

Food challenge procedure: Optimal choices for clinical practice

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ABSTRACT

The diagnosis of food allergy depends on thorough medical history-taking that may be supplemented with trials of dietary eliminations, skin testing, and specific IgE antibody measurement. However, the reliability of such procedures is often suboptimal. For most cases, oral challenge testing is needed to confirm the diagnosis of food allergy and to identify the causative food(s). Though blinded challenges are ideal, open challenges can be appropriate in some cases, particularly in young children. An optimal design of the procedure would depend on the age of the patient, the anticipated symptoms, and the provoking food quantity. The test is much safer than many surgical and medical procedures being routinely performed. This article presents a practical guideline that can reliably and safely encourage an increased use of this important test in the diagnosis of food allergy.

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Key words: Allergy, food allergy diagnosis, food challenge procedure, food challenge testing, provocation testing, skin tests, specific IgE

Food allergy (FA) is a common, if not the most common, self-diagnosed ailment. It may be manifested by a wide variety of symptoms that are mostly nonpathognomonic.¹ It can be suspected through medical history and screening tests, such as trials of elimination diets, skin testing, or specific IgE antibody measurement.² The medical history and screening tests can be positive to multiple foods or may be totally negative (Table 1). For definitive documentation of a cause-and-effect relationship between a specific food and certain symptoms, appropriately designed food challenge testing is necessary.

Food challenge testing is under-utilized, even by allergy specialists. Responsible factors are multiple,³ and include lack of training on the procedure, increased reliability on screening methods (medical history, skin testing, *in vitro* tests), extensive time needed, fear of risk, and suboptimal fee reimbursement. The objectives of this article are to address these issues and provide a practical guideline for conducting the procedure that should enhance its use reliably and safely.

TYPES OF FOOD CHALLENGE PROCEDURES

Generally, the challenge test should be preceded by a duration of dietary elimination.⁴ All suspected foods should be strictly avoided for a duration at least equal to the longest symptom-free period the patient had had. If the patient remains asymptomatic, or with minimal symptoms, while on no or minimal symptomatic medications, then the challenge test can be carried out. If the result of the test is equivocal, that particular food should be subjected to another elimination trial and challenge (Fig. 1). The challenge may be conducted in any of three methods: open, single-blind, and double-blind.⁵ (Table 2.)

Open Food Challenge

Open food challenge is the easiest to perform and has some advantages, but can have a high degree of bias. The latter can be on the part of the observer, but more likely on the part of the patient, depending on the age, personality type, psychological status, type of symptoms, and number of claimed offending foods. For example, the bias may be minimal in the case of an infant whose eczema becomes exacerbated after eating egg or an adult whose acute urticaria occurs within minutes of eating shrimp. In contrast, the bias can be substantial in the case of a boy being claimed to be hyperactive hours or days after eating sugar. Another example would be a middle-aged woman who has been divorced and unemployed complaining of headache, fatigue or depression after eating any of numerous foods.

Single-Blind Placebo-Controlled Food Challenge

Single-blind placebo-controlled food challenge would be appropriate for most cases in clinical prac-

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Table 1 Causes of a "false" result of food skin testing or specific IgE antibody testing

"False" positive test result

Variability in test method or scoring
Cross reactivity with other allergens
Sensitization without clinical allergy

"False" negative test result

Error in the test
Variability in testing method or material
IgE antibodies are mainly in the shock organ
Non-IgE mediated hypersensitivity

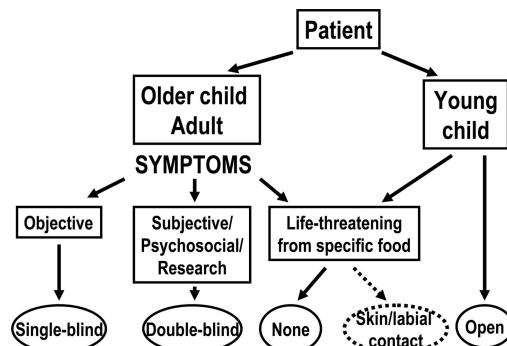


Figure 2. Optimal choices of food challenge type according to age and symptoms. (Modified from Ref. 6.).

its risk in any particular patient, some steps often need to be individualized. (Table 3)

