Epinephrine treatment is infrequent and biphasic reactions are rare in food-induced reactions during oral food challenges in children

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Background: Data about epinephrine use and biphasic reactions in childhood food-induced anaphylaxis during oral food challenges are scarce.
Objective: To determine the prevalence and risk factors of reactions requiring epinephrine and the rate of biphasic reactions during oral food challenges (OFCs) in children.
Methods: Reaction details of positive OFCs in children between 1999 and 2007 were collected by using a computerized database. Selection of patients for OFCs was generally predicated on ≤50% likelihood of a positive challenge and a low likelihood of a severe reaction on the basis of the clinical history, specific IgE levels, and skin prick tests.
Results: A total of 436 of 1273 OFCs resulted in a reaction (34%). Epinephrine was administered in 50 challenges (11% of positive challenges, 3.9% overall) for egg (n = 15, 16% of positive OFCs to egg), milk (n = 14, 12%), peanut (n = 10, 26%), tree nuts (n = 4, 33%), soy (n = 3, 7%), wheat (n = 3, 9%), and fish (n = 1, 9%). Reactions requiring epinephrine occurred in older children (median, 7.9 vs 5.8 years; $P < .001$) and were more often caused by peanuts ($P = .006$) compared with reactions not treated with epinephrine. There was no difference in the sex, prevalence of asthma, history of anaphylaxis, specific IgE level, skin prick tests, or amount of food administered. Two doses of epinephrine were required in 3 of 50 patients (6%) reacting to wheat, cow's milk, and pistachio. There was 1 (2%) biphasic reaction. No reaction resulted in life-threatening respiratory or cardiovascular compromise.
Conclusion: Older age and reactions to peanuts were risk factors for anaphylaxis during oral food challenges. Reactions requiring multiple doses of epinephrine and biphasic reactions were infrequent. (J Allergy Clin Immunol 2009;124:1267-72.)

Key words: *Food allergy, autoinjector, self-injectable, epinephrine, children, anaphylaxis, oral food challenge, food-induced anaphylaxis, peanut allergy, tree nut allergy, cow's milk allergy, milk allergy, egg allergy, allergic reaction*

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.[1] Epinephrine is the drug of choice for the treatment of anaphylaxis.[1-3] Allergic reactions to foods affect as many as 6% of children,[4] and food allergy is the most common cause of anaphylaxis in children (81% of reactions).[5] Children with food-induced anaphylaxis may require more than 1 dose of epinephrine.[6-8] Most information about the rate of multiple doses of epinephrine and biphasic reactions in children comes from reactions occurring in the community. A recent report with a focus on food-related anaphylactic reactions was based on a retrospective chart review of 19 patients (children and adults) who presented to the emergency department; 3 patients (16%), all adults, were administered a second dose of epinephrine.[6] Using a questionnaire, the Anaphylaxis Campaign in the United Kingdom found that a second dose of epinephrine was given in 10% of children with anaphylaxis requiring epinephrine in the community, although details about epinephrine administration were not available (when given, where, by whom, and so forth)[7] Our recent data using a retrospective questionnaire suggested that at least 2 doses of epinephrine were administered in 19% of food-induced anaphylactic reactions occurring in children with food allergy in the community.[8]

Biphasic reactions are those with recurrence of symptoms after resolution of the initial event in 1 to 78 hours.[9] They have been reported in 3% to 20% of anaphylactic reactions in adult and mixed age populations to both oral and parenteral agents.[9] The only study so far that focuses on a pediatric population reports an incidence of biphasic reactions to be 6% in children 1 to 11 years of age retrospectively analyzed from charts of 108 children hospitalized for anaphylaxis.[10] Four reactions were attributed to orally administered antigens (2 antibiotics, fish, and nuts), and 2 were caused by bee stings. In this small population, a delay in epinephrine administration seemed to be associated with a biphasic response. There were differences in the frequency of epinephrine administration, corticosteroid use, or serious cardiovascular or respiratory symptoms between those children experiencing biphasic versus uniphasic reactions. There were no distinguishing signs or symptoms that allowed one to predict whether a biphasic

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Abbreviations used
GCRC: General Clinical Research Center
OFC: Oral food challenge
SPT: Skin prick test

response might occur. We are unaware of pediatric studies that assess the incidence of biphasic reactions to ingested food allergens.

