

Risk of oral food challenges

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Background: Oral food challenges are essential to the diagnosis of food allergy; however, little has been reported regarding the risks of performing food challenges in children with suspected food allergy.

Objective: To examine the risk and reaction severity of failed oral food challenges.

Methods: A retrospective chart review was performed on children who underwent food challenges to milk, egg, peanut, soy, and/or wheat in a university-based pediatric allergy clinic over a 7-year period.

Results: Of the 584 challenges completed, 253 (43%) resulted in an allergic reaction. There were 90 milk, 56 egg, 71 peanut, 21 soy, and 15 wheat failed challenges. Of patients who failed, there were 197 (78%) cutaneous, 108 (43%) gastrointestinal, 66 (26%) oral, 67 (26%) lower respiratory, and 62 (25%) upper respiratory reactions. No patients had cardiovascular symptoms. There was no difference between foods in the severity of failed challenges or the type of treatment required to reverse symptoms. All reactions were reversible with short-acting antihistamines $\pm$ epinephrine, β -agonists, and/or corticosteroids. No children required hospitalization, and there were no deaths.

Conclusions: There are risks associated with food challenges, and the risks are similar for each of the foods studied. Given the benefits that result from a negative challenge, these risks are reasonable when challenges are performed under the guidance of an experienced practitioner in a properly equipped setting. (*J Allergy Clin Immunol* 2004;114:1164-8.)

Key words: Food allergy, oral food challenge, risk, severity

Abbreviation used

kU_A/L: Kilounits of allergen-specific IgE per liter

to their role in the initial diagnosis of food allergy, oral food challenges are essential in determining when foods can be safely reintroduced into the diet of the patient with food allergy. An oral challenge should be offered when oral tolerance is suspected on the basis of the length of time since the last reaction and results of diagnostic tests such as food-specific IgE levels⁴⁻⁶ or skin prick tests.^{7,8}

Oral food challenges pose inherent and significant risks and can result in symptoms ranging from mild cutaneous to systemic and potentially life-threatening reactions. Although previous studies have examined the relationship of skin prick tests⁷⁻⁹ or food-specific IgE levels^{4-6,10,11} and challenge outcome, limited data are available about the risk and severity of reactions associated with oral food challenges. We performed a retrospective chart review to examine these risks and the severity of reactions in a highly atopic group of patients undergoing oral food challenges at a tertiary care center. Data gathered from the current study will assist physicians and patients in the food challenge decision-making process by weighing the benefits of passing a food challenge against the risk and severity of a failed challenge.

METHODS

Study population and oral challenges

The study population included patients who underwent an oral food challenge to milk, egg, peanut, soy, and/or wheat at the Johns Hopkins Pediatric Allergy Clinic from 1997 to 2003. Patients were largely referred from primary care and secondary care settings for the evaluation and management of food allergies. As previously reported,⁶ open food challenges were performed in a stepwise fashion when oral tolerance was suspected. Some patients underwent more than 1 challenge to the same food, and some patients had challenges to multiple foods. Repeat challenges to the same food were performed in patients after a period of continued avoidance when oral tolerance was again suspected.

Briefly, challenges were administered in escalating doses every 15 minutes until 4 g (<5 years old) or 8 g ($\geq$ 5 years old) of food protein was ingested. The challenge was terminated when objective symptoms were noted by the practitioner or subjective symptoms such as abdominal pain worsened during the challenge. The percentage of the challenge food ingested was recorded for all participants, and patients were deemed to have passed the challenge if they were able to tolerate 100% of the intended dose without untoward effects. All patients were observed in the clinic for a minimum of 4 hours or until signs of clinical reactivity subsided for those patients who failed the

Food allergy is a significant and potentially life-threatening disease affecting as many as 8% of children.¹ Although reports of adverse food reactions are common, the diagnosis of food allergy can be difficult and complicated. There is significant discordance between reported food reactions and the actual incidence of food allergy, and both skin and radioallergosorbent tests have poor positive predictive accuracy.² Oral food challenges remain the gold standard for diagnosis of food allergy³ and should be used when the diagnosis is unclear. In addition

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challenge. Patients were informed about late-phase reactions before discharge from the clinic and instructed to contact the supervising physician immediately if symptoms recurred.

