

# Skin Testing and Food Challenges in Allergy and Immunology Practice

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## Introduction

Over the last two decades, significant progress has been made in understanding allergic reactions to foods. The value of skin testing to foods is much better understood now than in the 1970s, and at least one of the *in vitro* diagnostic techniques may emerge as an additional aid to management (CAP-FEIA, *vide infra*). The double-blind, placebo-controlled food challenge (DBPCFC) has been established as the only tool able to prove definitively the presence of food allergy (short of anaphylaxis); however, there remains a place for open food challenges. With the simple tools of skin tests and challenges, typical IgE-mediated food allergy can be fairly simply characterized. Unusual complaints related to foods may also be investigated by modification of these techniques. In this chapter, we will attempt to provide a practical approach to the use of skin tests and challenges for diagnosis of food allergy. Use of these techniques should minimize patient risk both from diagnostic procedures and from inappropriately restrictive diets.

## Approach to Adverse Food Reactions

Before discussing the details of testing procedures, we will briefly consider the indication for such tests. Figure 1 is a simple algorithm that outlines common pathways for evaluation of typical IgE-mediated food allergy by history, skin testing, and challenge. At the

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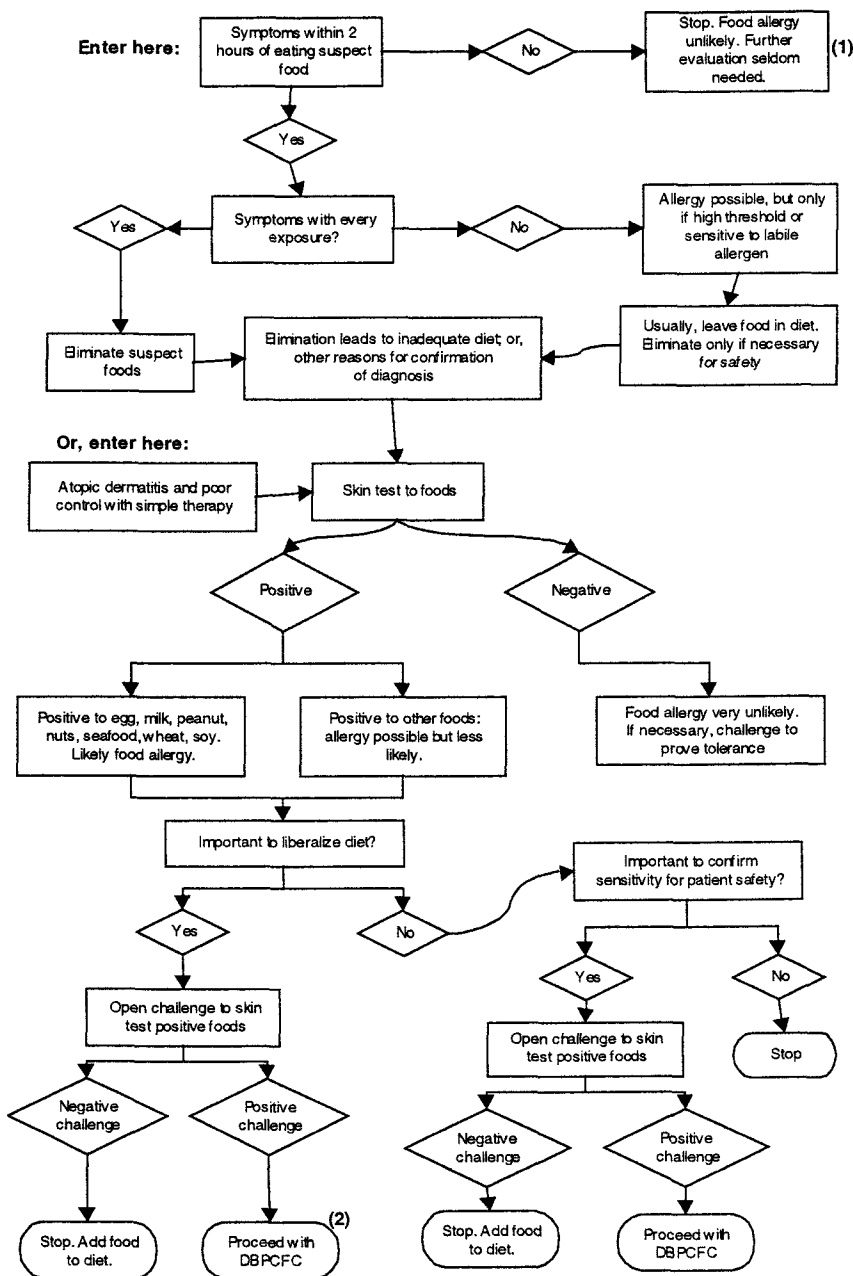