Oral food challenges (OFCs) are the gold standard for initial diagnosis of food allergy.[11,12] Furthermore, they are used in determining when foods can be safely introduced or reintroduced into the diet. Reactive (failed or positive) challenges can elicit skin, respiratory, or gastrointestinal symptoms that may be severe and require medications.[13,14] We are aware of only 1 study that reports the rate of epinephrine administration in failed OFCs (11%), but no risk factors for use of epinephrine, need for multiple doses of epinephrine, or rate of biphasic reactions were reported.[15] We sought to determine the incidence and risk factors of reactions treated with either a single or multiple doses of epinephrine in food-induced anaphylaxis during OFCs in a pediatric population. Furthermore, we assessed the incidence of biphasic reaction in this carefully selected population to serve as an additional resource for clinicians performing food challenges regarding the risks involved with food challenges.

METHODS

Subjects

Review of subjects less than 18 years of age who participated in the OFCs performed for the research purposes in the Mount Sinai General Clinical Research Center (GCRC) between September 2000 and July 2007 was performed by using a computerized database. Children were primarily referred from the Mount Sinai Pediatric Allergy Clinics for OFCs because they had a positive history of reaction to the food in question and/or detectable food-specific IgE. Selection of subjects for OFCs was generally based on the expectation that a child would have $\leq$50% likelihood of a positive challenge on the basis of the food-specific IgE level,[4,16] SPT wheal size,[17] and a lack of history of recent allergic reactions or exposures to known food allergens, but we also considered the age, history, and family preferences.[18] Subjects with a history of severe anaphylaxis (shock, loss of consciousness) in the past 2 years were not challenged. Children who had specific IgE levels or skin tests wheals greater than those that would predict >50% likelihood of a positive challenge were included if they were believed to have a history of recent accidental exposures to a small amount of the food in question without clinical symptoms indicating possible tolerance. Some of the children with the higher food-specific IgE antibody levels were challenged on the basis of the inclusion criteria for a specific research study in which they participated. Details were collected for all positive challenges including age, comorbidities such as asthma, specific IgE levels and SPT results, foods challenged, symptoms, and treatments given. Those with a presentation consistent with food protein–induced enterocolitis syndrome were excluded from further analyses because the management of a food protein–induced enterocolitis syndrome reaction is different than a typical IgE-mediated one, and epinephrine is not used in the treatment. Data were included for individual subjects with positive food challenges to 1 or several foods.

Skin prick test

Skin prick tests (SPTs) were performed with a sterile bifurcated needle (Precision Medical Products, Inc, Denver, Pa) by using glycerinated food extracts (Greer Laboratories, Inc, Lenoir, NC) and a saline and histamine control. The size of the skin test response was calculated as a mean of the longest diameter and its longest orthogonal measured at 10 to 15 minutes.

Serum specific IgE measurements

Sera were analyzed for antigen-specific IgE antibody concentration with the ImmunoCAP System (Phadia, Uppsala, Sweden). Results were expressed as kU_A/L of specific IgE antibody.