Choosing a Placebo or a Vehicle

Whereas in open food challenge, where the food is given openly in its usual form, in blind challenges the food should be hidden in a palatable vehicle that does not allow recognition of the test food in any way (taste, odor, color, or texture). Freeze-dried or powder foods may be administered in opaque capsules, and the placebo can be sucrose, starch, or wheat flour. Only a few foods can be easily available in powder form (*e.g.*, milk, soy, wheat, egg, fruits, vegetables). The wet or native food weight equivalence may be difficult to estimate. Also, there should be a concern about possible change in food allergenicity by processing.^{9–12}

Test Material

The test material should be administered in a gradually increasing quantity, preferably on an empty stomach for rapid absorption and not to suspect a previously ingested food. The starting dose should be safe to the patient being tested, depending on the reaction's severity and the food quantity that caused it. The dose may be increased every 20–30 minutes to a cumulative dose equal to or exceeding the usually eaten quantity by the patient.

In the case of food additives, the challenge doses are generally very small and vary widely from one substance to another. The cumulative dose may be up to 30 mg for food dyes, 3000 mg for monosodium glutamate, and 300–400 mg for sulfiting agents and other additives.¹³

In the case of food-dependent, exercise-induced reactions, the usual quantity of food is given in one dose followed by exercise as determined by the medical history. In the majority of patients, the reaction develops shortly after exercise, but it may be delayed for 5 hours or more.¹⁴

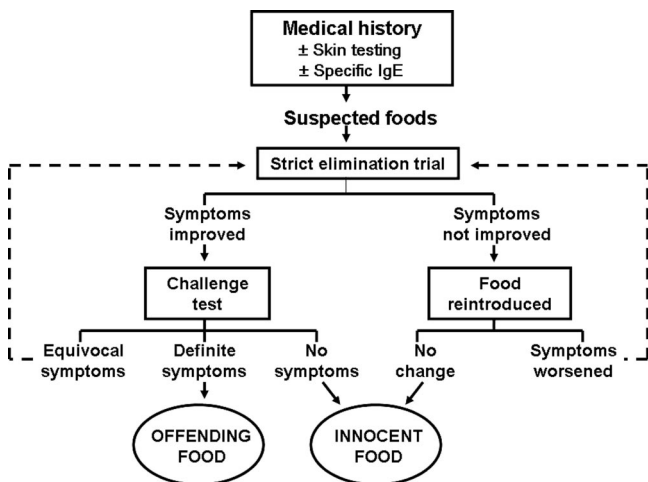


Figure 1. Flow diagram for the food elimination-challenge test. (Modified from Ref. 4.).

tice. Because the observer knows the nature of the challenge substance, there is a risk of bias by the observer. The patient may also develop a bias if the observer exhibits more concern during a certain test visit than during another.

Double-Blind Placebo-Controlled Food Challenge

Double-blind placebo-controlled food challenge is often referred to as the "gold standard" method because it is least associated with bias. It is ideal for research and in selected patients in clinical practice.

In deciding on the optimal type of challenge procedure with maximal safety and minimal bias, the nature of anticipated symptoms and the patient's age should be taken into consideration (Fig. 2).⁶

PREPARING AND ADMINISTERING THE FOOD CHALLENGE

Although standardization of the challenge procedure has some advantages,^{7,8} it would be unrealistic to provide a single protocol that can be appropriate for every patient. To maximize the test's reliability and minimize

Table 2 Types of food challenge procedures

A. Open food challenge

Food is given in its usual form

Both the observer and patient know

Acceptable in infants and young children with objective symptoms

Useful for preliminary screening of foods that are at a low level of suspicion

Possible advantages

Simple

Reproduce the natural exposure (form of food, quantity, method of exposure)

When the suspected foods are numerous and the anticipated reaction is not severe, the least suspected foods may be screened by open challenge at home, and then the claimed positive results may be verified by blind challenge. This would save time and cost because only about 30% of suspected foods give a positive blind challenge.

B. Single-blind food challenge

Needs an appropriate placebo

Food should be well disguised (taste, odor, color, texture)

Observer knows but not the patient

Tests must be administered in the same way

Result is revealed to the patient after all challenges are done

Applicable to most cases in clinical practice

Possible advantages

In patients suspected of having a psychologic component, the placebo test may be done first so that, if it causes symptoms, each substance that gives a positive reaction should be tested at least twice.

In patients undergoing challenges with several foods, if some give a negative result, testing with a placebo may not be needed.

