

Dose-response in double-blind, placebo-controlled oral food challenges in children with atopic dermatitis

Scott H. Sicherer, MD, Ellen H. Morrow, and Hugh A. Sampson, MD

New York, NY

Background: Double-blind, placebo-controlled oral food challenges (DBPCFCs) are considered the "gold standard" for diagnosing food hypersensitivity, but the dose that elicits positive challenges, or determinants that may predict dose-response relationships, have not been reported.

Objective: Our purpose was to determine the quantity of food that elicits reactions during DBPCFCs and to evaluate parameters that may predict the provocative dose and severity of reaction.

Methods: We reviewed challenge data for all positive challenges to 6 common allergenic foods in children with atopic dermatitis evaluated for food allergy over a 13-year period. Challenge food was generally administered in 6 doses at 10- to 15-minute intervals beginning with 400 to 500 mg and completing with a total of 8 to 10 g of food. An open feeding of a larger portion followed negative challenges. At the physician's discretion, a lower starting dose was occasionally used (100 mg, 250 mg). Food-specific IgE antibody concentrations (radioallergosorbent test [RAST]) were determined on stored sera of 20% of the challenges selected randomly and 99.6% had prick skin tests (PSTs) performed to the challenged food. **Results:** A total of 196 children (45% male; median age 5 y 9 mo; atopic dermatitis 98%, asthma 62%) had 513 positive challenges distributed as follows: egg 267, milk 117, soy 53, wheat 40, peanut 24, fish 12. The percentage of children reacting at the first dose (500 mg or less) was as follows: egg 49%, milk 55%, soy 28%, wheat 25%, peanut 26%, and fish 17%. Twenty-six milk challenges and 22 egg challenges were positive at a first dose of 250 mg; 3 milk challenges and 7 egg challenges were positive at a first dose of 100 mg. Eleven percent of the reactions that occurred on the first dose were severe. The percentage reacting after the final dose of the DBPCFC (or during open challenge) were egg 11%, milk 12%, soy 19%, wheat 12.5%, peanut 8.7%, and fish 25%. There was not a strong correlation between PST absolute wheal size or score (adjusted for histamine controls) and dose at reaction or severity of reaction (R_s range -0.22 to 0.39 for particular foods).

Serum concentration of food-specific IgE did not correlate well with the dose causing a reaction or with severity (R_s range -0.40 to 0.55 for particular foods).

Conclusions: This food-allergic population may react to as little as 100 mg of food, possibly less, and the dose causing a reaction and the severity of reaction is not predicted by PST or RAST. Lower doses (100 mg or less) should be investigated for their appropriateness in initiating DBPCFCs. (*J Allergy Clin Immunol* 2000;105:582-6.)

Key words: Food hypersensitivity; double-blind, placebo-controlled food challenge

Thirty-seven percent of children with atopic dermatitis have food allergy,¹ but the diagnosis can be difficult to secure and depends on results from history, elimination diets, and oral food challenges.² The double-blind, placebo-controlled food challenge (DBPCFC) is considered the "gold standard" for diagnosing food allergy because patient and observer bias is removed.³⁻⁵ Although the procedure can be modified to an office setting, it is time consuming and labor intensive.⁶ Positive challenges can elicit skin, respiratory, or gastrointestinal symptoms with reactions that may be severe and require medications.⁶

Although dosing regimens for oral food challenges have been discussed in the literature,⁶⁻⁸ little has been reported about the typical dose or minimal doses that elicit reactions. Further, no attempts have been made to determine factors that may predict the dose at which patients react. We undertook this study to determine the quantity of food that elicits reactions during DBPCFCs and to evaluate parameters that may predict the provocative dose and severity of reaction.

METHODS

Subjects

Children with atopic dermatitis with positive DBPCFCs to egg, milk, wheat, soy, peanut, and fish during the evaluations for food allergy were included in this retrospective study. Data were reviewed for challenges performed between 1980 and 1993. Challenges subsequent to 1993 were not evaluated because after that period selection for challenges to these major allergens was influenced by the results of food-specific IgE concentration,⁹ with exclusion of challenges for patients most likely to have positive challenges. Data were included for individual subjects with multiple food challenges to one or several foods.