OFCs

Challenges were performed in the Mount Sinai GCRC, and both single-blind/double-blind, placebo-controlled food challenges and open challenges were included. Blind OFCs were performed as previously described.[13,14] In blind challenges, a maximum of 8 to 10 g dry weight of dehydrated food or equivalent liquid form was camouflaged in a food product (vehicle) and given over a 70-minute period. Seven doses of food were given in progressively larger quantities as follows: 1%, 4%, 10%, 20%, 20%, 25%, and 25%. Subjects received 2 blind challenges per day, 1 placebo and 1 test food. Dietitians in the GCRC prepared the food and randomized the challenges. Negative (asymptomatic) blind OFCs were followed with open feedings within 2 hours. In the open challenges, patients received a meal-size portion for age and were observed for another 2 hours after food consumption. Challenges were stopped at the discretion of the investigators when objective signs and symptoms were observed or subjective symptoms such as throat itching or abdominal pain consistently worsened during the challenge. Medications were administered immediately on detection of an allergic reaction, and administration was based on clinical judgment. Patients were observed for at least 4 hours after an allergic reaction. After discharge, parents were asked to call the research staff in case of late-phase reactions. Biphasic reactions were classified as those with recurrence of symptoms after resolution of the initial event in 1 to 78 hours.[9] Symptoms were considered consistent with anaphylaxis if they occurred rapidly within minutes to several hours after food ingestion and affected at least 2 major organ systems according to the recently established guidelines.[1]

Treatment was prescribed for positive challenges on the basis of the type and severity of reaction according to the guidelines,[1] including epinephrine administered intramuscularly every 10 to 30 minutes or as needed to reverse symptoms and methylprednisone 1 to 2 mg/kg (maximum dose 60 mg) given intravenously for anaphylactic symptoms. Informed consent was obtained from the participants, and the study was approved by the Institutional Review Board of the Mount Sinai School of Medicine, New York, NY.

Statistics

Data were analyzed by using SigmaStat (Version 2.03; SPSS Inc, Chicago Ill). The Mann-Whitney rank-sum test was used for comparisons of medians and the t test for comparisons of means. The χ^2 test and Fisher exact test were applied to determine differences in proportions. A P value <.05 was considered statistically significant, except for multiple comparisons, for which a Bonferroni adjustment was applied.

RESULTS

There were 436 (34%) positive challenges from a total of 1273 challenges (Table I). The most common foods challenged were cow's milk, peanut, hen's egg, and soy, in decreasing order. The children ranged from 1.25 to 18 years, and those with positive challenges were significantly older (median, 6 years) than those with negative challenges (median, 5 years; $P < .001$). Challenges to cow's milk and hen's egg were more commonly positive than the challenges to all other foods combined ($P < .001$ for both), with an especially high rate of positive challenges to egg (74% of all egg challenges). In contrast, OFCs to peanut and foods other than the 9 most common food allergens such as chicken, beef, oat, corn, barley, other meats, fruits, and vegetables were more

TABLE I. Demographics and challenge details of all OFCs

	All challenges N = 1273	Positive challenges N = 436 (34%)	Negative challenges N = 837 (66%)	*P* value
Age (y), median (25% to 75%)	5 (1.25-18)	6 (4.3-8.8)	5 (3.0-8.0)	<.001
Male sex	741	252 (34%)	466 (66%)	.90
Food				
Cow's milk	243	115 (47%)	128 (53%)	<.001*†
Hen's egg	170	96 (74%)	74 (26%)	<.001*†
Peanut	190	38 (20%)	152 (80%)	<.001*†
Soy	138	40 (29%)	98 (71%)	.20†
Wheat	76	34 (45%)	42 (55%)	.063†
Fish	43	11 (26%)	32 (74%)	.29†
Tree nuts	39	12 (31%)	27 (69%)	.77†
Seed (sesame, mustard)	27	6 (22%)	21 (78%)	.26†
Shellfish	27	2 (7%)	25 (93%)	.006†
Other food‡	320	82 (26%)	238 (74%)	<.001*†

Percentages are calculated from all the challenges.
*Statistically significant difference when Bonferroni adjustment for multiple comparisons was applied.
†Statistical difference is assessed between the positive and negative challenges to the food in question and all other foods. Challenges to cow's milk and hen's egg were more likely positive and challenges to peanut and other foods were more likely negative compared with all other foods combined.
‡Includes most commonly chicken, beef, oat, corn, and barley followed by other meat, fruits, and vegetables.

commonly negative ($P < .001$ and $P < .001$, respectively), and there was also a trend for shellfish to be more often negative ($P = .006$). Male sex was found equally as commonly in positive and negative challenges.