Fig. 1. Common pathways in management of IgE-mediated food allergy. This algorithm is specific for IgE-mediated food allergy. It does not necessarily apply to other forms of adverse reactions to foods, such as formula protein intolerance or reactions with reported onset many hours or days after ingestion of the food. (1) This box applies to IgE-mediated sensitivity. Some patients with significant and potentially dangerous food protein intolerance will not have a reaction within 2 h. If the history is compelling, further study may still be indicated. (2) If only one or two foods are positive on open challenge, DBPCFC may not be necessary unless there is a need to add the food to the diet. DBPCFC often would show the food is tolerated.

top of the algorithm, a patient may enter with symptoms that are temporally related to ingestion of a food. Alternatively, we study some patients because of suspicion that food is involved in the pathogenesis of the patient's atopic dermatitis (left side of algorithm). Before any testing, accurate recording of the history is important. The timing and nature of the putative reaction are critical. Reactions with onset more than 2 h after the ingestion are unlikely to have an IgE-mediated mechanism, but exceptions occur (1,2) Reactions that involve skin, GI tract, and respiratory tract are frequently IgE-mediated; the authors have not personally confirmed any behavioral or neurologic reactions that involved an allergic mechanism. Frequently, the history alone will clearly eliminate sensitivity to a food that the patient has assigned as a cause of symptoms. An obvious example is the mistaken assignment of symptoms to milk ingestion in a child who develops no symptoms on ingestion of other milk products, such as ice cream or yogurt. Similarly, in infancy, sensitivity to eggs is often mistakenly attributed to multiple items when the offending allergen is the egg in prepared foods. Thus, if symptoms are attributed to a food, the history should include inquiries for tolerated foods that contain the supposed allergen in amounts thought to produce symptoms.

The history is also important in avoidance of potentially dangerous challenges. As a rule of thumb, foods that have caused life-threatening reactions when consumed in isolation (so that no confusion exists regarding the offending food) are not challenged. The major exception is the need for eventual challenge in infants with anaphylaxis to milk or egg, because of the expectation that these foods will be tolerated at some point. For safety reasons, challenges are undertaken in a medical care setting, but in a few situations, challenge in the office is not necessary. For example, an office challenge is not likely to be necessary in the patient who has never had a reaction to a food, but has had the item eliminated on the basis of a positive prick skin test (PST) to members of the same botanical family, or on the basis of low-grade radioallergosorbent test (RAST) (class 1 or 2) to the food. Also, foods to which there is no history of reaction despite repeated consumption and for which the skin test is negative may be simply added back to the diet. This exception is most applicable to foods unlikely to be allergenic, such as vegetables and fruits. The safest site for reintroduction of highly allergenic foods (egg, peanut, milk, soy, nuts, wheat, fish, and other seafoods) eliminated without history of reaction, but for which the PST is positive, might still be the clinic.

## Skin Testing

The value of skin tests has been well documented in the literature. For the protein-rich foods that most commonly induce IgE-mediated

sensitivity, the most useful statistical descriptors of the value of PST are the positive predictive accuracy and the negative predictive accuracy (2). These statistical measures are dependent on the sensitivity and specificity of the tests and on the prevalence of the disorder in the population studied, as the formulas below indicate:

$$\text{Positive predictive accuracy} = (sP) / [sP + (1 - f)(1 - P)] \quad (1)$$

$$\text{Negative predictive accuracy} = [f(1 - P)] / [f(1 - P) + (1 - s)P] \quad (2)$$

where  $s$  = sensitivity,  $f$  = specificity, and  $P$  = prevalence (number of confirmed positive cases divided by the number of cases under study).

Most reported calculations of the positive and negative predictive accuracy are based on studies of patients with very severe atopic dermatitis (3). This population differs from a routine allergy office practice, but sufficient similarity exists to make valid inferences that may guide in management of a typical office population. The predictive accuracy values give an estimated probability that a skin test-positive patient will react (positive predictive accuracy) when given the food in a DBPCFC and the probability that the skin test-negative patient will not react (negative predictive accuracy) when similarly challenged. In a population with a high prevalence of food allergy, negative predictive accuracy for the common food allergens (egg, peanut, milk, wheat, soy, fish) are all quite high (>95%). In a low-prevalence population, the negative predictive accuracy is even higher as it varies with the inverse of the prevalence (2,4).