Treatment of failed challenges

Medication was prescribed for failed challenges on the basis of the type and severity of reaction. Short-acting antihistamine doses were diphenhydramine 1.5 to 2 mg/kg (maximum dose, 50 mg) or hydroxyzine 1 to 2 mg/kg (maximum dose, 50 mg) orally. The same dose was repeated orally or intramuscularly if the patient vomited within 30 minutes of receiving the dose. Epinephrine 0.01 mg/kg (maximum, 0.3 mg) per dose was administered intramuscularly every 15 to 30 minutes as needed to reverse symptoms. Albuterol 2.5 to 5 mg was also administered by nebulization for persistent chest symptoms. Prednisone 1 to 2 mg/kg (maximum dose, 60 mg) was given orally for refractory lower respiratory or gastrointestinal symptoms. The steroid dose was repeated if vomiting occurred within 30 minutes of the dose.

Systems and severity categories

Symptoms observed during the failed challenges were categorized into 6 systems: skin, oral, upper respiratory, lower respiratory, gastrointestinal, and cardiovascular. The skin category included any rash, erythema, pruritus, worsening eczema, angioedema, and swelling of the eyes or face. Oral symptoms were defined as throat pain, palatal erythema or hives, or itching of the palate, tongue, or lips. Upper respiratory symptoms included rhinorrhea, nasal congestion, nasal pruritus, and sneezing. Lower respiratory symptoms consisted of cough, wheeze, shortness of breath, stridor, or hoarseness. Gastrointestinal symptoms included nausea, vomiting, diarrhea, and abdominal cramp or pain. Cardiovascular symptoms included hypotension, light-headedness, syncope, or collapse.

Severity of failed challenges was further categorized on the basis of the combination of systems involved (Fig 1). Mild reactions included skin and/or oral symptoms. Moderate reactions included any upper respiratory or gastrointestinal symptoms or the involvement of any 3 systems. Severe reactions included any lower respiratory or cardiovascular symptoms or any 4 systems.

Laboratory studies

Serum samples were analyzed before challenge for food-specific IgE antibody by using the Pharmacia CAP system FEIA (Pharmacia and Upjohn Diagnostics, Uppsala, Sweden).

Statistical methods

Statistical analyses were performed by using STATA SE 8.0 (College Station, Tex). The distributions of the continuous variables, such as food-specific IgE, were skewed and were therefore compared by using the Mann-Whitney *U* test. Proportions were compared by using the χ^2 test. The Cuzick's test for trend was used to assess trends in food-specific IgE or dose of food received across strata of severity or treatment for each food. Cutoffs for strata of CAP-RAST were based on previously published findings^{5,6} and the distribution of the data. $P < .05$ was considered to be statistically significant.

RESULTS

Five hundred eighty-four challenges were performed in 382 patients, of which 253 (43%) were failed challenges, with the following failure rates for each food: milk, 90 of

Mild	Skin and / or oral symptoms only
Moderate	Upper respiratory and / or gastrointestinal symptoms only OR Any 3 systems
Severe	Lower respiratory and / or cardiovascular symptoms OR Any 4 systems

FIG 1. Severity of allergic reactions for failed challenges on the basis of system involvement.

161 (56%); egg, 56 of 133 (42%); peanut, 71 of 171 (42%); soy, 21 of 75 (28%); and wheat, 15 of 44 (34%). The median age of those failing challenges was 5.2 years, and 77% were male subjects (Table I). All of the participants who failed a wheat challenge were male subjects. The median food-specific IgE for the failed challenges was 2.0 Kilounits of allergen-specific IgE per liter (kU_A/L) for milk, 1.2 kU_A/L for egg, 1.9 kU_A/L for peanut, 9.3 kU_A/L for soy, and 19.6 kU_A/L for wheat. The median percent of challenge food ingested was 30% for all foods. The study population was highly atopic, with 67% with concomitant eczema, 59% with asthma, 50% with allergic rhinitis, and 86% with other food allergies.

