough search for an offending food allergen (29).

Specific IgE Antibodies

The prototypical test for measurement of specific IgE antibodies is the radioallergosorbent test (RAST), where allergens, coupled to nitrocellulose paper, are incubated with patient's serum containing aller-

gen-specific IgE antibodies. After several washings, radioactively labeled antihuman IgE antibody is added, binding to the IgE antibodies. By measuring the radioactivity level of the disks, the specific IgE to the questioned allergen can be quantified. The quality of the test is dependent on the allergen extract used for coupling.

RASTs were compared to food challenges to assess their positive predictive value (20). The results were very similar to skin tests but were much lower for milk (7%), wheat (52%), and soy (18%). In general, RAST testing is less sensitive than skin testing.

The utility of RAST in place of skin-prick testing is evident in several situations, including the presence of extensive eczema (where no site is available for skin testing), and the inability of the patient to discontinue antihistamines for a suitable time prior to skin testing. Less foods are available for RAST testing compared to epicutaneous tests, the cost is considerably higher, and the results of RAST are not immediately available.

Many commercial laboratories use the ImmunoCAP® system (Pharmacia, Uppsala, Sweden) for measurement of specific IgE antibodies. This modification of RAST utilizes a new type of solid phase (a hydrophilic polymer encased in a capsule) allowing increased availability of bound antigen *in vitro*. Although there have been no published direct comparisons between results of RAST and the ImmunoCAP system for foods, there are reports for insect venom (30). The ImmunoCAP system was more sensitive than RAST, picking up patients with low-level sensitization that are missed by RAST. Reports on the superiority of the ImmunoCAP system are mixed, with a recent study finding the positive predictive value of the specific IgE antibodies by the ImmunoCAP system to be 39% when compared to oral food challenge, which is no higher than RAST (31).

Other Tests

Several other *in vitro* tests are utilized in the research of food allergies. In general, these tests do not provide distinct advantages over current tests; that is, they are no more sensitive than RAST or skin tests.

The clinical use of basophil histamine release assays in diagnosis of food allergy is controversial. Basophils from allergic patients can be challenged to food extracts *in vitro* resulting in measurable histamine release. This increase can be measured and utilized to identify foods suspected of inducing a reaction. The concordance rate of basophil histamine release assays with the RAST and skin-prick tests were 87 and 74%, respectively, and 50% when compared to the food challenges (32).

Assay of intestinal mast cell histamine release is similar to the basophil histamine release assay, but utilizes mast cells from intestinal

biopsy specimens. After treatment with the suspected food antigen, the concentration of histamine released is measured. Intestinal mast cells responded to challenge with antigen only when the patients allergic symptoms were localized to the gut (e.g., diarrhea) (33).

A recent prospective study evaluated the diagnostic value of intestinal mucosal IgE plasma cells, serum IgE levels, and their relationship in cow's milk intolerance confirmed by elimination and challenge tests (34). Mucosal IgE plasma cells were found in 90% of patients with proven cow's milk protein intolerance compared to 1 of 15 patients without cow's milk protein intolerance ($p < 0.01$). These IgE plasma cells were also found in some children with cow's milk protein intolerance, even in the absence of abnormal RAST or elevated serum IgE concentrations. Intestinal mucosa biopsies for the presence of IgE plasma cells in conjunction with standard measures of specific IgE to cow's milk protein may lead to the diagnosis of cow's milk protein allergy in some children that otherwise would not be made. Further studies are required, but these tests may be helpful in some children with isolated gastrointestinal symptoms after food ingestion.

In patients who are undergoing DBPCFC, a group of patients with positive food challenge had a significant mean rise in serum histamine concentrations compared to baseline values (35,36). The determination of plasma histamine is not suitable for routine use because of the rapid clearance from the circulation, and reproducible simple assays are not commercially available.

The usefulness of urinary 1-methylhistamine and serum tryptase concentrations were assessed in 32 children with atopic dermatitis and suspected food allergy during oral food challenges (37). Urinary methylhistamine had a sensitivity of 92%, but a specificity of only 37.7%. Serum tryptase concentrations had a specificity of 100%, but a sensitivity of only 25%. Neither test was superior to clinical observation.

Elevated specific IgG antibody concentration to cow's milk protein and soy has been proposed as a predictive of the response to an exclusion diet in infants with atopic dermatitis (31). However this assay offered no more information than the oral food challenge and RAST.

Intragastric provocation with food antigens under endoscopic control (IPEC) has been performed in food allergic patients (38–40). This test utilizes a small amount of the food antigen applied to the mucosa of the stomach. In patients with previously documented adverse reactions by DBPCFC, macroscopic reactions occurred including swelling, erosions, and petechial bleeding. Although the test is specific, there are no reports of the sensitivity of this procedure and many patients had systemic symptoms during the challenge.

In some food-sensitive patients with atopic dermatitis, enhanced DNA synthesis by peripheral blood mononuclear cells can be demon-

strated after in vitro food antigen challenge (41). After elimination diets, this proliferative response decreased. Although this response could be an index of the effect of elimination diet in atopic dermatitis, it may be of little practical value, since it is no better than clinical observation.

Recent evidence has suggested that fecal IgE may be useful to identify children at risk for food allergies. IgE, detectable using a radioimmunoassay, was found in 15 of 22 children with gastrointestinal allergy and atopic dermatitis compared to 6 of 17 children with hay fever and/or asthma (42) whereas <10% of healthy infants, children, and adults had detectable IgE in their fecal extracts (43). Fecal IgE is significantly higher in stools of children within 24 h of an oral challenge with a food previously confirmed by a DBPCFC to cause allergic symptoms (44). At age 18 mo, the prevalence of atopic disease (through use of a questionnaire) was higher in children with elevated fecal IgE levels at age 1 mo (50%) than those with low levels (14%) (45). Further studies are required to determine if this is a valid noninvasive method to identify children with food allergy or who are at risk for atopy.