Of the total 436 positive OFCs, 50 reactions were treated with epinephrine (11% of the positive challenges, or 3.9% of all challenges; Table II). Of the reactions treated with epinephrine, 47 subjects were given a single dose, and 3 subjects (6% of the reactions treated with epinephrine or 0.06% of all reactions) were given 2 doses of epinephrine. The children who were treated with epinephrine were significantly older (median, 7.9 years) than those not treated with epinephrine (median, 5.8 years; $P < .001$). The foods responsible for the reactions treated with epinephrine were hen's egg (n = 15), cow's milk (n = 14), peanut (n = 10), tree nut (n = 4), soy (n = 3), wheat (n = 3), and fish (n = 1). Thirty-three percent of the tree nut reactions and 26% of peanut reactions were treated with epinephrine, compared with 16% of egg reactions, 12% of milk reactions, and <10% of other food reactions ($P = .006$ for peanut compared with all other foods). In contrast, reactions to foods other than the more common allergens were more often not treated with epinephrine ($P < .001$). The groups receiving and not receiving epinephrine were comparable regarding their sex, rate of asthma, history of anaphylaxis, food-specific IgE levels, and SPTs, as well as the manner in which the OFC was performed (double-blind, single-blind, or open) and the median quantity of food protein eliciting the reaction.

Among subjects treated with epinephrine, food-specific IgE was undetectable in 9 subjects: egg in 5, tree nut in 3, peanut in 2, and milk in 1 (3 patients' results to both specific IgE and SPT were missing). Of these, all except 1 had a positive SPT. There was 1 subject who had a negative SPT wheal (although this subject had an SPT flare) and no detectable egg-specific IgE, but the subject developed anaphylaxis after 75% of the total challenge dose to egg during the OFC. There were also 2 subjects who had a negative SPT, 1 to peanut and 1 to wheat. In both subjects, specific IgE was detectable.

When positive OFCs were analyzed according to the 3 most common foods challenged (for which sufficient numbers were available for comparisons), the children treated with epinephrine were older than those not treated with epinephrine only for egg challenges ($P = .009$; Table III). Children treated with epinephrine for milk reactions had significantly higher median milk-specific IgE levels than those with reactions not treated with epinephrine (5.7 vs 1.9 kU_A/L; $P = .01$), but specific IgE levels were comparable for peanut and egg in those treated and not treated with epinephrine. The rate of male sex and asthma, the SPT wheal size, and the quantity of food eliciting the reaction were comparable for milk, egg, and peanut in those treated and in those not treated with epinephrine.

Antihistamines, steroids, albuterol, and oxygen via mask were administered more often for reactions treated with epinephrine than for those not treated with epinephrine, as expected ($P < .001$, $P < .001$, $P < .001$, and $P = .003$, respectively; Table IV). Intravenous fluids were administered for 10 reactions not treated with epinephrine because of profuse vomiting without other signs of anaphylaxis in patients with existing peripheral intravenous access to maintain hydration. None of the reactions resulted in respiratory or cardiovascular compromise.

All 3 subjects treated with 2 doses of epinephrine were male, age 3.2, 6, and 9.7 years, and 2 had asthma. Foods responsible for these reactions were wheat, cow's milk, and pistachio, and the subjects reacted to 15%, 35%, and 1% of the challenge dose, respectively.

Respiratory symptoms were the most common symptom, seen in 67%, followed by urticaria in 52% of the subjects who received a single dose of epinephrine. In comparison, respiratory symptoms and urticaria were seen in all 3 subjects who received 2 doses of epinephrine. The median time of onset of reaction from the last dose of challenge food was 5 minutes (range, 1-60 minutes) in those patients who received a single dose of epinephrine, and symptoms developed quickly within 10 minutes in 2 of the 3 subjects who received 2 doses of epinephrine. In 1 individual (subject 2), anaphylactic symptoms appeared an hour after the challenge to milk had been discontinued for milder symptoms. The first dose of epinephrine was administered within a median of 7 minutes (range, 1-60) from the onset of symptoms suggestive of anaphylaxis in the majority of the children requiring a single dose, and in the remaining 6 children, epinephrine was administered

