
Evaluation of IgE-Mediated Food Hypersensitivities [Supplement Contents]

Bock, S. Allan

Departments of Pediatrics, National Jewish and Medical Research Center, University of Colorado Health Sciences Center, Denver, Colorado, U.S.A.

Address correspondence and reprint requests to Dr. S. Allan Bock, Boulder Valley Asthma and Allergy Clinics, 3950 Broadway, Boulder, CO 80304-1199, U.S.A.

Abstract

ABSTRACT: During the past 25 years the diagnostic assessment of IgE-associated food hypersensitivity has improved substantially. The double-blind placebo-controlled food challenge has become the “gold-standard” against which all other diagnostic approaches can be measured. Having a standard which gives a correct answer almost all of the time, has enabled us to move to more accurate diagnoses in both the clinic and the laboratory. Food allergy has gone from being a medical mystery to being a clear component of allergy evaluation. Histories are obtained from patients which may be used to design food challenges. The role of skin testing and its interpretation has moved from the fringe to having a central role in eliminating foods incriminated as causes of immediate-onset allergic reactions. The material used for skin testing for foods has improved and we have learned when we must use fresh substances to supplement the commercial extracts. Recently the CAP radioallergosorbent test has shown promise in raising the probability of food reactions to the point that for a few foods in specific individuals, challenges may not be needed. Progress in this area will continue. We have been able to clarify which foods have a high probability of producing symptoms and which foods and which constellation of complaints are unlikely to be confirmed. These patterns of food allergic reactions have now been reproduced in many research centers throughout the world giving us confidence in their validity.

It has now been a quarter century since May conducted his first double-blind, placebo-controlled food challenge (DBPCFC) at National Jewish Medical Research Center. Although May credits a few predecessors (1–3) with the notion of performing blinded food challenges, he was the first investigator to explore food allergy systematically by using this technique (4). In the 25 years since those first challenges the DBPCFC has become the gold standard in research and in the clinic. The technique has been adopted and adapted by many centers (5–24). In this discussion we will review the blinded challenge and the changes it has undergone during the latter part of the 20th century. Many clinicians have objected to using the DBPCFC, claiming that it is too tedious, time consuming, and impractical (and not generally remunerative). However, for research purposes, we must have a rigorous gold standard against which other tests can be compared. May had a wonderful expression that he used to make this point, “To be practical is to be correct.” The DBPCFC remains the only means by which to be absolutely correct.

In addition to food challenges, this discussion reviews the current status of in vivo and in vitro testing, especially the recently developed technique for measuring specific food antibodies with the CAP fluorescent enzyme immunoassay (CAP-FEIA). This is an especially exciting development that may, for the first time, obviate the need for food challenges in some youngsters until such time as it becomes highly unlikely that

they will react to the food under investigation.

CLINICAL ASSESSMENT

History

The goal of taking a history in subjects who are having adverse food reactions is twofold. The first objective is to determine whether the pattern of the symptoms coincides with patterns of adverse food reactions described previously. Years of research in food hypersensitivity have established certain predictable patterns of reproducible symptoms that are associated with certain conditions (7). Thus, the history may allow the physician to counsel a patient that food is an unlikely trigger of the observed symptoms. (An example is that behavioral changes in older children are rarely triggered by food ingestion [7].)

The second goal of history-taking is to define the problem accurately so that a food challenge can be designed. For this purpose certain facts must be ascertained (Table 1). These include but are not be limited to a description of the symptoms, the time from ingestion of the food to the onset of the symptoms, the number of occasions when the food ingestion has been associated with the symptoms, the most recent occurrence of the reaction, and the association of other factors with the reaction and food ingestion (e.g., exercise).

	TABLE 1. Historical information to be obtained
Description of symptoms	
Timing from food ingestion to onset of symptoms	
Quantity of food required to produce symptoms	
Number of occasions that food has elicited symptoms	
Age at first occurrence and at most recent occurrence	
Association with exercise	

The reproducible severity of the reaction in comparison with the dose of food ingested is also very important in the evaluation of anaphylaxis to food.

In children with a history of a severe or anaphylactic reaction to food, the diagnosis is usually accepted if the food was ingested alone or with other foods known to be tolerated and if there are positive skin test or in vitro test results supporting the diagnosis. There are, however, important caveats in the diagnosis of anaphylaxis to food, because it is crucial to identify the correct offender. An incorrect diagnosis may result in the patient's avoiding the wrong food and having further reactions subsequently. Of course, challenges for food anaphylaxis require the utmost precaution and must be administered in an intensive care unit. Most of

the difficulty arises when evaluating subjects with idiopathic anaphylaxis. Some research protocols investigating anaphylaxis may also require challenges. This maybe become more important as treatments for food anaphylaxis are developed.