Elimination Diet

If a limited number of foods has been identified as suspect by history, food/symptom diary, and/or skin tests or RAST, removal of those foods from the diet should resolve those symptoms within days. In addition parents must be given other names of ingredients found in foods which indicate the presence of specific proteins suspected to cause allergy (e.g., albumin for eggs, casein and whey for milk). If removal of one or several foods has been unsuccessful in improving symptoms, if multiple foods are suspected, or if no foods are identified, a more strict 2-wk elimination diet may be warranted (10). In children <4 mo old, this consists of a casein hydrolysate formula; from 4–8 mo, casein hydrolysate formula plus rice cereal and peas; from 9–24 mo, casein hydrolysate, rice cereal, peas, rice, squash, and lamb. For children >24 mo, fresh lettuce, potato, sunflower oil, and sugar are added to the other foods (46). Other elimination diets in older patients include use of fruits, such as apples, apricots, and peaches; vegetables, such as carrots and sweet potato; meats, such as chicken; and salt, olive oil, and honey (47). In some extreme cases, Vivonex® (an elemental formula) may be utilized. If possible, medication should be avoided during the elimination diet to avoid possible symptoms which may be related to the medication. If symptoms persist on the restricted diet, the restricted foods are not the cause of the symptoms.

If there is satisfactory improvement noted in all symptoms, the eliminated foods should be reintroduced one at a time as a means of verifying and identifying suspect food(s). Reintroduction of foods into

the diet should only be considered when the symptoms are not life threatening, and in most instances the patient should be observed under medical supervision.

The success of any elimination diet is dependent on:

1. Correctly identifying the foods causing the symptoms;
2. The patient's ability to adhere to the diet completely free of all forms of the suspect foods;
3. The family's cooperation with the diet; and
4. Other foods, which have not been eliminated, not provoking similar symptoms.

Confirmation

Food Challenges

Confirmation by an oral challenge to the suspect food is necessary in many instances to show "cause and effect" (47–50). *No food which is suspected of inducing anaphylaxis should be given as an oral challenge.* In general, oral challenges should be performed under medical supervision with facilities at hand to treat possible severe reactions.

Challenges are usually performed after suspect foods are eliminated from the diet for 7–14 d. Symptoms should be resolved and use of antihistamines should be avoided for 5–7 d before the challenge. Challenges should be performed in the morning on an empty stomach. The initial dose of the food should be approximately one-half the amount that has previously induced a reaction (doses as low as 10–30 mg can be used) and the time between doses should be greater than the time needed to induce symptoms based on the history (usually 15–60 min). The dose of food is usually doubled until symptoms occur or until a reasonable serving size has been ingested. If no reaction has occurred, the food should be reintroduced into the diet and the parents advised that no avoidance of the challenged food is necessary.

Open Food Challenges

This technique can be very helpful in a clinical practice setting. In infants and children, when objective signs can be seen, a positive challenge in an open fashion is acceptable and does not necessarily need to be confirmed by a DBPCFC. If the symptoms are vague and subjective, or if parents are extremely anxious, overinterpretation of findings can occur, which may invalidate the procedure. Challenges in this situation should be double-blind and placebo-controlled.

Single-Blind Challenge

During this challenge, the patient and parents are unaware of the food that is being given, while the observer has that specific knowl-

edge. Blinded challenges could be considered in older patients in which the anticipated reaction has subjective rather than objective symptoms. The food is given either by capsules or hidden in a liquid disguising its flavor. The patient is tested with either the disguised food or placebo. Single-blind challenges eliminate the patient's or parents' biases, but does not discount the physician's.

DBPCFC

The DBPCFC is considered the "gold standard" for confirming or refuting a history of an adverse reaction to a food (48). The end point of the challenge is from 8–10 g with dry food or 60–100 g of wet food as a single dose. A placebo day is incorporated in which patients ingest an increasing number of capsules or a liquid which has no allergen. If the double-blind component of the challenge is negative, the food must be consumed openly at the end of the challenge. The ability of the patient being able to ingest the food openly will eliminate many of the questions about factors which may alter the food (e.g., preparation, digestion). If the food is tolerated after the open challenge, the child is not clinically sensitive to that food.

Some difficulties may be encountered in interpreting results of food challenge tests (47). A positive-challenge test indicates the cause-and-effect relationship, but does not indicate the underlying mechanisms. This may be derived from the nature of the clinical reaction on history and/or from the results of either skin tests or RASTs. Disguising the foods can be difficult because of quantity or specific characteristics, such as strong flavors. Also, in some types of reactions, other factors in addition to the food may be necessary (e.g., food-induced exercise-associated anaphylaxis) which cannot be duplicated in a clinic setting.

Conclusions

The diagnosis of hypersensitivity reactions to foods in infancy and childhood requires the use of clinical skills and laboratory diagnostic methods to identify suspect foods. Patients and parents occasionally may need to keep food/symptom diaries to explore the association of foods and adverse reaction. Skin testing or RAST may shorten the list of potential allergens because of their excellent negative predictive value.

Except for obvious serious allergic reactions after ingestion of a single food, confirmation of the reaction may be ideally confirmed by a DBPCFC, especially if the reported symptoms are subjective in nature. Equivocal responses should be repeated.

Although many *in vitro* and *in vivo* diagnostic methods have been developed to potentially improve the diagnosis of food allergy in children, no test has been able to predict the results of the DBPCFC

with any greater accuracy than skin tests or RAST. The "perfect" test with excellent positive and negative predictive values has yet to be developed.

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