Predictive Values for Food Challenge-Induced Severe Reactions: Development of a Simple Food Challenge Score

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ABSTRACT: **Background:** Skin-prick tests (SPT), food-specific immunoglobulin E level (sIgE) and clinical history have limited value *individually* in predicting the severity of outcome of the oral food challenge (OFC).

Objectives: To develop a score that accounts for SPT, sIgE and clinical history to predict the risk of severe reaction to the OFC.

Methods: A 5 year retrospective chart review was performed on 983 children who underwent OFC to egg, milk and peanut.

Results: Using multilogistic regression, four major indicators were found to be independently associated with failed OFC: sIgE (odds ratio = 1.04, $P < 0.0001$), wheal size of the SPT (OR = 1.23, $P < 0.0001$), a history of any prior reaction to the food (OR = 1.13, $P < 0.01$), and a history of a prior non-cutaneous reaction (OR = 1.99, $P < 0.01$); and three were independently associated with anaphylaxis: wheal size (OR = 1.16, $P < 0.001$), a history of a prior non-cutaneous reaction (OR = 4.24, $P < 0.01$), and age (OR = 1.07, $P < 0.03$). A Food Challenge Score (0–4) was developed which accounted for SPT wheal, sIgE, a history of a prior non-cutaneous reaction, and age. A score of 0–1 had a negative predictive value for multisystem reaction to the OFC: 95% for milk, 91% for egg and 93% for peanut. A score of 3–4 had a positive predictive value for anaphylaxis: 62% for milk, 92% for egg and 86% for peanut.

Conclusions: Severe reaction to milk, egg and peanut OFC can be predicted using a simple score that takes into account clinical data that are commonly available prior to the challenges.

IMAJ 2012; 14: 24–28

KEY WORDS: food allergy, oral food challenge, skin-prick test (SPT), immunoglobulin E (IgE), anaphylaxis

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The recommended evaluation for food allergy includes a detailed history and physical examination, followed by selected in vivo and in vitro tests based on the patient's history. Oral food challenges are performed either because the food allergy is not supported by the history or because a newly developed tolerance needs to be established [1]. The demand for OFC for evaluation of food allergies has greatly increased in the last decade due to the rising prevalence of food allergy [2] and the growing number of elimination diets based solely on the presence in the serum of specific immunoglobulin E to food detected using commercially available in vitro testing [3]. However, OFCs are commonly associated with inherent risks, as seen in a study where up to 28% of these tests resulted in systemic and potentially life-threatening reactions [4]. The increased demand for OFC has created a need to identify those patients with the highest risk to develop anaphylaxis following an OFC. Hence, easy-to-follow parameters that could predict severe reaction to the OFC must be determined to better assess the risk-benefit ratio of each patient undergoing OFC.

Previous studies examining the relationship of skin-prick tests [5-7] or food-specific serum immunoglobulin E levels [4,6,8,9] to challenge outcome show that both SPT and sIgE tests are *individually* very useful but limited in their predictive accuracy [10]. A recent article has suggested that a more complex model incorporating test results and clinical history had a better predictive ability compared with sIgE and SPT used either alone or in combination [11]. So far, sIgE and SPT have not been found useful for predicting severe reaction when used in isolation [4,12]. The initial presentation as predictor of type of future outcome has also not proven a good parameter to predict severity of OFC [3,13]. Other factors such as history of asthma, older age, or previous history of multi-organ system reaction have been reported to be associated with more severe reactions in children with food allergy but not as factors predicting the severity of the reaction induced by OFCs [13-17]. In the present study we hypothesized that a simple score for predicting which children are at increased risk of severe reactions to the OFC could be developed based on clinical parameters commonly available to providers at the time of the OFC.