C. Double-blind food challenge

Food is well disguised (taste, odor, color, texture)

Neither observer nor patient knows

Food and placebo are prepared and coded by a third person

Test substances are given in a random fashion, exactly in the same way

After all challenges are done, the code is opened and results are discussed

Ideal for research and for some cases in clinical practice

Modified from Ref. 5.

Setting

Food challenges should be designed and carried out by experienced health care professionals in a facility where close monitoring can be done and measures for treatment of potential life-threatening reactions are available. Admission to the hospital, or occasionally the intensive care unit, may be needed in certain cases.

Patient

Symptomatic medications should be discontinued 12–24 hours before challenge. Unlike the case with allergy skin testing, it is very unlikely for antihistamines taken 12 hours earlier to inhibit a reaction to the food quantity used for a challenge.

After the last dose of the test substance, the patient should be observed for 1–2 hours to allow for absorption. Documentation of reaction should depend on accurate recording of the developing symptoms and signs before each dose. Fig. 3 shows an example of a

record form used by the author for the procedure. Measurement of peak expiratory flow rate should be included, particularly in patients with history of asthma or anaphylaxis. In special cases, evidence of mast cell degranulation may be documented by measuring the level of plasma histamine (within 30 minutes) or tryptase (at 1–2 hours). Rarely, a delayed reaction (usually mild) develops later during the subsequent several hours. Patients with negative challenge may start next day to cautiously consume that food openly.

CAN THE OUTCOME OF CHALLENGE TESTING BE PREDICTED?

In general, the stronger the skin-prick test (SPT) reactivity or the higher the specific IgE (sIgE) titer, the more likely is that food to be positive by challenge. In a series of children mostly with atopic dermatitis, the outcome of the food challenge test was compared with

Table 3 Preparing and administering food challenge

Choosing a placebo
Sugar, starch, or wheat flour in opaque capsules.
Elemental diet (EleCare, Neocate, Vivonex).
Pure beef burger
Selected fruit juice, soup, broth, jam, applesauce, etc.
Carob syrup for cocoa
Test Material
Start with a safe dose
Increase every 20–30 min by 50–100%
Cumulative dose should be at least equal to the usually eaten quantity
One test material per visit
Setting
Close supervision in clinic, hospital ward, or ICU
Monitor for 1–2 hr after last dose
Measures for treating life-threatening reactions
Patient
Strictly avoid all suspected foods
No or minimal symptoms at challenge
No or minimal symptomatic medications for the preceding 12–24 hr
Preferably empty stomach

the sIgE level measured by the ImmunoCAP-FEIA (Phadia, Kalamazoo, MI).¹⁵ The 90% and 95% positive predictive levels of sIgE varied widely among the six foods tested. In other series, different predictive values were observed.^{16–19} In a large study on peanut and tree nut sensitivity,²⁰ a CAP-sIgE level of 15 kU/L or more was noted in only 30% of patients who had the most severe reactions, and the serum test was considered falsely negative in 22% and falsely positive in 40%.

As with the case of sIgE level, the predictive size of SPT reactivity varied from one study to another, from one food to another, and by age.^{20–26} In a study on nut allergy,²⁰ a SPT wheal reaction of 3 mm or more to a tolerated nut was noted in 46% of cases, and in patients with the most severe clinical reactions, only 22% had a wheal of 8 mm or more. For proper interpretation of sIgE or SPT result, several factors should be considered, including total IgE level, patient's age, type of allergy manifestation, severity of allergy manifestation, type of food allergen, and duration and degree of avoidance of the offending food at the time of testing.

SITUATIONS WHERE FOOD CHALLENGE MAY NOT BE NECESSARY

In instances where a specific single-item food has caused a life-threatening reaction, particularly if on more than one occasion, food challenge in any form should be avoided. If there is any doubt about that

food, skin or labial contact may be done cautiously. Oral challenge should be avoided in patients who react to the food by skin contact or inhalation.^{27,28} Challenge may not be necessary when only one food out of many tested is strongly positive by SPT or sIgE, or was suspected by the medical history, and the symptoms improved on avoidance. In patients with intermittent acute reactions, foods that were eaten on multiple occasions with impunity between the episodes are obviously nonoffending and may not be tested by challenge, even when positive by SPT or sIgE testing.