Prick skin tests

Prick skin tests (PSTs) were performed as previously described.⁵ Briefly, glycerinated food extracts (1:10 or 1:20, Greer Laboratories, Lenoir, NC) were applied by the prick technique with use of a

From the Elliot and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mt Sinai School of Medicine, New York, NY.

Supported in part by grants No. R01 AI24439, RR 00052, and RR 00071. S. H. S. was supported in part by the Jaffe Food Allergy Institute and by grant No. HD 28822-08.

Received for publication Nov 14, 1999; revised Dec 7, 1999; accepted for publication Dec 7, 1999.

Reprint requests: Scott H. Sicherer, MD, Division of Allergy/Immunology, Mt Sinai Hospital, Box 1198, One Gustave L. Levy Place, New York, NY 10029-6574.

Copyright © 2000 by Mosby, Inc.

0091-6749/2000 \$12.00 + 0 1/1/104941

doi: 10.1067/mai.2000.104941

Abbreviations used

DBPCFC: Double-blind, placebo-controlled food challenge
PST: Prick skin test
RAST: Radioallergosorbent test

bifurcated needle. Histamine and saline solution were applied as positive and negative controls. Skin test results were recorded by circling the wheal with ink, transferring to paper with cellophane tape, and measuring the mean of the greatest diameter and its orthogonal. Tests were evaluated both as the absolute size of the wheal in millimeters (less the saline solution control) and in a scoring system that took into consideration the histamine controls as follows: 0 for no discernible wheal, 1 for food extract wheal diameter less than one half histamine diameter, 2 for food extract wheal diameter greater than or equal to one half histamine diameter but less than histamine diameter, 3 for food extract wheal equal to histamine wheal plus or minus 1 mm, 4 for food extract wheal greater than histamine diameter but less than twice the histamine diameter, and 5 for food extract wheal greater than or equal to twice the histamine wheal.

Radioallergosorbent tests

Stored sera from a subset (20%) of patient challenges selected randomly from a previous study⁹ were analyzed for antigen-specific IgE antibody concentration with use of the Pharmacia CAP System FEIA (Pharmacia and Upjohn Diagnostics, Uppsala, Sweden) as previously described.⁹ Results were expressed as kU_A/L of specific IgE antibody.

Challenges

Selection of patients for DBPCFCs was predicated on the expectation that a severe clinical reaction was not highly likely to occur because no severe recent reaction had been documented. DBPCFCs were performed as previously described.^{5,6,10} A maximum of 8 to 10 g dry weight of dehydrated food, or equivalent liquid form, was camouflaged in a food product and given over a 90-minute period. Six doses of food were given in progressively larger quantities as follows: before 1992, 0.4 g, 0.8 g, 3 doses of 1.6 g, and a final dose of 2 g; 1992 and afterward, 0.5 g, 1 g, 3 doses of 2 g, and a final dose of 2.5 g. Patients received 2 challenges per day, 1 placebo and 1 test food. Dietitians in the clinical research unit prepared the food and randomized the placebo challenges. Negative DBPCFCs were followed with open challenges. In the open challenge patients received a larger quantity of food (a meal-size portion for age). Challenges were stopped at the discretion of the evaluating physician when objective signs and symptoms indicated a positive response, and medications were administered as needed. A previously described scoring system was used to determine the severity of the challenge reactions,¹¹ which were scored as minimal, mild, moderate, or severe.

Statistics

Spearman correlation coefficient (R_s) was calculated with use of a statistical package (Graphpad Prism, San Diego, Calif). Correlation coefficients outside the range of -0.6 to 0.6 and P values $<.05$ were considered significant.

RESULTS

Subjects and challenge results

A total of 196 children had positive DBPCFCs. The median age was 5 years 9 months and 55% were male.

Ninety-eight percent had active atopic dermatitis and 62% had asthma. A total of 513 positive challenges were distributed as follows: egg 267, milk 117, soy 53, wheat 40, peanut 24, and fish 12. Food-specific IgE concentration determinations were performed randomly on stored sera obtained at the time of challenge from 20% of the challenges (as part of another study⁹) and 99.6% had PSTs performed to the challenged food.