There are numerous reports of food's producing symptoms that involve only the gastrointestinal tract and that have some characteristics of IgE-mediated reactions (prompt onset of vomiting and abdominal pain, followed shortly by diarrhea) for which IgE detection by skin testing or in vitro testing is quite variable (25–29). Careful exploration of the history of these reactions is crucial for both investigating and understanding the pattern of the problem and also for designing a challenge to be administered.

Physical Examination

The physical examination may or may not be particularly helpful when evaluating patients with possible food hypersensitivity. The main stigmata of food hypersensitivity are skin changes, especially atopic dermatitis and occasionally urticaria. However, most patients with food-induced urticaria do not exhibit the lesions at the time they are evaluated unless they have recently eaten the food that is responsible and are undergoing examination when acutely ill. Other manifestations that may be observed are listed in Table 2.

	TABLE 2. Physical examination
Nasal findings: edema, mucus, color of mucosa	
Ocular findings: edema, chemosis	
Oral findings: edema	
Chest signs: cough, wheezing, rhonchi	
Abdominal signs: tenderness, altered bowel sounds	

In Vivo Evaluation Skin Testing

Immediate-hypersensitivity skin testing (Table 3) has played an important role in the understanding of food hypersensitivity during the past 25 years. Skin tests have been applied by the prick–puncture technique, scratch technique, and intradermal technique. Early studies showed that food prick–puncture skin tests were an excellent and consistent means of detecting IgE antibodies to food in children. Intradermal skin tests were also shown to detect antibody to food but exhibited a poor correlation with the elicitation of symptoms during a food challenge (30–33). Prick–puncture skin tests have been found to have a high negative predictive

accuracy for the major foods producing immediate hypersensitivity reactions in children (30–33). Unfortunately, the converse is not true. The positive predictive accuracy has been found to be extremely variable and often quite low, rendering it a poor method for predicting clinical symptoms during food challenges.

	TABLE 3. <i>In vivo testing</i>
Skin testing	
Commercially available extracts	
Fresh food extracts	
(assure validity of both)	
Patch testing	
Commercially available extracts	
Fresh food extracts	
(role needs further definition and validation)	
Intraoral testing	
Labial challenge	
Oral mucosal challenge	
(role of both requires further research)	

In children less than 2 years of age, it may be that positive skin test results are more likely to be significant than negative ones. In younger children, the negative predictive accuracy of the skin test is not as good as in older children (7,30,31). However, it is likely that we should give careful attention to positive skin test results in this age group. Further studies are needed to confirm this hypothesis.

One of the major problems in skin testing of children with food hypersensitivity is the selection of the appropriate extracts to use. Many children have undergone skin testing with far too many extracts, and the result is many positive skin test responses that must then be explained by the physician. Highly atopic children frequently have positive skin responses to many allergens, which cause no clinical symptoms when those foods are ingested. Therefore, it is wise to choose to test with only those allergens that are likely to cause symptoms upon ingestion of the foods. Using the history as a guide to selecting extracts to be used in testing is far more efficacious than using panels of allergens that may include foods that the patient consumes without difficulty.

The composition and quality of the extracts are also a significant consideration. For the major foods causing food hypersensitivity the commercially available extracts are usually adequate. Nevertheless, each new bottle of extract should be verified to demonstrate that it contains active ingredients. Until a new bottle of extract has elicited a wheal-and-flare response in a sensitized patient, it is never certain that it contains potent material.

For fruits and vegetables, the commercially available extracts are often inadequate. They may not detect antibody that is present because of instability and poor shelf life. Therefore, it is extremely helpful to use fresh fruits and vegetables in skin tests for these substances. The prick-and-prick technique is effective for this purpose. The technique is accomplished by pricking the food to be tested and then pricking the skin of the patient under evaluation (34). Similar data may be obtained using scratch chambers (Finn chambers) (35). It is essential that at least one other person (unlikely to be sensitized) be used as a negative control to insure the validity of the testing technique. It is possible that the extract could be an irritant; this would be confirmed by the use of a negative control.

This same principle may be applied to the use of other substances for which there are not commercially available extracts. Spices are a prominent example. In the evaluation of patients with anaphylaxis the question of a spice as the causative factor is often raised. Numerous spices have been confirmed as the culprits causing anaphylaxis in a number of subjects. Yet the evaluation of these histories is hampered by the absence of available testing material. Extracts of spices can be made using some method to grind the material into a powder and then extracting it with diluent used for skin testing. In this situation a positive result is helpful (with a negative control subject) and a negative response to the test is not revealing and cannot be regarded as proving that sensitization is not present.

Patch Testing

It has recently been suggested that patch testing for food hypersensitivity may add helpful information to the study of food-allergic subjects. These results should be considered preliminary and in need of confirmation by additional investigators (36).