PATIENTS AND METHODS

We performed a retrospective analysis of children who underwent OFC to milk, egg and peanut at The Children's Hospital of Philadelphia Pediatric Day Medicine Unit from August 2004

OD = odds ratio

OFC = oral food challenge
SPT = skin-prick test
sIgE = serum immunoglobulin E

to December 2010. Clinical data of serum milk, egg white and peanut-specific IgE antibody levels, SPT results, previous history of systemic reaction, history of asthma or eczema, and oral challenge outcomes of children were collected with approval of the hospital's internal review board. Briefly, OFCs were performed with a starting dose of 0.1 ml, followed by 0.5, 1, 2.5, 5, 10, 30, 60, 120 and 240 ml for liquid foods (milk). For solid foods (peanut, egg powder, milk powder), the challenge doses were 125, 250 and 500 mg, 1, 2, 4 and 8 g, and ad lib (minimum 8 g). Each dose was administered with an interval of 15 to 20 minutes until ad lib doses were reached or the patient experienced a reaction within 2 hours of the last dose [13]. Challenges were stopped in the event of gastrointestinal reactions, respiratory symptoms, non-contact cutaneous reactions, or multisystem reactions (for details, see supplementary material online). All investigations were approved by the internal review board.

CLASSIFICATION OF REACTIONS

Reactions on presentation and following challenges were classified as cutaneous, respiratory, gastrointestinal, multi-organ system, and anaphylaxis. Cutaneous reactions were hives, urticaria, erythematous flushing, cutaneous angioedema, and flaring of atopic dermatitis on non-contact areas. Respiratory reactions included rhinitis, sneezing, voice change, throat tightness, cough, wheeze, shortness of breath, and tachypnea. Gastrointestinal reactions were emesis and diarrhea. Multi-organ system reactions included symptoms in more than one organ system but not anaphylaxis. Finally, anaphylaxis was a life-threatening reaction that involved more than one organ system plus either hypotension or use of rescue medications (intravenous fluids, multiple doses of albuterol, or epinephrine) [15].

SKIN TESTING AND SERUM IGE

Skin-prick tests were performed by the prick method using commercial extracts (Bayer Laboratories, Spokane, WA; Greer Laboratories, Lenoir, NC, USA) and bifurcated needles measuring maximal wheal and flare diameter at 15 minutes [15]. Serum samples were analyzed for egg white, milk and peanut-sIgE antibody concentrations by means of the Pharmacia CAP system FEIA (Pharmacia and Upjohn Diagnostics, Uppsala, Sweden). The lower limit of detection was 0.35 kU/L (for details, see supplementary material online).

STATISTICAL METHODS

The Mann-Whitney *U* test was used to compare wheal and flare diameter between groups, assuming skin tests were not normally distributed. Student's *t*-test was used to compare age in the different groups. The chi-square analysis of independent variables was used to compare the initial reaction and the history of asthma and eczema to the reaction observed on the challenge, and each food allergen to the reaction seen on the challenge. The relationships between the different types of OFC outcomes and other clinical characteristics were analyzed by calculating the odds ratio and confidence intervals using a univariate or multivariate logistic regression [18]. To determine the cutoff point of food-specific serum IgE level and wheal size with the optimum sensitivity and specificity to predict positive OFC, we used the receiver operating characteristic curve to evaluate sensitivity and specificity [19]. We performed an ROC analysis of definite OFC outcome for sIgE or wheal size and tested the null hypothesis of whether the area under the ROC curve was 0.5 [20].

The optimal balance of sensitivity and specificity indicated by the ROC output was used to determine the positive/negative cutoff points. $P < 0.05$ was considered significant. All tests were performed with STATA (version 11.0 for Windows; STATA Inc, College Station, TX, USA). (See supplemental material online)

RESULTS

We analyzed history of asthma and eczema, type of previous reaction, history of prior ingestion, sIgE and SPT-wheal size with regard to specific foods, and outcome of food challenges in 983 open OFCs to milk, egg or peanut. Most of the children had had comorbidity with eczema, asthma, or both. The children were primarily male (68%) and had a mean age of 5 years.