TABLE II. Demographics of subjects of 436 positive OFCs that were treated or not treated with epinephrine

	Epinephrine N = 50	No epinephrine N = 386	*P* value
Age (y), median (25% to 75%)	7.9 (5-10.5)	5.8 (4-8.5)	<.001
Male sex, n (%)	30 (60)	223 (57)	.89
Asthma, n (%)	27 (54)	122 (31)	.369
History of anaphylaxis, n (%)	79 (20)	10 (20)	1.0
Specific IgE (kU_A/L), median (25% to 75%)	1.4 (0.47-6.4)	1.8 (0.58-4.6)	.79
SPT wheal (mm), median (25%-75%)	6 (4-7.3)	6 (4-7.1)	.55
Food†			
Cow's milk (n = 115), n (%)	14 (12)	101 (88)	.95†
Hen's egg (n = 74), n (%)	15 (16)	81 (84)	.13†
Peanut (n = 38), n (%)	10 (26)	28 (74)	.006†
Soy (n = 40), n (%)	3 (7)	37 (93)	.57†
Wheat (n = 34), n (%)	3 (9)	31 (91)	.82†
Fish (n = 11), n (%)	1 (9)	10 (91)	.82†
Tree nuts (n = 12), n (%)	4 (33)	8 (67)	.051†
Seed (sesame, mustard; n = 6), n (%)	0	6 (100)	.81†
Shellfish (n = 2), n (%)	0	2 (100)	.55†
Other food‡ (n = 82), n (%)	0	82 (100)	<.001*†
Type of OFC			
DBPCFC (n = 171), n (%)	16 (9)	155 (91)	.36§
SBPCFC (n = 80), n (%)	10 (12)	70 (88)	.95§
Open (n = 160), n (%)	12 (7)	148 (93)	.07§
Not defined (n = 15), n (%)	2 (13)	13 (87)	.80§
Median percentage of food (25% to 75%) eliciting reaction of the total challenge dose	35% (15-75)	40% (10-100)	.79

DBPCFC, Double-blind, placebo-controlled food challenge; *SBPCFC,* single-blind, placebo-controlled food challenge.
Percentages are calculated from all the positive challenges.
*Statistically significant difference when Bonferroni adjustment for multiple comparisons was applied.
†Statistical difference is assessed between the challenges to the food in question and all other foods.
‡Includes most commonly chicken, beef, oat, corn, and barley followed by other meat, fruits, and vegetables.
§Statistical difference is assessed between the type of challenge and all other types of challenges.

between 40 to 60 minutes from the onset of symptoms because of progression of symptoms such as wheeze, urticaria, and abdominal pain that did not respond to other treatments. In those children who subsequently received a second dose, the first dose of epinephrine was administered within 1 to 9 minutes after the onset of the reaction. Of these, 2 did not respond to the first dose of epinephrine and were quickly (within 2 to 10 minutes) administered a second dose. In contrast, subject 2 responded within minutes to the first dose of epinephrine, but symptoms reappeared after an hour and were treated with a second dose. This reaction has characteristics of a possible biphasic reaction, with a calculated incidence of 2% in this population. There were no biphasic reactions with an onset beyond an hour. There were no reported late symptoms after discharge from the GCRC.

DISCUSSION

We report that epinephrine was administered in 11% of positive OFCs in children (in 3.9% of all challenges), and 2 doses of epinephrine were administered in 6% of reactions treated with epinephrine. The children treated with epinephrine were significantly older than those not treated with epinephrine. Milk, egg, and peanut were responsible for the majority of reactions treated with epinephrine. To our knowledge, the current study is the first one to report the rate of administration of multiple doses of epinephrine during OFCs in a pediatric population, and one of the few studies to assess the incidence and the risk factors of food-induced anaphylaxis treated with epinephrine. In our study, the rate of treatment with epinephrine is used as approximation of anaphylaxis. Without any doubt, all anaphylactic reactions were treated with epinephrine. It is rather unlikely that we have used epinephrine unnecessarily for the treatment of milder reactions, given the extensive experience of our research staff performing multiple OFCs on a daily basis.