The patient population seen in a routine allergy practice is likely to have a relatively low prevalence of food allergy; thus, in a routine office setting, a negative PST to a food is very strong evidence that the food may be consumed without systemic symptoms. On the other hand, a positive skin test to a food is not strong evidence for the existence of food allergy (with the exception of confirmation of sensitivity after anaphylaxis to an isolated ingestion of a food). The positive predictive accuracy, even in a high-prevalence population, is never more than about 70% for the most predictive skin test (egg) and is lower for other foods (3). Since the positive predictive accuracy varies directly with the prevalence, it is lower if a population with a lower prevalence is studied. Therefore, in a typical office practice, no positive skin test to a food is likely to have high positive predictive accuracy. Patients, and many physicians, commonly assume that a positive skin test to a food proves allergy to the food; indeed, skin test data in isolation are anything but diagnostic. Much inappropriate food elimination is begun because of this assumption.

The studies that defined these statistical parameters employed prick skin test techniques. There is no role for intradermal skin testing

(at this time) in evaluation of food allergy, since it is well demonstrated that only false positives (clinically irrelevant IgE) are found by adding intradermal skin testing to prick skin tests (1). In addition, studies in the 1970s demonstrated that the reactions on PST <3 mm larger than the negative control were not predictive of reaction on DBPCFC (1,2). The exact device used appears not to be critical, but comparison to the negative control is.

Because of the low predictive value of positive skin tests, indiscriminate, multiple-food skin tests in patients suspicious that they have a food allergy are likely to cast more confusion than light on their management. The algorithm of Fig. 1 shows several common pathways that may lead to rational testing. Certainly, patients with a history suspicious for a reaction to a specific food or foods may be tested. Children with atopic dermatitis who require daily medications for more than a few months should also be tested, since they have about a 30% prevalence of food sensitivity proved by DBPCFC (5). By the same criteria, children with very severe atopic dermatitis have an even higher probability of food sensitivity, as high as 65% (6). When no specific food is implicated by history, testing to a broad panel of foods in hopes of finding a cause for symptoms is seldom helpful, except possibly in severe atopic dermatitis. More than 80% of reactions to foods are caused by five common foods: milk, egg, peanut, wheat, and soy (4,7). Even in the setting of atopic dermatitis, where the expectation of food allergy is probably highest, a recent publication suggests that PST with seven foods (milk, egg, peanut, wheat, soy, cod/catfish, and cashew) will detect 99% of children with a food allergy (7).

There are testing options other than prick skin testing. RAST testing has been evaluated in comparison to skin testing. Sampson and Albergo showed that RAST to the common childhood food allergens had no specific advantage over skin tests to predict reactions on DBPCFC (2). If a class 3 RAST result is defined as positive, the RAST yields about the same positive and negative predictive accuracy as the PST, but fails to detect a few who react on challenge. Use of class 2 RAST as positive greatly increases the false-positive rate (2). Recently, this group has published another analysis of in vitro tests in similar patients with severe atopic dermatitis. They report an improved predictive value for the Pharmacia CAP-fluorescent enzyme immunoassay (FEIA) for allergen-specific IgE (3). This test detects allergen-specific IgE over a range from 0.35 to 100,000 kU/L. In an analysis of several hundred patients studied with CAP-FEIA and DBPCFC, CAP-FEIA results for egg, peanut, milk, and fish, could be calculated that were associated with a >95% probability of a reaction on DBPCFC. Unfortunately, for most of these foods, a value that was even 90% predictive of failure to react on challenge could not be determined, i.e., a significant risk of reac-

tion remained even when the food-specific IgE was  $<0.35$  kU/L. These calculations have not yet been replicated by other groups; however, it is likely that eventually such tests will allow estimation of patient risk with fewer challenges and will aid in appropriate timing of challenges to foods that typically are eventually tolerated.

The preceding discussion of the predictive value of testing for IgE to foods demonstrates one of the basic principles of food allergy—that IgE to the food is necessary for an immediate hypersensitivity reaction, but it is not sufficient in isolation for a reaction. Thus, unequivocally positive skin tests or RAST is seen in patients who tolerate the tested food. In addition, for foods to which infants typically lose sensitivity, the skin test is frequently still positive even when the patient has lost sensitivity on challenge. Factors that are not yet understood control mast cell degranulation even in the presence of cell-bound IgE on cutaneous mast cells.