Oral-Labial Testing

Recent studies have suggested that foods applied to the lip (37) and to the oral mucosa would be sensitive enough to make a firm diagnosis of food hypersensitivity and eliminate the need for food challenges. From a practical point of view, most people experiencing oral symptoms from a food immediately cease eating it and often remove it from their mouths. Further research in this area may well confirm this notion, although we have observed that some people have oral symptoms consistently when food contacts the mucosal surface of the mouth, but they do not react if a large quantity is ingested masked in some other food or administered by capsules.

In Vitro Testing

At this time, the most useful in vitro measurement in the diagnosis of immediate-hypersensitivity food allergy is the determination of specific IgE to food allergens ([Table 4](#)). There are now several techniques for making this measurement. The original test was the radioallergosorbent test (RAST). Enzyme-linked immunoassays have been replacing methods that use radiation. A newer approach is the CAP FEIA. This test has the potential to provide physicians with some quantitative information that, for some foods, may replace the DBPCFC. As with skin testing, the variants of the RAST depend on the quality of the reagents, especially the allergen extracts. It is also important to take into account potential interference from high total IgE and high specific IgG.

	TABLE 4. <i>In vitro</i> testing
Immunoglobulin E	
Radioallergosorbent test	
CAP fluorescent enzyme immunoassay	
Total immunoglobulin E	
Basophil histamine release	
Non-immunoglobulin E	
Eosinophils and eosinophil degranulation products	
Complement	
Tryptase	
Cytokines	
Lymphocyte stimulation tests	
Immunoglobulin G and subclasses: no proven use at this time	
Immune complexes: no proven use at this time	

In the past, use of these tests has been frustrated by the same problem as skin testing—that is, high specificity and high negative predictive accuracy and low sensitivity and low positive predictive accuracy. Because there are many people in whom there is a positive skin test result and a negative DBPCFC result or a positive in vitro result but a negative DBPCFC result, it has been impossible to establish cutoff levels that would discriminate between subjects with or without actual clinically significant reactions to ingested foods. Recently, Sampson et al. ([28,38–40](#)) have begun using optimal decision point analysis with receiver operating characteristic (ROC) curves. This analysis has yielded some encouraging preliminary data, suggesting that upper and lower limits can be established that predict more accurately which patients will react (or not react) to food challenges.

Further research is needed to determine the utility of these measurements in patients who are the subject of this conference. It is my opinion that many of the patients with chronic gastrointestinal tract symptoms in whom we are interested, are experiencing a sequence of immunologic events and that determination of specific IgE by a very sensitive technique may eventually be helpful in understanding the mechanism of these reactions.

Thus far, the determination of total IgE in the serum does not appear to be helpful as a screening test or as a test to determine whether a specific patient is likely to have food hypersensitivity.

Basophil histamine release has some theoretical advantages that support its use as a diagnostic test. However, thus far, it has usually not been found to be more predictive than skin testing or specific IgE serum determinations, and its disadvantages have relegated it to a research procedure. Whether it will have a different role in the future remains to be determined.

The determination of levels of specific IgG, IgG4, IgA, and IgM has been pursued. Many claims have been made about the diagnostic accuracy of the IgG tests using the IgG RAST for the diagnosis of delayed-onset food allergy. It should be sufficient to note that outside of the illnesses that are the topics of this conference, it has been rare for anyone to demonstrate that there are a significant number of patients with delayed-onset food hypersensitivity. Furthermore, the evidence that measuring IgG antibodies to food in these or any other subjects is totally lacking. The same statement may be made for the determination of immune complexes to food (41). It is my contention that all subjects, especially children, make IgG antibodies to foods that they ingest. In fact, if a youngster were identified in whom there was no IgG antibody to any of the common foods, I would be concerned about that child's immune system.

Measurements of lymphocytes and lymphocyte stimulation tests have been examined for their utility in the diagnosis of food allergy. There is a body of work that claims that these tests are useful (42,43). However, a careful examination of this work by Sampson (44) has not reproduced these results. At this time, judgment should be reserved about these tests, but it appears that further work must be undertaken by additional investigators to confirm their utility.

It is possible to measure certain mediators and other biochemical substances that may be released during food challenge. Study of these substances may yet prove useful in diagnosis, but at present, their primary role is in the examination of the mechanism of these diseases. Plasma histamine can be measured during DBPCFC and has been found to be elevated. Serum tryptase that should be elevated in episodes of anaphylaxis (and has been found in insect sting-sensitive patients) has not been regularly elevated in food-allergic people having a reaction including anaphylaxis (45).

We (46) and others have measured serum complement changes during positive and negative DBPCFC without finding the measurements to be particularly discriminating.