The systems involved during failed challenges are presented in Table II. Skin reactions were most common (78%), followed by gastrointestinal (43%), lower respiratory (26%), oral (26%), and upper respiratory (25%) symptoms. No patients had cardiovascular symptoms. Patients who failed peanut challenges were more likely to have oral ($P \leq .01$) and upper respiratory symptoms ($P \leq .01$) compared with other foods. All of the patients who failed a wheat challenge had skin symptoms ($P = .03$). There were no statistically significant trends for lower respiratory or gastrointestinal symptoms for any of the foods.

Of the reactions observed during the 253 failed challenges, 98 (39%) were mild, 83 (33%) were moderate, and 72 (28%) were severe (Table III). The distribution of the severity categories was similar for each food, and none of the foods was significantly associated with more severe reactions. The distributions of food-specific IgE in each severity category were compared (Table IV), and a statistically significant trend for having a more severe reaction with increasing IgE level was found only for peanut ($P < .05$). There was no relationship between reaction severity and the median IgE level for other foods.

The median amount ingested for each food by reaction severity is presented in Table V. To examine further the relationship between the percent of challenge food ingested and reaction severity, we divided participants into 4 groups on the basis of the amount ingested (<25%, 25% to 50%, 51% to 75%, or >75%). Participants were not likely to have more severe reactions when larger doses of the challenge food were ingested. Rather, a more severe reaction was significantly related to reacting to a lower dose of the challenge food, as illustrated in Fig 2 ($P = .05$). Further analysis of each food revealed similar significant trends for milk and wheat, and this relationship remained

TABLE I. Patient demographics for the 253 failed challenges

	Milk N = 90	Egg N = 56	Peanut N = 71	Soy N = 21	Wheat N = 15	Total N = 253
Median age (y)	5.1	5.5	5.7	3.8	3.0	5.2
% Male	82	73	65	86	100	77
Median food-specific IgE (kU _A /L)	2.0	1.2	1.9	9.3	19.6	—
Median % ingested	25	40	30	50	75	30
% With eczema	60	80	59	70	93	67
% With asthma	57	80	42	50	80	59
% With allergic rhinitis	47	54	51	45	53	50
% With other food allergy	89	95	70	100	100	86

TABLE II. System involvement during failed challenges

	Milk N = 90	Egg N = 56	Peanut N = 71	Soy N = 21	Wheat N = 15	Total N = 253
Skin	68 (75%)	43 (77%)	55 (77%)	16 (76%)	15 (100%)*	197 (78%)
Oral	23 (26%)	12 (21%)	27 (38%)†	3 (14%)	1 (7%)	66 (26%)
Upper respiratory	16 (18%)	15 (27%)	25 (35%)†	4 (19%)	2 (13%)	62 (25%)
Lower respiratory	24 (27%)	19 (34%)	15 (21%)	4 (19%)	5 (33%)	67 (26%)
Gastrointestinal	37 (41%)	31 (55%)	28 (39%)	9 (43%)	3 (20%)	108 (43%)
Cardiovascular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

P* = .03 for probability of system involvement as compared with all other foods.†*P* ≤ .01 for probability of system involvement as compared with all other foods.TABLE III.** Severity of reactions during failed food challenges

	Milk N = 90	Egg N = 56	Peanut N = 71	Soy N = 21	Wheat N = 15	Total N = 253
Mild	33 (37%)	18 (32%)	28 (39%)	9 (43%)	10 (67%)	98 (39%)
Moderate	33 (37%)	17 (30%)	25 (35%)	8 (38%)	0 (0%)	83 (33%)
Severe	24 (27%)	21 (38%)	18 (25%)	4 (19%)	5 (33%)	72 (28%)