Dose-eliciting positive challenges, low-dose reactions, and severity

The distribution of doses that elicited positive challenges for each food is shown in Fig 1. The percentage of children reacting at the first dose (500 mg or less) was as follows: egg 49%, milk 55%, soy 28%, wheat 25%, peanut 26%, and fish 17%. At the physician's discretion, starting doses were sometimes less than 400 mg. Twenty-six milk challenges and 22 egg challenges were positive at a first dose of 250 mg; 3 milk challenges and 7 egg challenges were positive at a first dose of 100 mg. Thus a total of 25% of the milk challenges and 11% of the egg challenges were positive after a first dose less than 400 mg. The percentages reacting after the final dose of the DBPCFC (or during open challenge) were egg 11%, milk 12%, soy 19%, wheat 12.5%, peanut 8.7%, and fish 25%. Twenty-one challenges (4% of the total challenges) were positive only during open challenges as follows: egg 5, milk 8, wheat 2, soy 2, peanut 1, fish 3.

DBPCFCs elicited symptoms affecting the skin, gastrointestinal, and respiratory systems, as shown in Table I. The severity of challenge reactions for each food is depicted in Fig 2. There was not a strong correlation between the dose at reaction and severity of reaction for any of the 6 foods (R_s -0.4 to 0.03 ; P value range $<.001$ to $.8$) as may be expected because the supervising physician discontinued challenges once symptoms indicated a clear reaction. Eleven percent of the reactions that occurred on the first dose were severe.

Result of PSTs and RASTs

Correlation coefficients for dose and severity of reactions with measures of specific IgE antibody for each food are shown in Table II. The correlation between PST absolute wheal size or score and the dose causing a reaction was weak or negligible (R_s range -0.22 to 0.34 , P value range $.04$ to $.86$) for any of the 6 foods. PSTs also did not correlate strongly with severity of reaction for any of the foods (R_s range -0.07 to 0.39 , P value range $<.0001$ to $.82$).

Serum concentration of food-specific IgE was not strongly correlated with the dose causing a reaction (R_s range -0.07 to -0.4 , P value range $.09$ to $.91$) or with the severity of the reaction (R_s range 0.16 to 0.55 , P value range $.007$ to $.56$).

Analysis of the results of first challenges for all subjects (elimination of data from serial challenges) gave results that fell within the ranges given above for the entire data set (data not shown).

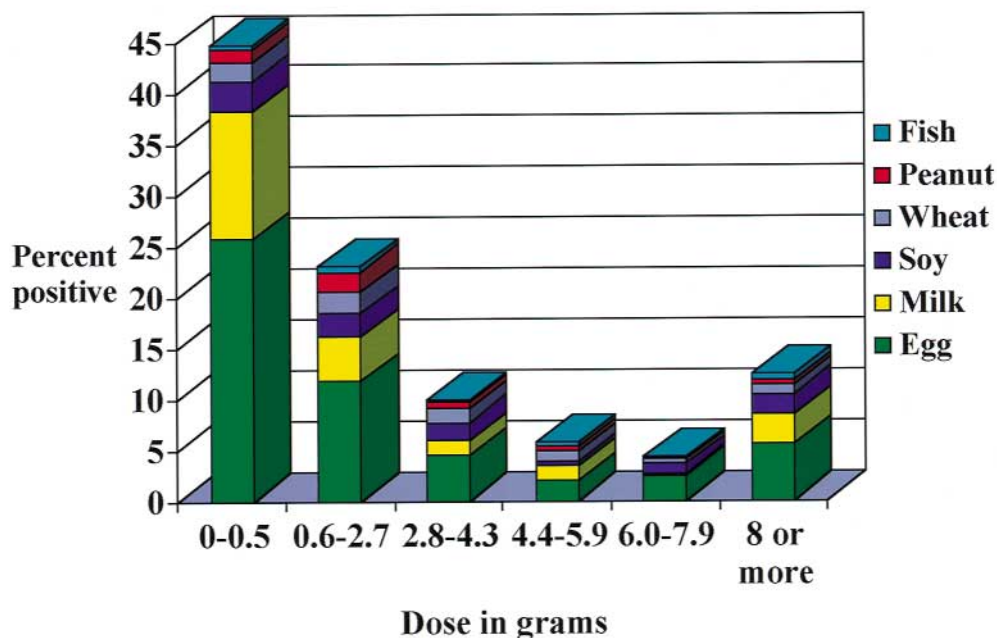


FIG 1. Dose of challenge substance resulting in onset of symptoms during DBPCFCs. Percentage of 513 challenges resulting in positive reactions at each dose are shown with distribution resulting from each of the 6 foods indicated in the legend.