Forty-seven percent of the challenges were positive, with the following failure rates for each food: milk 144 of 290 (50%), egg 190 of 410 (47%) and peanut 130 of 282 (46%). No difference in failure rate was found between those with a history of prior ingestion of the challenged food and those without. The systems involved during positive OFC were skin in 56% of cases, upper respiratory tract in 45.5%, lower respiratory system in 29.5%, and gastrointestinal tract in 59%; 24% of patients developed a multisystem anaphylactic reaction (any combination of two organs), and 10.7% developed anaphylaxis at a dose less than 1 g of the ingested food. No difference in failure rate was found between those with a history of prior ingestion of the challenged food and those without. Similar system involvement and associated severity of positive OFCs were observed for milk, egg and peanut.

The subjects' previous reactions to the challenged food were no exposure in 23% of cases, cutaneous only in 41%, and non-cutaneous in 36%. Those with not only a cutaneous reaction had either a multisystem reaction (58%) or a reaction involving either the respiratory system (11%) or the gastrointestinal tract (41%). More than 96% of children had a positive SPT and/or a positive sIgE prior to the challenge. These results are similar to other studies on OFC [4,11,13]. Similar to previously reported results, children who failed the OFC had a larger SPT-wheal size and higher IgE level for each of the specific foods tested [4,13].The mean wheal size for milk was 8.15 mm in those

ROC = receiver operating characteristic

who failed OFC vs. 4.8 mm in those who passed ($P < 1x10^{-4}$), for egg 6.7 vs. 4.7 mm ($P < 1x10^{-4}$), and for peanut 8.8 vs. 4.36 mm ($P < 1x10^{-4}$). The mean specific IgE levels for milk were 10 kU/L in those who failed OFC vs. 4 kU/L in those who passed ($P < 1x10^{-4}$), for egg 7 vs. 2.93 kU/L ($P < 1x10^{-4}$), and for peanut 13.4 vs. 1.54 kU/L ($P < 1x10^{-4}$).

Children who failed the OFC compared to those who passed also had a higher incidence of previous reaction (80% vs. 70%, $P < 1x10^{-4}$), previous reaction involving the gastrointestinal tract, airways or multisystem (53% vs. 41%, $P < 1x10^{-4}$), and higher prevalence of asthma (52% vs. 42%, $P < 1x10^{-4}$). The children who had a multisystem reaction compared to those who did not were older (mean age 5.7 vs. 4.8 years, $P < 1x10^{-2}$) and had more often a past history of a non-cutaneous reaction (77% vs. 44%, $P < 1x10^{-4}$).

DEVELOPMENT OF THE SCORE SYSTEM

Using univariate regression analysis, we first identified clinical factors that were associated with a positive OFC or with OFC resulting in anaphylaxis. SPT-wheal size ($P < 1x10^{-4}$), sIgE ($P < 1x10^{-4}$), history of asthma ($P < 1x10^{-4}$), history of previous reaction to the tested food ($P < 1x10^{-4}$), and history of a non-cutaneous reaction to the tested food ($P < 1x10^{-4}$) were associated with failed OFC, but not gender, age, history of eczema, or history of prior ingestion of the tested food. In the event of an anaphylactic reaction only SPT-wheal size ($P < 1x10^{-4}$), sIgE ($P < 1x10^{-2}$), age ($P < 1x10^{-4}$), history of previous reaction to the tested food ($P < 1x10^{-4}$) and previous non-cutaneous reaction ($P < 1x10^{-4}$) were statistically significantly associated with a multisystem reaction. In order to evaluate which variables were independently associated with either OFC or OFC resulting in an anaphylactic reaction, we performed a multilogistic analysis of the data, which showed that only SPT-wheal size, sIgE levels, history of prior reaction, and history of previous non-cutaneous reaction were independently associated with a failed OFC [Table 1]. On the other hand, only SPT-wheal size, history of previous non-cutaneous reaction and age were independently associated with OFC resulting in a multisystem reaction [Table 1].