A situation that is sometimes encountered in routine clinical practice is a patient (or parent) who strongly believes that the avoidance of a particular food or food additive prevents certain symptoms. In such cases, if the food is not nutritionally essential and the patient is comfortable with its elimination, the challenge tests may be circumvented because its result would unlikely change the patient's belief. Of course, the diagnosis remains unconfirmed.

ADVANTAGES OF FOOD CHALLENGE TESTING

At present, challenge testing is the most reliable procedure for verification of the causative food, particularly when done in a blind fashion. According to a review of several studies,⁵ double-blind challenges were positive in only 17–37% (mean 28%) of the suspected foods and in only 29–65% (mean 50%) of patients suspected of having FA. Hence, the several advantages of performing the challenge test (Table 4).

LIMITATIONS OF FOOD CHALLENGE TESTING

Difficulties

Some difficulties can be encountered in planning, performing, or interpreting the results of the food challenge test. A positive test merely indicates a cause-and-effect relationship between the test materials and the reproduced reaction. An inference on the underlying mechanism may be derived either from the type of clinical reaction or from the results of relevant *in vivo* or *in vitro* tests (Table 5).

To reproduce an oral allergy syndrome, the respected fruit should be fresh (unprocessed) and should come in contact with the oral mucosa during chewing. In such cases, the placebo can be one or two tolerated fruits shredded or cut into very small pieces, and having strong flavor and color to mask the test fruit. In one study, shredded fresh apple was hidden in a mixture of cabbage, turnip and apple microwaved at 95°C for 5 minutes.²⁹

The Test Result May be False

A falsely positive challenge test is primarily caused by bias, mostly on the patient's part but can be on the

RECORD FOR ORAL CHALLENGE TESTING

Name: _____; Age _____; MR# _____; Date _____

Allergy diagnosis: _____

Medications within last 12-24 hr: _____

Challenge method: () open, () single-blind, () double-blind. Placebo/vehicle _____

Test material: _____; Suspected by (score 1 to 4 +): history _____, SPT _____, sIgE _____

Form: () powder; weight per capsule _____; equivalence to wet weight _____
() liquid; quantity per ounce _____
() prepared at home _____
() commercial preparation; brand name _____

Starting dose _____ Subsequent doses: _____; _____; _____; _____; _____; _____

At intervals of _____ minutes; Maximum cumulative dose: _____

Anticipated symptoms: _____

Present symptoms/signs: _____

Baseline vital signs: T _____, HR _____, RR _____, BP _____, PEFR _____

Dose given	Time given	Time evaluated	Resulting reaction	PEFR
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____

Conclusion: () positive challenge; () negative challenge; () equivocal challenge _____

Recommendation: _____

Signature _____ Name _____

Figure 3. Example of oral challenge test record.

Table 4 Advantages of food challenge testing

Verification of causal relationship between food and the patient's symptoms
Identification of the truly offending food(s) or additive
Limiting the dietary elimination would
 Reduce the burden of management
 Improve the quality of life
 Enhance the compliance
 Prevent potential mal- or under-nutrition, particularly in children
Excluding food allergy would allow investigation for other causes of the patient's symptoms

Modified from Ref. 2.

observer's part. Hence the advantages of double-blind testing. If the test result is equivocal, the test may need to be repeated. If the test material is not pure, a contaminant or an additive may be the cause of the reaction rather than the main food.

A falsely negative challenge test may result from any of several factors that interfere with reproducing the natural exposure. An area that is only partially explored is the involvement of concomitant factors, *e.g.*, exercise, hormones, stress, intercurrent illness, and combination with another food or inhalant allergen. In 2 out of 11 patients reported with food-dependent, exercise-induced anaphylaxis, the reaction was limited

Table 5 Limitations of food challenge tests

Positive test merely indicates a cause-and-effect relationship, not necessarily immunologic
Foods to be tested depend on the screening method(s) used
Disguising the food may be difficult
 Food may not be available in a powder form
 Eructation may allow identification, even when using capsules
 Large quantities of certain foods are difficult to disguise
Patient's or observer's bias may occur, particularly when the challenges are few
Reproducing the natural exposure may be difficult
 Food's allergenicity may depend on its form
 Exposure by inhalation or oropharyngeal contact is excluded by using capsules
 Difficulty in estimating weight equivalence of powder to wet form.
 Incorporation of possible concomitant factors, *e.g.*, exercise, GI disorders, hormonal changes, intercurrent viral illness, food combinations, inhalants, emotional stress