A distinctly different picture of the value of skin testing has developed for patients with the complex of symptoms dubbed “oral allergy syndrome” (8,9). These patients typically report oral itching or discomfort, and sometimes oral and lip swelling, related to consumption of foods that are rarely implicated in the food allergy studies described above. Common inciting foods are fruits and vegetables. This area continues to be problematic because of overlap with patients who experience systemic symptoms and because investigators have not uniformly adopted a blinded challenge protocol to confirm the symptoms (that are often subjective). Nevertheless, it appears clear that some patients have IgE antibodies to aeroallergens that crossreact to proteins in fruits as demonstrated by *in vitro* tests (10). Common patterns include ragweed sensitivity and oral symptoms with melons (11), and birch sensitivity and oral symptoms with apple (10). These patients are typically negative on PST with conventionally prepared extracts of the implicated fruit, but are often skin test-positive if tested with a drop of fresh juice from the fruit or by the prick-prick technique (12) (prick device first used to prick into the flesh of the fruit, then to prick the patient). Investigators in the field have assumed that a very labile allergen is being detected by the prick-prick testing. Estimates of the positive and negative predictive accuracy of prick-prick testing for oral allergy syndrome have been published (12). However, the values were derived without blinded challenges. Our knowledge in this area would benefit from better methods of confirming the diagnosis (more objective challenge techniques) and a uniformly applied case definition.

## Food Challenges

Often symptoms are ascribed to a food without any proof. Although this may be harmless, in many patients there is potential

harm from false assignment of sensitivity to a food. The harm may be physical, by failure to avoid a true food allergen when symptoms are assigned to the wrong food, or psychological, when an unfounded fear of reactions is allowed to limit the patient's activities unnecessarily (often in the setting of secondary gain from the diagnosis of food allergy). Challenge procedures add the precision needed to avoid these adverse outcomes of overly casual diagnosis. A positive DBPCFC not only unequivocally assigns the diagnosis to a real allergenic culprit, but allows an estimate of the dose required to induce symptoms. This dose threshold is also useful information, since the patient who reacts to a DBPCFC after 50 mg of peanut is clearly a more difficult avoidance problem than the one who reacts only after 10 g of peanut. A negative challenge (open or blinded) allows liberalization of the diet and reduces difficult avoidance measures in school and daycare settings. All these considerations demonstrate the value of challenges in diagnosis and management of the potentially food-allergic patient.

The clarification of sensitivity that a challenge offers is especially useful in the school-aged child. School children are often falsely labeled as food allergic; since many such children obviously tolerate the food in question, the school staff is led to pay little attention to "food allergy." The child who is indeed anaphylactically sensitive to a food then needs extra information to compel attention by the staff to the dietary restriction. Confirmation that the patient has had a reaction on challenge is often the evidence compelling the school to develop a management plan. Schools in the United States are required by several statutes to make reasonable accommodations to such medical problems. These laws include the Rehabilitation Act of 1973, the Individuals with Disabilities Education Act, and the Americans with Disabilities Act (further information available from the Food Allergy Network, Fairfax, VA).

Food challenges may be open, single-blinded (when only the patient is unaware of the food ingested), or double-blinded (when physician, staff, and patient all are blinded) (13). The advantage of the double-blinded challenge is the great reduction in false-positive challenges. In open challenges, patient anxiety frequently leads to designation of trivial symptoms as indicative of reaction. Indeed, the power of suggestion and emotional bias is so great that quite convincing reactions may not be confirmed on DBPCFC. On the other hand, a negative open challenge is definitive proof that the patient is not sensitive to the food challenged. Thus, the decision to challenge by open or blinded technique is influenced by several clinical factors. An open challenge may be favored if there is statistically little probability of a positive result (that would require a DBPCFC for confirmation). Such a situation

might occur with a patient who wants to add the food to the diet and has very little evidence of sensitivity, e.g., negative skin test or history not very suggestive. Patients who have had numerous positive skin tests without confirmatory history might also be screened rapidly for these foods with open challenges. A DBPCFC would be the better initial choice in settings where the patient or family have centered their existence around food avoidance, and thus may have a strong psychological bias toward positive challenge. Also, if the food being tested is relatively likely to be positive, as with egg, milk, and peanut in the skin test-positive, young atopic dermatitis patient, the DBPCFC will often be preferred, because though more complex, it will detect positives without requiring multiple repeat challenges.