TABLE IV. Median food-specific IgE (kU_A/L) level and reaction severity

	Milk N = 90	Egg N = 56	Peanut* N = 71	Soy N = 21	Wheat N = 15
Mild	1.9	0.84	1.3	10.1	15.8
Moderate	1.6	1.3	2.1	4.9	—
Severe	2.2	1.3	2.2	24	30.2

P* < .05 for trend.TABLE V.** Reaction severity and median percentage of challenge food ingested

	Milk N = 90	Egg N = 56	Peanut N = 71	Soy N = 21	Wheat N = 15	Total N = 253
Mild	50	40	10	65	100	50
Moderate	25	50	75	45	—	45
Severe	15	30	45	63	40	30

statistically significant for milk after controlling for the milk-specific IgE level (*P* = .04).

None of the failed challenges resulted in death or hospitalization, and 21% did not require treatment. None of the patients had late-phase symptoms after discharge from the clinic. Treatment with antihistamines was most common, with 77% of those failing a challenge receiving antihistamines (Table VI). Treatment with other medica-

tions was less common, with 11% receiving epinephrine, 6% receiving steroids, and 4% receiving albuterol. A higher percentage of patients received epinephrine during failed egg and wheat challenges and antihistamines during failed peanut challenges, but these trends were not statistically significant. Median soy-specific IgE levels were higher for participants who received antihistamine and epinephrine treatment during failed soy challenges.

There was not a significant difference between median food-specific IgE level and treatment for other foods.

DISCUSSION

The diagnosis of food allergy can be a tremendous burden for patients and families because strict avoidance measures must be taken to decrease the risk of food anaphylaxis. In addition to the inconvenience, the elimination of major food allergens can pose significant nutritional risk. To decrease the risks associated with dietary restrictions, food challenges are often needed to confirm the diagnosis or to determine when oral tolerance has developed. Furthermore, passing a food challenge to a potent allergen like peanut can significantly decrease anxiety associated with meals, school attendance, and social situations involving food. Despite the benefits of passing a challenge, many families and patients are reluctant to consent to food challenges because of the risk of an adverse reaction. To examine the risk and severity of failed food challenges, we performed a retrospective chart review of challenges performed in a tertiary care setting.

Of the 253 failed challenges, none of the patients required hospitalization, and all symptoms were reversible. The skin was the most common system involved, with 78% of failed challenges resulting in cutaneous reactions. Gastrointestinal reactions were also common, occurring in 43% of failed challenges. Oral, upper respiratory, and lower respiratory symptoms were less common and occurred in approximately 1/4 of failed challenges. There was a statistically significant trend for having oral or upper respiratory symptoms with peanut challenges and skin involvement with wheat challenges, but none of the foods were more likely to cause lower respiratory or gastrointestinal symptoms. Because cardiovascular and lower respiratory reactions are the most common life-threatening symptoms in an allergic reaction, it is encouraging that no cardiovascular symptoms were observed and only 26% of failed challenges resulted in lower respiratory symptoms.

Thirty-nine percent of patients were categorized as having mild reactions, 33% had moderate reactions, and 28% had severe reactions. Severity was evenly distributed across foods. Although more of the failed egg and wheat challenges were severe, these trends were not statistically significant. Despite fears about peanut reactions and the propensity for this allergen to cause severe reactions, peanut challenges were not more likely to result in severe reactions, and only 7 of 71 (10%) patients who failed a peanut challenge required epinephrine.