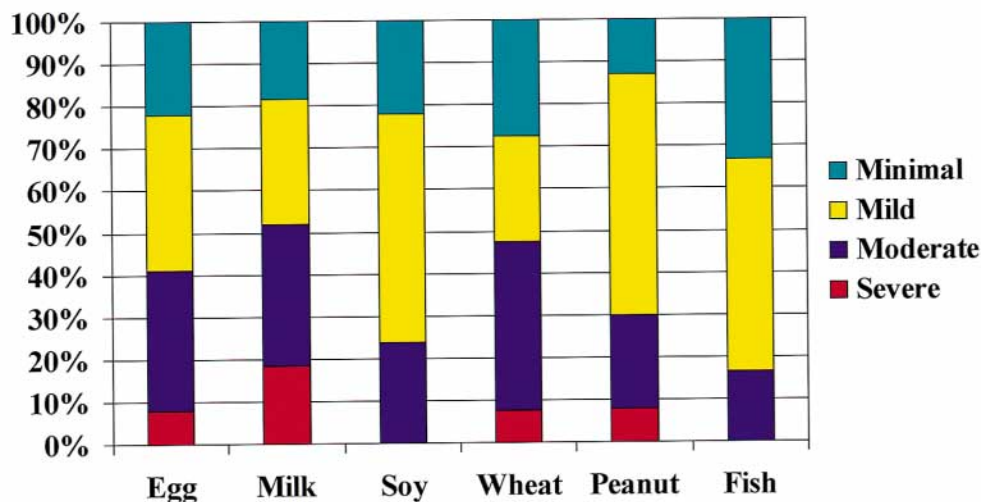


FIG 2. Severity of reactions caused by challenges during DBPCFCs to each of 6 foods. Distribution of challenges by severity is shown. Number of challenges for each food is indicated in Table I.

DISCUSSION

The diagnosis of food allergy often requires oral food challenges, particularly when food allergy is being considered in the context of a chronic disease, such as atopic dermatitis.¹² This is the case because a clinical history of reactivity and even positive diagnostic tests such as PST and RAST have poor specificity.^{3,5} Although a recent study indicated that oral food challenges can be deferred in a subset of children with atopic dermatitis who have significantly elevated concentrations of food-specific IgE antibody to egg, milk, peanut, and codfish,⁹ the use of

physician-supervised oral food challenges is ultimately the only diagnostic tool to determine clinical reactivity. Despite the widespread use of the DBPCFC, the "gold standard" for diagnosing food allergy, little has been studied in regard to dose-response relationships of reactions. Such information is vitally important for physicians performing these studies. In the current study we found that 45% of reactions began at doses less than 500 mg and that severity of reaction or dose causing a reaction was not strongly related to laboratory assessment of IgE by RAST or PST.

TABLE I. Symptoms elicited during DBPCFCs among 196 patients

Food	Total challenges	Cutaneous (% challenges)	Gastrointestinal (% challenges)	Respiratory (% challenges)
Egg	267	73	61	47
Milk	117	77	39	64
Soy	53	60	60	26
Wheat	40	78	45	45
Peanut	24	83	42	45
Fish	12	100	42	33
All foods	513	74	53	48

TABLE II. Spearman rank correlation coefficients comparing measures of specific IgE antibody (PST, radioallergosorbent tests [RASTs]) to dose of food eliciting positive DBPCFC and severity of symptoms during challenge

	Egg	Milk	Soy	Wheat	Peanut	Fish	All foods
Dose vs PST wheal	-0.22*	-0.14	0.25	-0.05	-0.09	-0.14	-0.17*
Dose vs PST score	-0.12*	-0.20*	0.34*	0.04	-0.04	0.08	-0.12*
Severity vs PST wheal	0.33*	0.36*	0.10	-0.07	0.18	0.39	0.29*
Severity vs PST score	0.28*	0.28*	-0.03	0.23	-0.07	0.20	0.25*
Dose vs RAST	-0.07	-0.16	-0.03	-0.4*	ID	ID	-0.13
Severity vs RAST	0.32*	0.55*	0.34	0.16	ID	ID	0.34*

ID, Insufficient data.