The nature of the food challenge material is important. For open challenges, any form of the food the patient will eventually eat is acceptable. It is helpful if the food is in a form that lends itself to measurement so that the challenge can be recorded in a quantitative fashion. Unless there is essentially no chance of reaction, this also aids in incremental administration beginning with a small quantity and then progressively larger doses, with a normal serving given over about an hour. Frequently, especially in young children, the most convenient challenge form is dried food suspended in a strongly flavored vehicle, such as Concord grape juice. The child who has not previously eaten a particular food may find the taste or texture unpleasant. Use of an acceptable vehicle can avoid this cause of refusal of the food. Dried egg white and dry powdered milk are easily given in a grape juice vehicle. Other common vehicles that may be applied are listed in Table 1. The older child may prefer the actual food for an open challenge. Foods that are thought to have extremely labile allergens (as suggested for the oral allergy syndrome) will need to be given in fresh form. Attention is usually focused on demonstrating that the food in its most common form is tolerated.

### ***Open Challenge Techniques***

The technique of open challenge may be as varied as the clinical situations for which it is employed. At its simplest, the open challenge is merely a serving of an implicated food, given under observation in the clinic. The techniques used are well described (13). Prior to the challenge, antihistamines are withdrawn long enough to allow a positive histamine skin test.  $\beta$ -agonists, theophylline, and cromolyn should probably be avoided for 12 h prior to the challenge. As a general rule, the challenge is being done in the office because there is at least some chance of a reaction. Where this possibility of reaction exists, the challenge protocol should specify incremental administra-

Table 1  
Vehicles for Blinded Food Challenges

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|                         |
|-------------------------|
| Common vehicles         |
| Capsules                |
| Infant formula          |
| Neocate                 |
| Ice cream               |
| Applesauce              |
| Milk shake              |
| Chocolate pudding       |
| Tapioca fruit mixture   |
| Grape juice             |
| Hamburger               |
| Canned tuna             |
| Popsicles <sup>TM</sup> |
| Lentil soup             |
| Mashed potato           |
| Cereal                  |

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tion of the food, beginning at about half the dose suspected to have caused a reaction. Since the reaction being sought is IgE-mediated, observation in the clinic for 2 h after the food is completely consumed is sufficient. In the situation where reactions of other types are suspected, the length of observation may need to be prolonged, depending on the reported temporal relation (if any) of the food to the symptoms and the nature of the reported symptoms.

If there is not a reliable history from which a suspect dose may be determined, an initial dose on the order of 100–500 mg of dried food would be reasonable. If dried food is not used, rough equivalents to this rule of thumb would be 3 mL of milk, or 1/4 of a peanut, or about 1/20 of the white of a hard-boiled egg. Other conversions of dried and wet foods are available (13). The total to be administered should approximate a serving of the food. Increments may progress by doubling for several steps. The largest increment is chosen to allow administration of the challenge over about 1 h with 10-min intervals between doses. If no reaction is seen during ingestion or the observation period, the challenge is judged negative. If the challenge has used dried food in a vehicle, the authors' practice is then to feed more of the food in conventional form to demonstrate further that it is tolerated. If the challenge ends with an equivocal result, usually because of subjective complaints, a follow-up challenge by DBPCFC may be necessary to clarify the status of the patient. Open challenges that cause florid urticaria or repetitive vomiting are likely to be confirmed on DBPCFC. Challenges judged positive because of a few small, transient hives limited to the face or hands, but

not accompanied by any GI or respiratory symptoms, often are negative on blinded challenge. These hives may be the result of contact urticaria and result from cutaneous mast cell response to allergen contacting the skin (14), rather than being a systemic response to ingested and absorbed allergen.

Several problems are commonly encountered in open challenges. Contact urticaria may confuse grading of any challenge; if the patient is a small child, attention must be paid to keeping the food off the hands and face. Small children often will resist consuming an adequate dose of a food that has been eliminated from the diet and is thus unfamiliar. Administration of an eliminated food (such as milk or peanut) that has a distinctive flavor or mouth-feel may meet resistance and sometimes vomiting on an emotional basis. Subjective symptoms associated with an emotional bias result in a positive open challenge that will be negative on repeat by DBPCFC. In addition, some patients with a previous adverse experience with a food will have a profound aversion to the food that limits the ability to challenge unless the food is disguised. It may be impossible to determine whether the patient refuses the food because of aversion to a new taste or because of a conditioned response to a previous adverse experience. Thus, with younger children, challenge with a palatable vehicle as for a blinded challenge is routinely advisable. In older children and adults, if the challenge is likely to be confused by issues of aversion, administration of 8–10 g of dried food in capsules may be advisable. The patient is then more likely to consume the food openly if the initial quantity has induced no symptoms.