We hypothesized that patients with higher food-specific IgE levels would have more severe reactions, but a statistically significant trend was found only for peanut. It is possible that a relationship between specific IgE levels and challenge severity for other foods was not found because food-specific IgE levels for the study population were all relatively low. It is also possible that close observation and

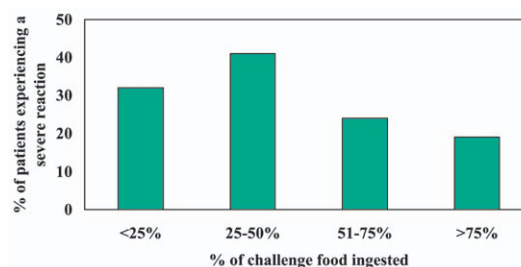


FIG 2. Percentage of patients experiencing a severe reaction during failed challenges for each ingestion category. $P = .05$ for trend.

prompt intervention of failed challenges prevented the progression to more serious reactions for some patients. Another explanation is that the IgE level may be a poor predictor of the degree of severity of failed challenges. Previous studies by Sampson and Ho⁴ and Sicherer et al¹² also found no relationship between reaction severity during failed food challenges and food-specific IgE levels. Although food-specific IgE levels serve as useful predictors of challenge outcome,^{5,6} clinicians should be cognizant of the fact that failed challenges can occur at any IgE level, including below detection, and that IgE levels may have little or no value in predicting reaction severity.

When the relationship between reaction severity and amount of the challenge food ingested was examined, we found that more severe reactions tended to occur at lower rather than higher doses, especially for milk. Wensing et al¹³ observed a similar pattern during peanut challenges, in which patients with more severe symptoms reacted at lower doses than those with mild reactions. Our data are also consistent with other studies that have demonstrated substantial variability in threshold dose among patients,^{14,15} all of which suggest that the relationship of severity and threshold dose is probably confounded by many variables, including individual patient characteristics such as the presence of asthma, food-specific IgE level, and possibly the length of time since exposure to the food. Perhaps more important is our finding that reaction severity did not increase as the amount of challenge food ingested increased. From a practical standpoint, this finding suggests that cumulative exposure does not increase the risk of reaction severity and that most challenges can be performed safely by giving increasing doses over a period of 60 to 90 minutes.

Twenty-one percent of patients did not require treatment, and most needed only a short-acting antihistamine. It is likely that stepwise dosing of the challenge food was helpful in preventing more severe reactions, because challenges were terminated at the first signs of clinical reactivity or when subjective symptoms worsened during the challenge. This method reduced total exposure to the challenge food, resulted in early intervention, and likely prevented progression to more serious reactions for most of the failed challenges. It is of some concern that there was considerable discordance between the occurrence of severe reactions (28%) and the use of epinephrine (11%).

TABLE VI. Treatment administered during failed challenges

	Milk N = 90	Egg N = 56	Peanut N = 71	Soy N = 21	Wheat N = 15	Total N = 253
None	22 (24%)	11 (20%)	9 (13%)	7 (33%)	3 (20%)	52 (21%)
Antihistamine	68 (76%)	44 (79%)	62 (87%)	13 (62%)	12 (80%)	199 (77%)
Epinephrine	5 (6%)	10 (18%)	7 (10%)	3 (14%)	3 (20%)	28 (11%)
Steroids	2 (2%)	6 (11%)	4 (6%)	1 (5%)	1 (7%)	14 (6%)
Albuterol	2 (2%)	2 (3.4%)	5 (7%)	0 (0%)	2 (13%)	11 (4%)

This finding is not consistent with recommendations given to patients experiencing reactions in real-life situations,¹⁶ but rather reflects the fact that challenges were performed in a controlled setting under close supervision, where additional treatment could be implemented at a moment's notice.

There are significant risks associated with oral food challenges, and in the current study, 26% of patients had lower respiratory symptoms, and 28% were categorized as having a severe reaction. It is important to note that the risk was similar regardless of the food being challenged. Although performing challenges with well-trained personnel in a closely monitored setting should minimize these risks, clinicians should be prepared to treat severe reactions regardless of the food being challenged. On the positive side, our findings provide reassurance that challenges can be performed safely and that symptoms during failed challenges should generally be reversible with prompt treatment and termination of the challenge at the earliest dose eliciting symptoms. Ideally, this information will assist both practitioners and patients in making more informed decisions about the risks versus the benefits of oral food challenges.

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