More encouraging work may yet be published that supports some preliminary reports suggesting that measurement of eosinophil products may help in understanding the mechanism of atopic diseases (47–49). Certainly, the illnesses under discussion at this meeting have a large number of eosinophils identified in the intestine at many levels (29). It would appear that these cellular products are important in the eosinophilic gastroenteritis group of illnesses. Measurements of cytokines, especially those involved in eosinophil activity (interleukin [IL]-5) may also be useful (50).

I feel certain that the future holds great promise in the ability of the laboratory to be helpful in unraveling the mechanism of these bowel diseases and in achieving accurate diagnoses with less invasive procedures. In fact, what is needed now is less invasive means to examine the gastrointestinal tract at many levels. In the mean time, the DBPCFC may be used to be certain that we are studying populations of subjects who can be objectively shown to have the diseases in question (51).

FOOD CHALLENGES

The oral food challenge has been established as the gold standard for the diagnosis of adverse food reactions caused by any mechanism. Despite the criticism that has been leveled at the procedure, it gives investigators a strong standard against which to test in vivo and in vitro diagnostic procedures. Investigators have now begun using it as the standard for measuring the effectiveness of certain treatments for food hypersensitivity (52,53). In the future, this will become even more important as various treatments for food allergy vie for the attention of scientists and physicians. (Investigators in the area of food hypersensitivity have the advantage of having a gold standard. This cannot be said for the science of inhaled allergen diagnosis and treatment.)

Although the technique may require some arrangements to acquire the materials and administer the challenges, it clearly tells when the diagnosis is correct and when a new treatment is succeeding. The fact that we can “see what we eat” has been both the curse and the crutch of the study of food hypersensitivity. For difficult problems such as delayed reactions to food that can occur in the intestine, the arrangements require more ingenuity, but the observations may still be made with a substantial degree of certainty. As we move into the next era of molecular biological tests and treatment, we should be able to move beyond the necessity of conducting food challenges, but we will always be grateful to have a gold standard to which we can return.

Open Food Challenge

Open food challenges are sometimes very helpful and easily performed when histories of adverse food reactions are vague and unlikely to be accurate. Sometimes they can be performed outside a medical

environment. At other times they should be administered in a medical setting. The latter circumstance occurs when young children have a history of food hypersensitivity to egg or milk or a positive skin response to peanuts and have never had peanuts. These children should be challenged under observation so that unexpected but significant reactions may be treated promptly.

Frequently, children have a vague history of an adverse reaction to a food, a history of probable ingestion of the food, and no particular knowledge about what may transpire when the food is consumed. Open food challenges under direct observation may be very helpful with these subjects, to refute the history.

Physicians often question the setting in which open challenges should be administered. A physician's office, equipped with the emergency resuscitation measures that would be found in an allergist's office, is a safe place in which to perform open challenges where the likelihood of a systemic reaction is very low, according to the history. Most of these open challenges are short cuts to refuting very unlikely histories of reactions to foods when the physician is uncomfortable about allowing the challenge to be performed at home. If it is likely that there will be a systemic reaction, then the challenge should be blinded and should be performed in a setting with emergency equipment and additional personnel.

Single-Blind Food Challenges

Single-blind food challenges (SBFCs) are more useful than open food challenges, because the bias of the subject is eliminated. They can be used to document the absence of symptoms, particularly in situations in which it may be desirable to refute a history of vague or subjective symptoms without having to involve multiple personnel in the challenge. Single-blind challenges may also be useful in certain research situations for selection of patients who will then participate in the double-blind phase of a study. In many clinical settings the SBFC is a very practical technique for helping patients determine which foods from a long list are actually causing the problems.

Double-Blind Placebo-Controlled Food Challenge

The DBPCFC remains the gold standard for making the diagnosis of an adverse reaction to a food. This technique will work for any mechanism or timing if the challenge is designed correctly (4–24,28,29) (Tables 5 and 6). The food challenge must be designed to reproduce the patient's history with respect to all the information obtained during the acquisition of the history. Special attention is paid to the timing and dosage.

Gastrointestinal: nausea, vomiting, abdominal pain, colic, diarrhea, colitis, gastroenteritis
 Respiratory: rhinorrhea, sneezing, laryngospasm, cough, wheezing
 Cutaneous: atopic dermatitis, urticaria, angioedema, erythema
 Ocular: tearing; conjunctival swelling, scleral edema
 Cardiovascular: hypotension, cardiovascular collapse
 Anaphylaxis: multiple symptoms from those listed

TABLE 5.
Symptoms confirmed during double-blind, placebo-controlled food challenge

Eosinophilic esophagitis
 Eosinophilic or allergic gastropathy (enteropathy)
 Dietary protein enteropathy
 Cow's milk-induced gastrointestinal bleeding (Wilson-Heiner-Lahey)
 Dietary protein enterocolitis
 Benign eosinophilic proctitis
 Lymphoid nodular hyperplasia
 Gluten-sensitive enteropathy

TABLE 6.
*Intestinal syndromes that have been or could be confirmed under observation*Data from A.M. Lake.