### ***Blinded Challenge Techniques***

The blinded challenge adds a little complexity to the challenge scheme, but this small effort is rewarded with a great increase in certainty of diagnosis. The physician performing blinded challenges must have a process for producing and blinding the material for challenge. Clearly, the physician and nursing staff administering the challenge may not prepare and label the challenge material. Offices might have skin testing or immunotherapy personnel prepare challenge material. In an institutional setting, a dietician may be available to perform these tasks. The selected staff should understand the absolute necessity to label and record challenge material adequately and to prepare the prescribed materials exactly. The possibility of crosscontamination in the challenge preparation area should be controlled by allowing only one challenge material to be in preparation at a time. This rule also decreases the possibility of mislabeling and administration of the wrong food. Disposable containers, weigh boats, and transfer devices are preferable to decrease

the possibility of crosscontamination. A scale capable of accurately weighing gram quantities is necessary (an inexpensive triple-beam balance is sufficient) as are a few graduated cylinders for measurement of liquids. A magnetic stirrer may be helpful for getting dried foods into suspension, but is not critical. A blender or coffee grinders may be used to convert dry solids to powders; again, care must be taken to prevent crosscontamination.

The challenge technique is similar to an open challenge, except that two samples of challenge material are given, separated by several hours of observation. The challenge samples are labeled by code only; the code should be immediately available if needed. Antihistamines and other drugs are withheld as noted for open challenge. The challenge is administered in increments, starting at a dose less than that thought to have induced a reaction. A challenge of 100 mL of liquid might be conveniently given over 1 h by giving an initial 5 mL, waiting 15 min, and then giving doses at 10-min intervals of 10, 20, 20, 20, and 25 mL. After the first challenge is given, a 2-h wait should precede administration of the second challenge material. The exact timing of the challenges may depend on the office schedule. A possible routine would have the first challenge begin at 8:30 AM, with the observation complete by 10:30. The patient might then have a break with a light lunch and begin the second challenge at 12:30 PM. If no reaction is seen after completing the second challenge material, the blinded portion of the challenge is judged negative. It is important then to follow with open administration of the food in a form it will likely be eaten. This open administration confirms that the food is indeed tolerated (that the challenge material was not somehow reduced in allergenicity) and that there is not a reaction with a high-dose threshold. Once again, for small children who have not previously consumed the challenged food, some allowance may have to be made to avoid refusal of a strange food. Thus, a milk shake rather than whole milk may be needed in the open challenge phase, or egg in a pudding rather than a fried or boiled egg. The published data showing the impressive power of these challenges are predicated on inclusion of the open consumption of the food at the end of the challenge (2,5,13).

Many practitioners have the impression that blinding foods for challenge is difficult. On the contrary, a commonsense approach is all that is necessary to blind most challenges adequately. For older children and adults, powdered food in capsules is a simple and effective blinding technique. Corn starch or dextrose are convenient placebo capsule fillers. If the food has a significant odor that might prevent blinding, another strong flavor/odor agent may be added to both the active and the placebo capsules. For example, if encapsulated peanut has a detectable odor, addition of almond flavoring to the peanut and to the placebo may aid blinding. Also, freezing the capsules until just

Table 2  
Common Combinations of Foods and Vehicles

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|                           |                                                  |
|---------------------------|--------------------------------------------------|
| Milk (dry powder):        | grape juice, infant formula                      |
| Egg (dry powder):         | grape juice, infant formula, Neocate, milk shake |
| Egg (fresh, cooked):      | puddings, mashed potato                          |
| Peanut (roasted, ground): | chocolate pudding, capsules                      |
| Soy (flour):              | applesauce, lentil soup, hamburger               |
| Wheat (flour):            | applesauce, capsules, hamburger                  |
| Fish (fresh, cooked):     | canned tuna                                      |
| Nuts (ground):            | chocolate pudding                                |

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prior to administration will further reduce the odor. Shaking both the active and placebo capsules in flavored powdered sugar may also be considered. If a capsule challenge is impractical for the food or the patient, creation of a suspension in a strongly flavored liquid is frequently easy. For milk and egg, 8–10 g dry powdered milk or dried egg white may be conveniently suspended in 100 mL of Concord grape juice. The strongly flavored juice overpowers the minimal flavor of either of these powders and is almost always accepted by children. Corn starch again is a convenient placebo in a 6-g quantity. Peanut is less easily disguised in liquid, but 10 g roasted peanuts finely powdered in a grinder will be adequately disguised in 6–8 ounces of chocolate pudding. Strongly flavored fish may be impossible to mask completely; however, almost all fish-sensitive individuals tolerate canned tuna, since it has been essentially denatured by the canning process (15). Thus, fish or placebo (canned tuna) may be mixed into hamburger patties that will have similar taste and texture for use in blinded challenge, or the fish being challenged may be mixed directly into the tuna. Hamburger patties are also useful to hide cereal grains for challenge. Shrimp may be hidden in ice cream flavored with grape syrup. Table 1 includes other common vehicles. Table 2 includes some of the possible combinations of food and vehicles useful in blinding challenges.