Table 1. Multilogistic regression of factors associated with a positive OFC with outcome of anaphylaxis

	Positive OFC		Anaphylaxis	
	Odds ratio	*P*	Odds ratio	*P*
Wheal	1.23	< 1 x 10^{-4}	1.16	< 1 x 10^{-4}
sIgE	1.04	< 1 x 10^{-4}	1.01	0.177
Age	0.97	0.528	1.07	0.027
Asthma	1.13	0.516	0.97	0.456
Prior reaction	1.14	< 1 x 10^{-2}	1.06	0.333
Non-cutaneous previous reaction	1.99	< 1 x 10^{-2}	4.24	< 1 x 10^{-2}

For each food allergy, the relationship between sIgE and food allergy was investigated using logistic regression models [2].The optimal balance of sensitivity and specific-

Figure 1. Probability of developing different type of reaction after OFC challenge, calculated using a logistic regression. Positive OFC **[A-D]**, anaphylaxis **[E-H]**, or anaphylaxis for allergen < 1 g **[I-L]**. Wheal size **[A,E,I]**, sIgE **[B,F,J]**, wheal size if IgE > 0.34 kU/L **[C,G,K]**, and for total score **[D,H,L]** are also shown

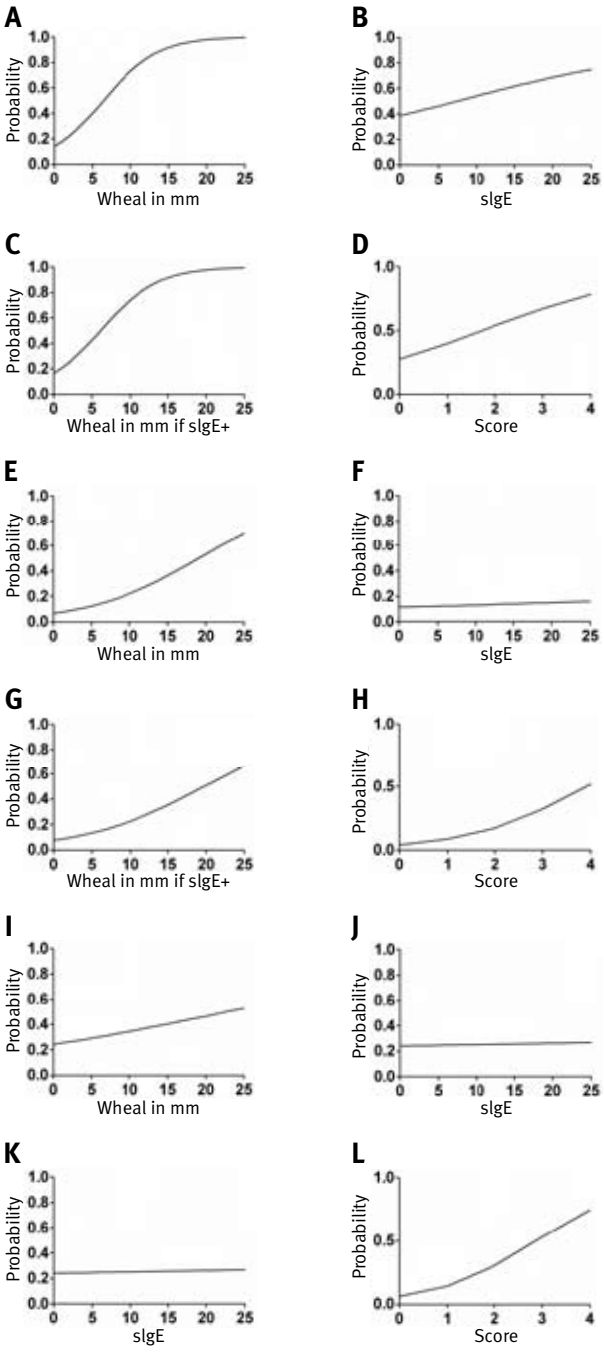
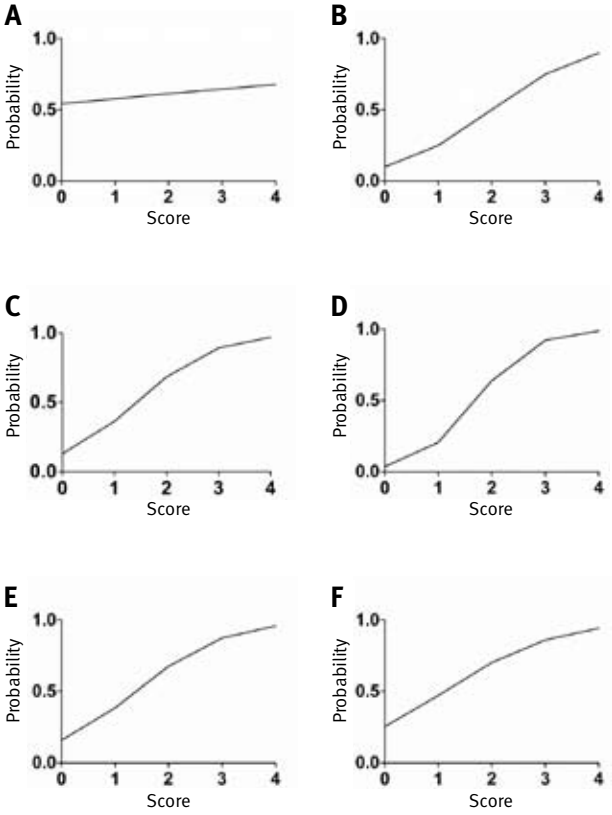