Data from A. M. Lake.

At present there are several protocols that are used for the administration of food challenges. One of the best approaches is to have a single day for the active food and a separate day for the placebo. Time constraints have resulted in administration of both challenges on the same day. This is an acceptable approach for immediate-onset symptoms so that the morning challenge may be consumed over a period of approximately 2 to 3 hours and then there can be an interval or more than 2 hours before the afternoon challenge commences. The afternoon challenge then follows the same procedure (see later discussion). The only potential limitation of this approach is that slow or delayed-onset symptoms could be missed or cause confusion. If this occurs, then the challenge must be repeated using separate active food and placebo days. In some instances, the actual use of placebo may be omitted because multiple foods are being tested blindly, and the other foods may serve as placebos as long as at least one food challenge is negative. When evaluating subjective symptoms, it may be useful to intermingle the active and placebo doses. This may be done in a random fashion, but the whole challenge is ingested on the same day. Thus, the subject ingests different numbers of capsules at different times in a seemingly random manner. This adds to the blinding of the procedure. Some investigators have felt that all challenges should contain the same number of capsules, and thus they have started with the placebo and then gradually replaced some placebo capsules with food

capsules. There also are instances in which the challenge must be altered after each dose, depending on the response. In this situation, the investigator sends the challenge to the study unit to be administered by a nurse. Then a written report is sent back to the investigator before the next challenge, so that the appropriate change can be made. By using an intermediary to transport the challenge and the progress report, the investigator is aware of the results of each challenge without prejudicing the outcome of subsequent challenges. This procedure has been most useful when studying subjective or vague symptoms that are reported to begin promptly after ingestion of the suspected food. For example, when studying children with headache, abdominal pain, or behavioral changes the ability to change the challenge from suspected food to placebo and back, during a single challenge day, has proved most helpful.

As noted, the dose and timing are determined by the history. By current convention, the starting dose is usually approximately one half the amount that is thought to be the minimum amount likely to produce an immediate-onset adverse reaction. Some studies use a more specific dose protocol so that every subject receives the same dose at the same intervals. There are multiple approaches that may work well, depending on the reactions under investigation.

The timing of challenges must be scheduled so that each challenge is slightly longer than the time predicted by the history for a reaction to occur (Table 7). The doses are doubled at the chosen interval. When the challenge is negative up to 8 to 10 g of dried food (single dose) or 60 to 100 g of wet food, then the challenge is stopped, and the results are presented to the patient and/or parents. Then an open challenge is administered.

Start with an amount less than the history suggests will elicit symptoms. Administer incremental quantities (doubling doses) at intervals slightly longer than expected, by history, to elicit symptoms. Maintain an hourly (or as appropriate) symptom record. If multiple doses over a few days are required, administer the quantity likely to produce symptoms one or more times each day. Use an appropriate placebo, and if the symptoms are subjective, multiple crossovers are necessary.	TABLE 7. Administration of double-blind, placebo-controlled food challenge
--	--

The challenge procedure in which there is no reaction is not considered complete until the food under study can be consumed in usual portions with no occurrence of symptoms. The ability of the subject to ingest the suspected food(s) without development of symptoms, eliminates many of the frequently posed questions

about the effect of preparation, digestion, and other variables on the blinded food challenge. The major consideration that is likely to yield a positive open challenge after a negative blinded challenge is the dose-response consideration, wherein the dose consumed during the blinded challenge is not high enough to trigger symptoms that then occur after a higher dose in the open challenge. This circumstance is infrequently encountered in clinical practice or in research studies (7) (H. A. Sampson, personal communication; A. W. Burks personal communication; September 1998).

The other explanation for a negative blinded challenge accompanied by a positive open challenge, is the subject's strongly held belief that consumption of the food will cause symptoms. This concern is often not assuaged by the negative blinded challenge, and symptoms occur when the patient can see the food as it is consumed.

An additional circumstance is contact between the food and the patient's oral tissues. Many of the earliest blinded challenge studies used capsules, and that meant that local oral symptoms may not have been detected, because the capsules did not allow the food to contact the oral mucosa. The advantage of capsule use was that it allowed challenges to determine whether systemic symptoms would occur in situations in which the challenge would have been halted because of oral symptoms.