Our rate of treatment with epinephrine (11% of positive OFCs) is in agreement with previous data for in-patient food challenges.[15] A second dose of epinephrine was needed in 6% of reactions treated with epinephrine. We identified older age and challenges to peanuts as risk factors for anaphylaxis. Previously identified risk factors for food-induced anaphylaxis in childhood include the following: older age, asthma, previous reactions involving the respiratory tract, peanut/tree nut allergy, and reactions to trace exposures.[19,20] We found that children who received epinephrine were older than those who did not, which was especially the case for egg and peanut. This may be because older children are considered better candidates for OFC, and greater risks of reactions are accepted. Although asthma was more frequently found among those who received epinephrine, it was not statistically significant. The amount of food triggering a reaction was not different in those who received epinephrine from those who did not, which is in contrast with the report by Perry et al.[15] They suggested that more severe reactions occurred at a lower dose of challenge food. The difference between these 2 studies may be explained by differences in the methodology and the total amount of food protein administered during the challenge. Last, in our study, subjects who received epinephrine had similar SPT wheal sizes to those who did not receive epinephrine, although a higher milk-specific IgE level was found in those

TABLE III. Details of OFCs to milk, egg, and peanut that were or were not treated with epinephrine

	Epinephrine N = 50	No epinephrine N = 386	*P* value
Age (y), median (25% to 75%)			
Cow's milk	7.0 (5.0-10.0)	6.5 (4.8-9)	.55
Hen's egg	7.8 (5.2-10.1)	5.3 (3.3-6.8)	.009*
Peanut	8.7 (7.9-10.4)	6.1 (4.9-8.9)	.043
Male sex, n (%)			
Cow's milk	9/14 (64%)	62/101 (61%)	1.0
Hen's egg	7/15 (47%)	55/81 (68%)	.57
Peanut	6/10 (60%)	24/28 (86%)	1.0
Asthma, n (%)			
Cow's milk	9/14 (64%)	60/101 (59%)	.58
Hen's egg	11/15 (73%)	39/81 (48%)	1.0
Peanut	5/10 (50%)	23/28 (82%)	.52
Specific IgE (kU_A/L), median (25% to 75%)			
Cow's milk	5.7 (2.5-13.1)	1.9 (0.65-3.6)	.01*
Hen's egg	0.96 (0-2.2)	0.63 (0.39-1.4)	.49
Peanut	1.1 (0.39-2.7)	1.4 (0.56-2.6)	.60
SPT wheal (mm), median (25% to 75%)			
Cow's milk	7 (5-10)	7 (6-8)	.80
Hen's egg	5 (2.5-7)	5 (4-7)	.63
Peanut	6 (5-8)	6 (4-9)	.95
Median percentage of food (25% to 75%) eliciting reaction of the total challenge dose			
Cow's milk	35% (25-100)	35% (5-100)	.41
Hen's egg	50% (6-75)	35% (5-65.5)	.91
Peanut	55% (20-100)	32.5% (5-72.5)	.13

*Statistically significant difference when Bonferroni adjustment for multiple comparisons was applied.

TABLE IV. Treatment of 436 positive OFCs that were treated or not treated with epinephrine

	Epinephrine N = 50	No epinephrine N = 386	*P* value
Antihistamines, n (%)	49 (98)	309 (80)	<.001*
Steroids, n (%)	29 (58)	21 (5)	<.001*
Albuterol nebulization, n (%)	7 (14)	3 (<1)	<0.01*
Intravenous fluids, n (%)	4 (8)	10 (<3)	.057
Oxygen via mask, n (%)	2 (4)	0	.003*

*Statistically significant difference when Bonferroni adjustment for multiple comparisons was applied.

with milk-induced anaphylaxis compared with those with a less severe reaction.