Table 6 Precautions to enhance the safety of food challenge testing

Personnel experienced in planning, carrying out, and monitoring the procedure
Food administered in titrated quantities, starting with an individualized safe dose
Measures for treatment of life-threatening reactions
Avoid challenge in instances of definite life-threatening reactions that occurred from a specific single-item food
To identify a food that caused severe anaphylaxis, the test would preferably be conducted in the hospital, even in ICU
Only foods that are remotely suspected of causing a mild reaction may be cautiously tested at home

to the time of menstruation.³⁰ In a patient who had anaphylaxis on multiple occasions to exercise after eating a certain commercially-prepared meal composed of 10 items, the reaction was only reproduced when he exercised after the intake of a combination of two particular components of that meal.³¹

Risk of Challenge Testing

Food challenge testing is simply a cautious trial of administering a food that the patient has been consuming but is suspected of causing the reaction. The food is given in a titrated fashion under supervision in a medical facility. A properly designed and conducted food challenge test should have minimal risk. Occasionally, however, the challenge causes a reaction severer than what is being anticipated by the medical history.^{32,33} Hence, precautionary measures should be always followed to minimize the risk (Table 6). Whereas the risk of accidental exposure to the offending food at a restaurant, school, or home can be lethal,^{34,35} to the best of my knowledge there have been no reported fatalities to appropriately-designed food challenge tests conducted in a medical facility.³⁶

CONCLUSIONS

To date, food challenge testing is the most reliable procedure for confirming a causative relationship between a particular food or food additive and an adverse reaction. Its use has several important advantages and should be included in the allergy practice. Though double-blind testing is recommended for research and in some cases in clinical practice, most patients can be reliably tested by single-blind or open challenges. In most cases, it can be done safely in the clinic, with measures for management of potential life-threatening reactions available. To maximize its safety, the method, the starting dose, and increments should

be individualized, and in certain instances the test may not be necessary.