* $P < .05$.

The method of food challenge used in this study is similar to that outlined by Bock et al and others^{3,4,6} for the diagnosis of IgE-mediated allergy. Gradually increasing amounts of the test food (or placebo) are given at 10- to 15-minute intervals from approximately 500 mg to 8 total grams (approximately equivalent to 5 mL to a total of 80 mL of, for example, cow's milk). If no reaction is elicited, an open challenge of a meal-size portion of food is given. Other workers throughout the world have used a number of other challenge protocols, including starting with small amounts applied to the inner lip (labial challenge),¹³ allowing longer intervals between doses (30 minutes or more),^{7,14,15} performing challenges over several days,^{14,16} or with lower starting doses.^{7,14} Although there is no standard method of performing challenges, ultimately a "relevant amount" of the food should be consumed to conclude there was nonreactivity.¹⁷ Further, a natural form of the food (broiled fish rather than lyophilized fish) should ultimately be tested (open challenge).

A common issue for patients and the food industry is the question of how small a dose of food can elicit a reaction. This question has been studied for peanut allergy with use of DBPCFCs in a small group of peanut-allergic adults.¹⁸ It was found that 50 mg of peanut was generally the lowest dose that elicited objective reactions. One patient in that study had subjective symptoms at only 100 μ g of peanut. However, to determine the "lowest reactive dose," one would be obligated to challenge the most highly allergic individuals, which is generally not possible for practical and ethical reasons. A variety of case reports have indicated that reactions to trace quantities of protein can elicit reactions. For example, the consumption of products contaminated with trace quantities of milk (8.8 to 14 ppm) have been reported to elicit reactions.^{19,20} Hydrolyzed formula with 30 to 90 ng/mL milk protein can apparently result in clinical reactions in highly

sensitive infants.^{21,22} Although the challenges in the current study were performed in children with atopic dermatitis who were not considered by history to be highly sensitive (they had no recent severe reactions to the foods to which they were orally challenged), they still had reactions to as little as 100 mg of the test substances. Ultimately, controlled studies in highly sensitive individuals would be needed to determine lowest provocative doses.

It would be clinically helpful to have laboratory parameters indicating risk for severity of reactions or for potential dose-response relationships so that physicians could be more confident in their dosing schedules and challenge settings (office versus hospital-based setting). It might be assumed that increasing concentrations of food-specific IgE antibody (reflected in larger PST size or elevated serum food-specific IgE) would correlate negatively with the dose required to elicit responses and positively with the severity of responses. However, this was not found to be the case in this study; there was no strong relationship of IgE concentration with dose causing a reaction (R_s more than 0.6 or less than -0.6). That severity does not relate to serum-specific IgE concentrations was noted in one previous study.⁹ A number of other variables may account for the dose at which symptoms are elicited and severity of reactions. Variables might include absorption rates and end-organ reactivity. Although asthma has been associated with increased severity of food-allergic reactions outside the challenge setting,^{23,24} this was not the case in this study as evaluated by multiple regression analysis (data not shown). Target organs affected during food-allergic reactions also appear unpredictable and may vary for different foods (Table I); this observation is the focus of continuing studies.

Several limitations in this study could account for the lack of relationship of reaction severity and eliciting dose to measures of specific IgE antibody. Because the physi-

cian supervising oral food challenges can discontinue the challenge at the first sign of a reaction and provide immediate medical treatment and may select lower starting doses, the progression of a reaction may be confounded and may account for the lack of correlation of severity with the measures of specific IgE antibody. Another confounder concerns the study population because children with atopic dermatitis generally have elevated IgE concentrations that could blur stronger relationships between the food-specific IgE antibody concentrations and dose-eliciting reactions and severity. Thus a similar study carried out with patients with acute IgE-mediated reactions but without atopic dermatitis may give different results.