The described procedures have been very successful when used to study subjects with immediate-onset symptoms. In fact, the literature shows that very few delayed-onset reactions have been confirmed except those found in the gastrointestinal tract. Nevertheless, the DBPCFC is used very successfully to evaluate delayed-onset symptoms. These subjects usually present one of two symptom and timing patterns. The first is that a single dose of food causes symptoms hours to days after ingestion. In this situation the food is administered under observation in the morning. The subject is then asked to return when the symptoms occur. Use of the placebo is crucial, and the challenge procedure should be "crossed over" two or three times, to assure that the challenge results are reproducible.

When the food must reportedly be ingested multiple times, especially during a period of multiple days, then the only optimal means to accomplish a true DBPCFC is in a setting where administration of all the doses can be supervised, and symptoms can be seen to develop by an objective observer. In this era, the resources to accomplish this goal are often unavailable. It is possible to have the patient ingest challenges at home, but it must be possible to administer food in a form that is difficult for the patient to discern. This may be accomplished with very cooperative subjects who have no significant biases. This procedure is most helpful when the challenge is negative. We have been helpful to subjects who have reported delayed-onset

subjective symptoms, such as headache and arthralgia, and gastrointestinal symptoms. In the subjects under consideration at this conference a modification of this procedure could be accomplished by having subjects come to the clinic each morning to ingest the challenge and then return on the day that symptoms appear. A crossover technique with this type of challenge is also important.

At this time there is not a standard protocol (or even protocols) that has invariably been shown to be successful for undertaking challenges in people with the various gastroenteropathies addressed at this symposium. Bock et al. (25) used a modified blinded challenge protocol to challenge young children with histories suggesting food protein enteropathies. His group had the luxury of keeping the children in a hospital study unit, under observation, until their reaction began. Then biopsies were performed. Because these challenges often lasted several days to weeks, it is unlikely that this approach can be used in the current medical economic climate. Kelly et al. (29) used an open challenge protocol in which the foods were administered at home by the parents for specified periods. The criteria for a positive challenge were carefully defined. Most recently Sicherer et al. (28) used a defined protein dose to challenge youngsters with food protein enterocolitis syndrome. This dose was modified depending on the historical severity of the reaction. As more research is performed on these diseases, additional protocols will be developed and tested. Important principles for these challenges are a good understanding of the history of the reaction and an estimate of the dose that probably caused the symptoms to appear. With this information, challenges can be designed that will reproduce the symptoms in a manner that can be controlled, to prevent severe outcomes requiring heroic resuscitation measures.

Over the years since food challenges began to be used systematically, numerous vehicles have been developed. Capsules were the first regularly used vehicle and remain the best method for blinding. However, many foods are now used for masking challenges. Table 8 contains a list of currently used examples. At this time, the vehicle chosen is dependent on the food under study and the quantity that must be administered.

Capsules
Infant formula
Applesauce
Neocate^a
Milk shakes
Chocolate pudding
Tapioca fruit mixture
Grape juice
Hamburger
Tuna fish
Ice cream (grape)
Popsicles
Lentil soup
Mashed potato
Cereal

^aSHS International, Rockville, MD, U.S.A.

TABLE 8. *Vehicles that have been used in double-blind, placebo-controlled food challenge^a*SHS International, Rockville, MD, U.S. A.

We often encounter patients who offer vague and subjective reports, frequently involving the gastrointestinal tract for which no obvious mechanism or explanation is clear. To be helpful, we often place the patient on a diet of few foods (also known as an oligoantigenic diet) to see whether the symptoms resolve ([Table 9](#)). If the symptoms resolve, then we usually allow the patient to consume a normal diet again to see whether the symptoms return. If they recur, we can reinstitute the diet of few foods, and when improvement occurs again we add foods to the diet openly, one at a time. The usual finding is a few foods that are suspect, and many foods that are absolved as culprits.

Rice or corn as the only grain
Two to four vegetables chosen by patient and physician
Two to four fruits chosen by patient and physician
Chicken
White vinegar, olive oil, honey, sugar (beet or cane), salt

TABLE 9. *A few-food (oligoantigenic) diet*

In conclusion, it is important to have a standard against which diagnostic tests and therapeutic treatments may be tested. For this purpose the DBPCFC remains unsurpassed. Our ability to design challenges that attempt to verify patient histories is only limited by our imagination.