The placebo arm of the challenge may also be tailored to the challenge and the patient. As noted, some strongly flavored challenge foods may require special effort to produce a placebo close enough in taste, smell, and texture to be truly blinded. Use of similar-tasting, tolerated foods in the placebo is useful, as is the use of strongly flavored vehicles.

Testing for the oral allergy syndrome need not differ much from above. In this syndrome, capsule challenges are probably contraindicated, since contact of the food with the oral mucosa may be required. Although the oral allergy literature does not discuss the issue, the authors believe that 15–30 g of pureed fruit may be used

in a lemonade base (or Neocate if a stronger masking taste is required) in the active arm of a challenge, and a nonimplicated bland fruit in the placebo arm. Artificial flavoring to mimic the tested fruit may be added to both the placebo and active arm for blinding. The diagnostic accuracy of this maneuver has not been tested. If the symptoms are entirely subjective, several repetitions of both the active and placebo arms may be necessary to validate the challenge. Since the literature suggests at least some risk of systemic reaction, incremental administration is advised.

### ***Challenges for Unusual Symptoms***

The challenges discussed above have centered on detection of immediate hypersensitivity reactions. Many symptoms that patients describe are very unlikely to involve an IgE-mediated mechanism, since they are purported to occur many hours to days after the consumption of the food begins. The techniques described above may be modified to investigate such atypical symptoms attributed to foods. Several principles are involved in appropriately altering these protocols. Because prolonged administration is required, preparation of challenge materials for home use is usually necessary. Since the symptoms being investigated are often subjective, several cycles of placebo and active material are probably advisable to avoid a 50% random choice rate for a single pair of placebo and active material. The administration period should be at least as long as the purported interval to symptoms and probably twice as long if practical. Materials for challenge should be issued one arm at a time to avoid any ability to compare the challenge materials directly. A washout period between challenge arms is advisable to ensure no carryover of effects from one arm of the challenge to another. Unless the challenge food has been recently eaten and clearly causes no immediate reaction, an initial challenge of the type described above is often indicated.

The algorithm for analysis of unusual symptoms (Fig. 2) describes this approach for patients whose symptoms are not of an immediate nature. Frequently patients read lay literature that leads them to suspect foods as a cause of multiple symptoms; however, they cannot assign symptoms to any particular foods. Some patients suspect symptoms related to multiple foods. In these situations, an elimination diet may clarify whether the food is inducing the symptoms. If a diet eliminating all suspect foods does not improve symptoms, the foods may be ruled out as the cause of symptoms. A few patients will be so certain of a food-related etiology that a hypoallergenic or elemental diet is needed to demonstrate lack of relation to symptoms (and a few will actually have objective changes related to