Peanut, milk, and egg were responsible for more than 75% of anaphylactic reactions (with tree nuts, soy, wheat, fish, and shellfish responsible for the remainder), for 57% of positive challenges, and for 47% of the total OFCs performed, further indicating their increased potential to induce anaphylactic reactions compared with other foods. In comparison, data from the US food allergen-induced fatality registries (n = 63) indicate that peanut or tree nuts were responsible for 87% and cow's milk for 8% of fatalities (fish and shellfish were responsible for the remainder).[21,22] Our report on food-induced anaphylaxis in the community similarly found peanut, tree nuts, and milk responsible for the majority of reactions requiring epinephrine. The high number of cases of egg-induced anaphylaxis, similar to that reported by Perry et al,[15] may be explained by the fact that egg was among the 3 most commonly challenged foods in our center. Furthermore, egg OFCs were performed by using scrambled egg, French toast, or egg powder, whereas the accidental ingestions of egg in the community usually occur with egg in well cooked foods that are better tolerated and induce less severe reactions.[23] The small number of tree nut–induced anaphylaxis cases is probably a result of the low number of tree nut challenges performed.

In our study, although small in number, the need for multiple doses of epinephrine did not appear to be associated with a delay in administration of epinephrine. This is in agreement with our recent report on administration of multiple doses of epinephrine in the community.[8] Increased symptom severity has been associated with the need for multiple doses in a previous study.[24] Because of the small number of subjects treated with multiple doses of epinephrine in the current study, it is impossible to draw conclusions on the symptoms severity in comparison with those treated with a single dose, except that treatment was successful.

In 2 out of 3 patients, the second dose of epinephrine was administered within 10 minutes because there was no response to the first dose. In 1 patient, symptoms responded to the initial dose but reoccurred after an hour, requiring administration of a second dose. The same patient had a delay in onset of his initial anaphylactic symptoms, which did not occur until an hour after his food challenge had already been discontinued because of milder symptoms. This presentation is suggestive of a biphasic pattern, with an incidence lower (2%) than has been reported previously for reactions occurring in the community (3% to 20%).[9] Although no data presented thus far allow us to predict conclusively the occurrence of a biphasic reaction, Tole and Lieberman[9] have extrapolated information from previous studies to give some insight: a delay in the administration of epinephrine, an inadequate amount of epinephrine given for the first response, or the requirement of larger doses of epinephrine suggests that a biphasic response is more likely. Failure to administer corticosteroids

seemed to predispose to a biphasic response, although data are controversial. All these risk factors were well controlled in our sample (including 58% who received corticosteroids) and might have contributed to the reduced rate of biphasic reactions, including none with an onset beyond an hour.

The limitations to the study include the fact that these results can be applied only to the pediatric population undergoing OFCs in which dose escalations are carefully done and aborted at the first sign of objective symptoms. These results can not be applied to anaphylactic reactions occurring in the field, where dose level of exposure is not selected and therefore are potentially associated with more serious reactions. The patient population is carefully selected to exclude those at risk for severe reactions. Furthermore, children with positive tests but no history of reactions were included, which is a bias toward more favorable outcomes with higher food-specific IgE levels. Nevertheless, our patient population represents a real-life cross-section of patients who may be considered for OFCs in an academic setting, and therefore, our study provides a valid assessment of the risk involved with OFCs in those settings.

In conclusion, although true risks exist, physician-supervised OFCs are safe in the hands of experienced personnel when performed on carefully selected subjects. Egg, milk, and peanuts were responsible for the majority of reactions treated with epinephrine, but no dose relationship was detected. Because of the low number of reactions, we were unable to identify risk factors associated with requirement for multiple doses of epinephrine. Biphasic reactions were infrequent, which may reflect the carefully selected patient population, carefully escalated allergen exposure, and prompt treatment with epinephrine and corticosteroids.

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Clinical implications: OFCs are safe in the hands of experienced personnel when performed on carefully selected patients. The need for epinephrine is infrequent, and biphasic reactions are rare.

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