REFERENCES

1. Loveless MH. Milk allergy: A survey of its incidence: Experiments with a masked ingestion test. *J Allergy* 1950; 21:489–500. [[Context Link](#)]
2. Loveless MH. Allergy for corn and its derivatives: Experiments with a masked ingestion test for its diagnosis. *J Allergy* 1950; 21:500–9. [[Context Link](#)]

3. Maslansky L, Wein G. Chocolate allergy: A double-blind study. *Conn Med J* 1971; 35:5–9. [\[Context Link\]](#)
4. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. *J Allergy Clin Immunol* 1976; 58:500–15. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
5. Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: A manual. *J Allergy Clin Immunol* 1988; 82:986–97. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
6. Sampson H, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 1989; 115:23–7. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
7. Bock SA, Atkins FM. Patterns of food hypersensitivity during 16 years of double-blind placebo-controlled food challenges. *J Pediatr* 1990; 117:561–7. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
8. Bernstein M, Day JH, Welsh A. Double-blind food challenge in the diagnosis of food sensitivity in the adult. *J Allergy Clin Immunol* 1982; 70:205–10. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
9. Onorato J, Merland N, Terral C, Michel FB, Bousquet J. Placebo-controlled double-blind food challenge in asthma. *J Allergy Clin Immunol* 1986; 78:1139–46. [\[Context Link\]](#)
10. Farah DA, Calder I, Benson L, MacKenzie JF. Specific food intolerance: Its place as a cause of gastrointestinal symptoms. *Gut* 1985; 26:164–8. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
11. Bock SA, Lee W, Remigio LK, May CD. Studies of hypersensitivity reactions to foods in infants and children. *J Allergy Clin Immunol* 1978; 62:327–34. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
12. Novembre E, de Martino J, Vierucci A. Foods and respiratory allergy. *J Allergy Clin Immunol* 1988; 81:1059–65. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
13. Pastorello EA, Stocchi L, Pravettoni V, et al. Role of the elimination diet in adults with food allergy. *J Allergy Clin Immunol* 1989; 84:475–83. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
14. Norgaard A, Bindslev-Jensen C. Egg and milk allergy in adults. *Allergy* 1992; 47:503–9. [\[Context Link\]](#)
15. Kivity S, Dunner K, Marian Y. The pattern of food hypersensitivity in patients with onset after 10 years of age. *Clin Exp Allergy* 1994; 24:19–22. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
16. James JM, Bernhisel-Broadbent J, Sampson HA. Respiratory reactions provoked by double-blind food challenges in children. *Am J Respir Crit Care Med* 1994; 149:59–64. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
17. Jakobsson I, Lindberg T. Cow's milk proteins cause infantile colic in breast-fed infants: A double-blind crossover study. *Pediatrics* 1983; 71:268–71. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
18. Lothe L, Lindberg T. Cow's milk whey protein elicits symptoms of infantile colic in colicky formula-fed infants: A double-blind crossover study. *Pediatrics* 1989; 83:262–6. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
19. Forsythe BWC. Colic and the effect of changing formulas: A double-blind multiple crossover study. *J Pediatr* 1989; 115:521–6. [\[Context Link\]](#)
20. Daul CB, Morgan JE, McCants ML, Hughes J, Lehrer SB. Provocation challenge studies in shrimp sensitive individuals. *J Allergy Clin Immunol* 1988; 81:1180–6. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
21. Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: Clinical relevance of food hypersensitivity reactions. *J Pediatr* 1988; 113:447–51. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
22. Burks AW, James JM, Hiegel A, et al. Atopic dermatitis and food hypersensitivity. *J Pediatr* 1998; 132:132–6. [Catalogo Biblioteca ISS Buy Now Bibliographic Links](#) [\[Context Link\]](#)

23. Hourihane JO, Kilburn SA, Nordlee JA, Hefle SL, Taylor SL, Warner JO. An evaluation of the sensitivity of subjects with peanut allergy to very low doses of peanut protein: A randomized, double-blind, placebo-controlled food challenge study. *J Allergy Clin Immunol* 1997; 100:596–600. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
24. Caffarelli C, Cavagni G, Giordano S, et al. Relationship between oral challenges with previously uningested egg and egg-specific IgE antibodies and skin prick tests in infants with food allergy. *J Allergy Clin Immunol* 1995; 95:1215–20. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
25. Bock SA, Remigio LK, Gordon B. Immunochemical localization of proteins in the intestinal mucosa of children with diarrhea. *J Allergy Clin Immunol* 1983;72:262–8. [\[Context Link\]](#)
26. Katz AJ, Twarog FJ, Zeiger RS, Falchuk ZM. Milk-sensitive and eosinophilic gastroenteropathy: Similar clinical features with contrasting mechanisms and clinical course. *J Allergy Clin Immunol* 1984; 74:72–8. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
27. Verdaguer J, Corominas M, Bas J, et al. IgE antibodies against bovine serum albumin in a case of eosinophilic gastroenteritis. *Allergy* 1993; 48:542–6. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
28. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr* 1998; 133:214–9. [Catalogo Biblioteca ISS Buy Now Bibliographic Links](#) [\[Context Link\]](#)
29. Kelly KJ, Lasenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: Improvement with an amino acid-based formula. *Gastroenterology* 1995; 109:1503–12. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
30. Bock SA, Buckley J, Holst A, May CD. Proper use of skin tests with food extracts in diagnosis of hypersensitivity to food in children. *Clin Allergy* 1977;7:375–83. [\[Context Link\]](#)
31. Bock SA, Lee W-Y, Remigio LK, Holst A, May CD. Appraisal of skin tests with food extracts for diagnosis of food hypersensitivity. *Clin Allergy* 1978;8:559–64. [\[Context Link\]](#)
32. Sampson HA, Albergo R. Comparison of results of prick skin tests, RAST, and double-blind placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 1984; 74:26–33. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
33. Sampson HA. Comparative study of commercial food antigen extracts for the diagnosis of food hypersensitivity. *J Allergy Clin Immunol* 1988; 82:718–26. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
34. Dreborg S, Foucard T. Allergy to apple, carrot and potato in children with birch pollen allergy. *Allergy* 1983; 38:167–72. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
35. Hannuksela M, Lahti A. Immediate reactions to fruits and vegetables. *Contact Dermatitis* 1977; 3:79–84. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
36. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996; 97:9–15. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
37. Rance F, Dutau G. Labial food challenge in children with food allergy. *Pediatr Allergy Immunol* 1997; 8:41–4. [Catalogo Biblioteca ISS Buy Now Bibliographic Links](#) [\[Context Link\]](#)
38. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997; 100:444–51. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
39. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions of peanut and tree nuts in children. *Pediatrics* 1998;102, available at <http://www.pediatrics.org/cgi/content/full/102/1/e6>. [\[Context Link\]](#)
40. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;101, available at <http://www.pediatrics.org/cgi/content/full/101/3/e8>. [\[Context Link\]](#)