Figure 2. Probability of developing anaphylaxis for score 0 to 4 **[A,C,E]** and anaphylaxis for allergen ‹ 1 g **[B,D,F]** for score 0 to 4 in milk **[A,B]**, egg **[C,D]** or peanut **[E,F]** food challenges were calculated using a logistic regression



ity indicated by the ROC output was used to determine the positive/negative cutoff points for sIgE (sIgE > 5 kU/L, NPV 76, PPV 58) and wheal size values (sIgE > 9 mm, NPV 78, PPV 59) as predictors of failed OFC or OFC that caused anaphylaxis [Figures 1 and 2]. These cutoffs are similar if not exactly the same as other published values [15]. There was no significant difference among the different allergens tested: milk (sIgE > 5 kU/L, NPV 70, PPV 58), egg (NPV 80, PPV 56) and peanut (NPV 81, PPV 63). An SPT-wheal > 9 mm had an NPV of 75 and a PPV of 58 for milk, NPV 76 and PPV 59 for egg, and NPV 80 and PPV 68 for peanut. A score of 1 point was assigned for the following criteria [18] for the Food Challenge Score:

- Age > 5 years old (PPV 70, NPV 60)
- Prior reaction gastrointestinal, respiratory, multi-organ, or anaphylaxis
- SPT > 9 mm
- sIgE > 5 kU/L

NPV = negative predictive value
PPV = positive predictive value

Table 2. Univariate logistic regression for positive OFC, anaphylactic reaction, and anaphylactic reaction at challenged dose ‹ 1 g

	Positive OFC		Anaphylaxis		Anaphylaxis ‹ 1 g	
	Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*
Wheal	1.32	‹ 1 x 10^{-4}	1.15	‹ 1 x 10^{-4}	1.04	0.527
sIgE	1.06	‹ 1 x 10^{-4}	1.02	‹ 1 x 10^{-2}	0.99	0.549
Age	1.05	0.058	1.12	‹ 1 x 10^{-4}	1.15	0.294
Non-cutaneous previous reaction	1.60	‹ 1 x 10^{-4}	4.44	‹ 1 x 10^{-4}	5.45	‹ 1 x 10^{-2}
Score	9.52	‹ 1 x 10^{-4}	25.18	‹ 1 x 10^{-4}	59.86	0.012