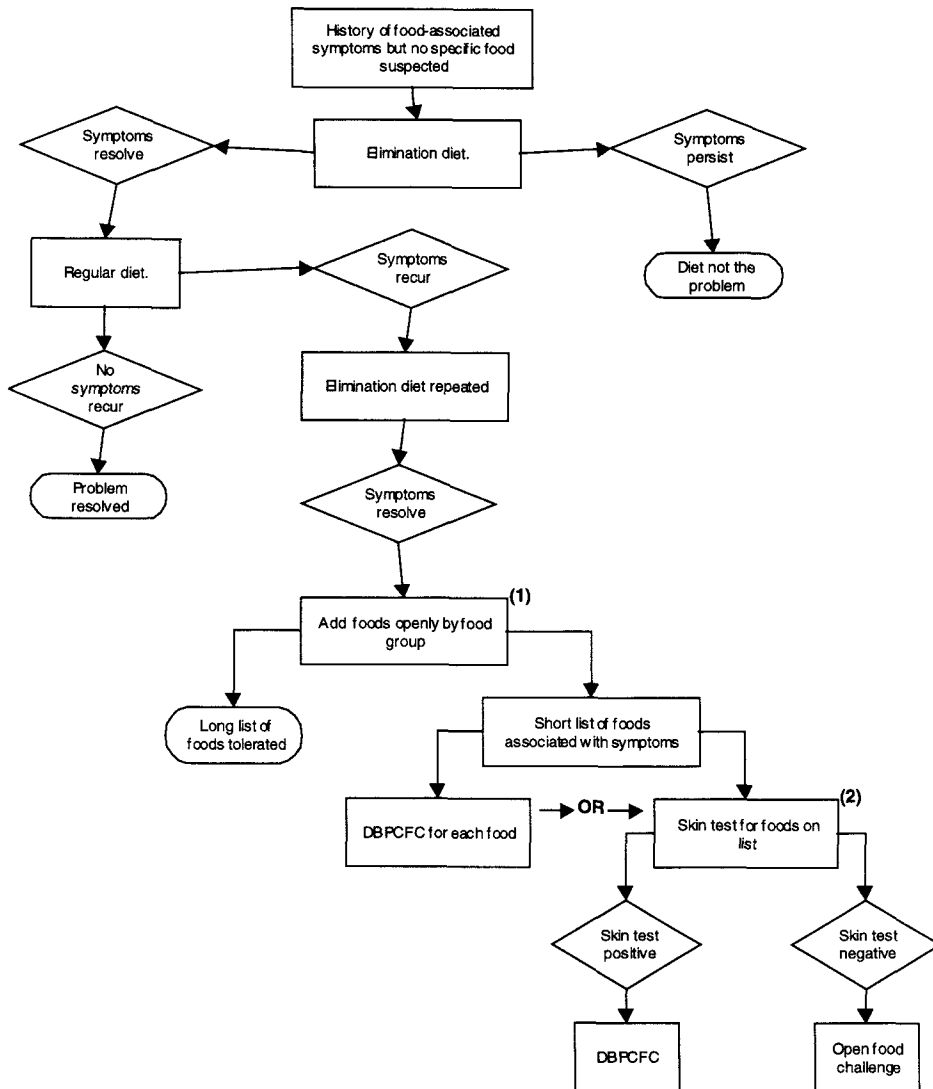


Fig. 2. Food challenge, skin tests, and elimination diet for analysis of unusual reactions to foods. This algorithm applies to situations not likely to be IgE-mediated. It may be generalized to all food reactions if appropriate steps are taken to avoid dangerous, immediate reactions (adapted from Food Allergy: A Primer for People, S. Allan Bock). (1) Foods are added openly at home only if not thought to provoke an IgE-mediated reaction or other potentially life-threatening reaction. (2) Prick skin tests might be employed here if it is thought that the reaction seen is IgE-mediated.

this extreme dietary maneuver). Adequate elimination diets are described elsewhere (13). If symptoms resolve on the elimination diet, but recur on reinstitution of regular diet, elimination is reinstituted and foods added openly by groups. Typically a short list of implicated foods will be generated. If the symptoms reported are possibly IgE-mediated, skin testing may then be indicated for guidance. If reported symptoms have the timing or characteristics of IgE-mediated reactions, caution should be used in adding eliminated foods to the diet. If the symptoms are not typical for IgE-mediated sensitivity, blinded challenges are required to determine if the foods are indeed causing symptoms.

A specific class of adverse food reaction frequently seen in younger children deserves special mention: the syndrome of food-protein-induced enterocolitis. This disorder must be remembered in the evaluation of infants suspected of reaction to formula. Since this disorder is not IgE-mediated, skin testing will be negative to formula proteins (milk or soy). However, on challenge, the patients may develop brisk diarrhea, to the point of hypovolemic shock, over the course of a few hours. Thus, the negative skin test cannot rule out the occurrence of a brisk and potentially life-threatening reaction. Almost all children with this disorder present in the first 6 mo of life with vomiting or diarrhea and are intolerant of milk or soy (16). A few patients present later in childhood, again with vomiting or diarrhea, and may be intolerant of other proteins besides milk or soy. On challenge, the patients usually react within an hour of administration of the implicated protein (16). Thus, infants with a history of isolated GI symptoms and without a positive skin test may react on challenge owing to this disorder.

## Summary

Skin tests by prick technique offer considerable guidance in the diagnosis of food allergy. Negative prick skin tests are powerful evidence against food allergy. Positive food skin tests are slightly to moderately predictive of reaction to a food on DBPCFC. Oral food challenge is necessary for confirmation of food allergy, except where the history is overwhelmingly convincing. Open, incremental food challenge as described is diagnostic if negative, but only 50% of all positive open challenges are confirmed on blinded challenge. DBPCFC can be designed for any food with simple blinding techniques. The technique of DBPCFC can be modified for investigation of atypical symptoms.

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