41. Sheffer AL, Lieberman PL, Aaronson DW, et al. Measurement of circulating IgG and IgE food immune complex. *J Allergy Clin Immunol* 1988; 81:758–9. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
42. Agata H, Kondo N, Fukutomi O, Shinoda S, Orii T. Effect of elimination diets on food-specific IgE antibodies and lymphocyte proliferation responses to food antigens in atopic dermatitis patients exhibiting sensitivity to food allergens. *J Allergy Clin Immunol* 1993; 91:668–79. [\[Context Link\]](#)
43. Kondo N, Fukutomi O, Agata H, et al. The role of T lymphocytes in patients with food-sensitive atopic dermatitis. *J Allergy Clin Immunol* 1993; 91:658–68. [\[Context Link\]](#)
44. Hoffman KM, Ho DG, Sampson HA. Evaluation of the usefulness of lymphocyte proliferation assays in the diagnosis of allergy to cow's milk. *J Allergy Clin Immunol* 1997; 99:360–6. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
45. Sampson HA, Mendelson LM, Rosen JP. Fatal and near fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; 327:380–4. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
46. Martin ME, Guthrie LA, Bock SA. Serum complement changes during double-blind food challenges in children with a history of food sensitivity. *Pediatrics* 1984; 73:532–7. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
47. Niggemann B, Beyer K, Wahn U. The role of eosinophils and eosinophil cationic protein in monitoring oral challenge tests in children with food-sensitive atopic dermatitis. *J Allergy Clin Immunol* 1994; 94:963–71. [\[Context Link\]](#)
48. Torpier G, Colombel JF, Mathieu–Chandelier C, et al. Eosinophilic gastroenteritis; ultrastructural evidence for a selective release of eosinophil major basic protein. *Clin Exp Immunol* 1998; 74:404–8. [\[Context Link\]](#)
49. Bengtsson U, Knutson TW, Knutson L, Dannaes A, Hallgren R, Ahlstedt S. Eosinophil cationic protein and histamine after intestinal challenge in patients with cow's milk intolerance. *J Allergy Clin Immunol* 1997; 100:216–21. [\[Context Link\]](#)
50. Jaffe JS, James SP, Mullins GE, Braun–Elwert L, Lubensky I, Metcalfe DD. Evidence for an abnormal profile of Interleukin-4 (IL-4), IL-5, and gamma-Interferon in peripheral blood T cells from patients with allergic eosinophilic gastroenteritis. *J Clin Immunol* 1994; 14:299–309. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
51. European Society for Paediatric Gastroenterology and Nutrition Working Group for the Diagnostic Criteria for Food Allergy. Diagnostic criteria for food allergy with predominantly intestinal symptoms. *J Pediatr Gastroenterol Nutr* 1992;14:108–12. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
52. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DYM. Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol* 1992; 90:256–62. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)
53. Nelson HN, Lahr J, Rule R, Bock SA, Leung DYM. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997; 99:744–51. [Catalogo Biblioteca ISS Bibliographic Links](#) [\[Context Link\]](#)

Accession Number: 00005176-200001001-00004

Copyright (c) 2000-2006 [Ovid Technologies, Inc.](#)
Version: rel10.3.2, SourceID 1.12052.1.159