The practical messages from the results of this study include the fact that physicians undertaking oral challenges must be prepared to deal with severe reactions without regard to the size of positive PSTs or the concentration of food-specific IgE antibody on RASTs because these parameters do not reflect the severity of reactivity in the challenge setting. Further, our analysis reveals that 45% of patients reacted at doses that were less than 500 mg (usual starting dose 400 to 500 mg). Thus we suggest starting standard challenges at 100 mg or lower. Although 100 mg may turn out to be a reasonable starting dose for oral food challenges in patients not considered at high risk for reactions (no recent or severe reactions), the most sensitive patients may react at even lower doses of food; thus specific recommendations will require the results of further study.

We thank Sylvan Wallenstein, PhD, for assistance with statistical analysis.

REFERENCES

- Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;101:E8.
- Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. *J Allergy Clin Immunol* 1999;104:S114-22.
- Bock S, Lee W, Remigio L, May C. Studies of hypersensitivity reactions to food in infants and children. *J Allergy Clin Immunol* 1978;62:327-34.
- May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to food in asthmatic children. *J Allergy Clin Immunol* 1976;58:500-15.
- Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 1984;74:26-33.
- Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, Sachs M, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988;82:986-97.
- Niggemann B, Sielaff B, Beyer K, Binder C, Wahn U. Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy* 1999;29:91-6.
- Rance F, Kanny G, Dutau G, Moneret-Vautrin D. Food hypersensitivity in children: clinical aspects and distribution of allergens. *Pediatr Allergy Immunol* 1999;10:33-8.
- 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.
- Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 1989;115:23-7.
- Sicherer SH, Furlong TJ, DeSimone J, Sampson HA. Self-reported allergic reactions to peanut on commercial airliners. *J Allergy Clin Immunol* 1999;103:186-9.
- Sampson HA. Food allergy, 2: diagnosis and management. *J Allergy Clin Immunol* 1999;103:981-9.
- Rance F, Dutau G. Labial food challenge in children with food allergy. *Pediatr Allergy Immunol* 1997;8:41-4.
- 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.
- Fukutomi O, Kondo N, Agata H, Shinoda S, Kuwabara N, Shinbara M, et al. Timing of onset of allergic symptoms as a response to a double-blind, placebo-controlled food challenge in patients with food allergy combined with a radioallergosorbent test and the evaluation of proliferative lymphocyte responses. *Int Arch Allergy Immunol* 1994;104:352-7.
- Hill DJ, Firer MA, Ball G, Hosking CS. Natural history of cows' milk allergy in children: immunological outcome over 2 years. *Clin Exp Allergy* 1993;23:124-31.
- Bruijnzeel-Koomen C, Ortolani C, Aas K, Bindeslev-Jensen C, Bjorksten B, Noneret-Vautrin D, et al. Adverse reactions to food [position paper]. *Allergy* 1995;50:623-35.
- 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.
- Gern J, Yang E, Evrard H, Sampson H. Allergic reactions to milk-contaminated "non-dairy" products. *N Engl J Med* 1991;324:976-9.
- Laoprasert N, Wallen ND, Jones RT, Hefle SL, Taylor SL, Yunginger JW. Anaphylaxis in a milk-allergic child following ingestion of lemon sorbet containing trace quantities of milk. *J Food Prot* 1998;61:1522-4.
- Vanderhoof JA, Murray ND, Kaufman SS, Mack DR, Antonson DL, Corkins MR, et al. Intolerance to protein hydrolysate infant formulas: an underrecognized cause of gastrointestinal symptoms in infants. *J Pediatr* 1997;131:741-4.
- Sampson HA, Bernhisel-Broadbent J, Yang E, Scanlon SM. Safety of casein hydrolysate formulae in children with cow milk allergy. *J Pediatr* 1991;118:520-5.
- 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.
- Yunginger JW, Sweeney KG, Sturmer WQ, Giannandrea LA, Teigland JD, Bray M, et al. Fatal food-induced anaphylaxis. *JAMA* 1988;260:1450-2.