REFERENCES

1. Bahna SL. Clinical expressions of food allergy. *Ann Allergy Asthma Immunol* 90:41–44, 2003.
2. Bahna SL. Diagnosis of food allergy. *Ann Allergy Asthma Immunol* 90:77–80, 2003.
3. Bahna SL. Food challenge procedures in research and in clinical practice. *Pediatr Allergy Immunol* 6:49–53, 1995.
4. Bahna SL. Practical considerations in food challenge testing. *Immunol Allergy Clin N Am* 11:843–850, 1991.
5. Bahna SL. Blind food challenge testing with wide-open eyes. *Ann Allergy* 72:235–238, 1994.
6. Bangash SA, and Bahna SL. Pediatric food allergy update. *Curr Allergy Asthma Rep* 5:437–444, 2005.
7. Niggemann B, Wahn U, and Sampson HA. Proposals for standardization of oral food challenge tests in infants and children. *Pediatr Allergy Immunol* 5:11–13, 1994.
8. Bindeslev-Jensen C, Ballmer-Weber BK, Bengtsson U, et al. Standardization of food challenges in patients with immediate reactions to foods: Position paper from the European Academy of Allergology and Clinical Immunology. *Allergy* 59:690–697, 2004.
9. Fiocchi A, Restani P, Riva E, et al. Heat treatment modifies the allergenicity of beef and bovine serum albumin. *Allergy* 53:798–802, 1998.
10. Maleki SJ, Chung SY, Champagne ET, and Raufman JP. The effects of processing on the allergenic properties of peanut proteins. *J Allergy Clin Immunol* 106:763–768, 2000.
11. Beyer K, Morrow E, Li X, et al. Effects of cooking methods on peanut allergenicity. *J Allergy Clin Immunol* 107:1077–1081, 2001.
12. Paschke A, and Besler M. Stability of bovine allergens during food processing. *Ann Allergy Asthma Immunol* 89:16–20, 2002.
13. Wilson BG, and Bahna SL. Adverse reactions to food additives. *Ann Allergy Asthma Immunol* 95:499–507, 2005.
14. Oyefara BI, and Bahna SL. Delayed food-dependent, exercise-induced anaphylaxis. *Allergy Asthma Proc* 28:64–66, 2007.
15. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 107:891–896, 2001.
16. Boyano-Martinez T, Garcia-Ara C, Diaz-Pena JM, et al. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy* 31:1464–1469, 2001.
17. Garcia-Ara C, Boyano-Martinez T, Diaz-Pena JM, et al. Cow's milk-specific immunoglobulin E levels as predictors of clinical reactivity in the follow-up of the cow's milk allergy infants. *Clin Exp Allergy* 34:866–870, 2004.
18. Niggemann B, Celik-Bigili S, Ziegert M, et al. Specific IgE levels do not indicate persistence or transience of food allergy in children with atopic dermatitis. *J Invest Allergol Clin Immunol* 14:98–104, 2004.
19. Celik-Bilgili S, Mehl A, Verstege A, et al. The predictive value of specific immunoglobulin E in serum for the outcome of oral food challenges. *Clin Exp Allergy* 35:268–273, 2005.
20. Clark AT, and Ewan PW. Interpretation of tests for nut allergy in one thousand patients in relation to allergy or tolerance. *Clin Exp Allergy* 33:1041–1045, 2003.
21. Sporik R, Hill DJ, and Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg, and peanut in children. *Clin Exp Allergy* 30:1540–1546, 2000.
22. Fiocchi A, Bouygue GR, Restani P, et al. Accuracy of skin prick tests in IgE mediated adverse reactions to bovine proteins. *Ann Allergy Asthma Immunol* 89:26–32, 2002.
23. Monti G, Muratore MC, Peltran A, et al. High incidence of adverse reactions to egg challenge on first known exposure in young atopic dermatitis children: Predictive value of skin prick test and radioallergosorbent test to egg proteins. *Clin Exp Allergy* 2:1515–1519, 2002.
24. Kagan R, Hayami D, Joseph L, et al. The predictive value of a positive prick skin test to peanut in atopic peanut-naïve children. *Ann Allergy Asthma Immunol* 90:640–645, 2003.
25. Hill DJ, Heine RG, and Hosking CS. The diagnostic value of skin prick testing in children with food allergy. *Pediatr Allergy Immunol* 15:435–441, 2004.
26. Verstege A, Mehl A, Rolinck-Werninghaus C, et al. The predictive value of the skin prick test wheal size for the outcome of oral food challenges. *Clin Exp Allergy* 5:1220–1226, 2005.
27. Tan BM, Sher MR, Good RA and Bahna SL. Severe food allergies by skin contact. *Ann Allergy Asthma Immunol* 86:583–586, 2001.
28. Bahna SL. Adverse food reactions by skin contact. *Allergy* 59:66–70, 2004.
29. Kinaciyan T, Jahn-Schmid B, Radakovics A, et al. Successful sublingual immunotherapy with birch pollen has limited effects on concomitant food allergy to apple and the immune response to the Bet v 1 homolog Mal d 1. *J Allergy Clin Immunol* 119:937–943, 2007.
30. Dohi M, Suko M, Sugiyama H, et al. Food dependent exercise induced anaphylaxis: A study of 11 Japanese cases. *J Allergy Clin Immunol* 87:34–40, 1991.
31. Aihara Y, Kotoyori H, Takahashi Y, et al. The necessity for dual food intake to provoke food-dependent exercise-induced anaphylaxis (FEIAN): A case report of FEIAN with simultaneous intake of wheat and umeboshi. *J Allergy Clin Immunol* 107:1100–1105, 2001.
32. Goldman AS, Anderson DW Jr., Sellers WA, et al. Milk allergy. I. Oral challenge with milk and isolated milk proteins in allergic children. *Pediatrics* 32:425–443, 1963.
33. Bahna SL, and Gandhi MD. Reliability of skin testing and RAST in diagnosis of food allergy. In *Food Allergy*. Chandra RK (ed.). St. John's, NL, Canada: Nutrition Research Foundation 84:139–147, 1987.
34. Yunginger JW, Sweeney KG, Sturner WQ, et al. Fatal food-induced anaphylaxis. *JAMA* 260:1450–1452, 1988.
35. Sampson HA, Mandelson L, and Rosen JP. Fatal and near-fatal food anaphylaxis reactions in children. *N Engl J Med* 327:380–384, 1992.
36. Chapman JA, Bernstein IL, Lee RE, et al. Food allergy: A practice parameter. *Ann Allergy Asthma Immunol* 96:S1–S68, 2006. □

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