VALIDATION OF THE FOOD CHALLENGE SCORE SYSTEM

Univariate logistic regression was performed with different possible outcomes of OFC: positive, multisystem reaction, and multisystem reaction at low dose of allergen (< 1 g) [Table 2]. The total Food Challenge Score was associated with more than one component and was increasingly associated with a more severe outcome of the challenge, displaying the highest correlation for anaphylaxis with low dose allergen in all patients [Table 2]. We analyzed the probability that the different SPT-wheal size, sIgE, SPT-wheal size if IgE > 0.34 kUI/L, and score would predict positive OFC, multisystem reaction, multisystem reaction for low dose allergen, anaphylaxis and anaphylaxis for low dose allergen. The total Food Challenge Score was found to be the best predictor for anaphylaxis with low dose allergen [Figure 1]. These findings were similar for all the tested allergens [Figure 1]. A score of 4 carries > 95% probability to develop anaphylaxis from low dose allergen. A score of 0–1 had a negative predictive value for multisystem reaction of 95% for milk OFC, 91% for egg, and 93% for peanut. A score of 3–4 had a positive predictive value for anaphylaxis of 62% for milk OFC, 92% for egg, and 86% for peanut. All allergens with the exception of milk had a less than 45% probability for developing anaphylaxis for score 1 or less, and above 95% for score 4.

DISCUSSION

We have performed approximately 1000 food challenges to milk, egg and peanut in the last 5 years. As previously reported, these foods are the predominant food allergens in children and account for most multi-organ system reactions on food challenges [13,21-23]. Our goal was to identify risk factors for a severe reaction. We hypothesized that by combining clinical variables (routinely available prechallenge) with allergy test results, we could develop a simple score system that would improve our ability to predict the severity of the outcome of a food challenge. To determine the risk factors for those reactions, a logistic regression model examining commonly available clinical data was designed [6,11]. This differs from using a single variable such as specific IgE or SPT to predict future reactions. Consistent with the concept that a single variable is

not robust, previous investigators examined the relationship of SPT [5-7] or food-specific IgE levels [4,6,8,9] to challenge outcome and showed that both skin and food-specific IgE tests have good NPV but low PPV in determining oral tolerance [10]. However, sIgE, SPT or prior clinical history has not been demonstrated consistently to be of value in predicting reaction severity when used alone [9,14,21,23]. Therefore, we used a univariate logistic regression and determined the factors associated with increased risk to develop positive OFC and multisystem reaction. The factors (sIgE levels, SPT-wheal size, history of any prior reaction to the tested food, history of an initial non-cutaneous reaction, and age) were identified and positively associated with either outcome: failed OFC or multisystem reaction on OFC [Table 1]. The Food Challenge Score also included previous non-cutaneous reactions as it was consistently associated with both positive OFC and multisystem reaction. Indeed, in our experience, families can accurately remember if skin and/or another organ (vomiting, coughing, sneezing, abdominal pain, wheezing) was involved in the initial reaction. The cutoffs were the optimal balance of sensitivity and specificity indicated by the ROC output.

To validate the Food Challenge Score, we performed a univariate analysis with the increasingly more severe type of OFC outcome (positive, multisystem reaction, multisystem reaction at low dose of allergen) [Table 2]. If the score was a good predictor of severe reaction, a higher value should be associated with a more severe reaction during OFC. This proved true, since the food challenge score was strongly associated with a more severe outcome of the challenge and displayed the highest correlation for anaphylaxis at low dose in all patients [Table 2], indicating the usefulness of the score. The total Food Challenge Score was superior to any individual element. Higher score (3 or 4) was a better predictor of anaphylaxis and anaphylaxis occurring at low dose, confirming that despite limited sensitivity (44%) it could predict a severe outcome with high specificity (80%). No significant difference was found among all the foods tested, although the Food Challenge Score predicted a severe reaction to egg and peanut at a higher rate than milk OFC.

This simple Food Challenge Score will make it easier to determine which OFCs are high risk. This is important given the high demand for these tests. There is an increasing need to perform OFC in the doctor's office, which may or may not be located in the immediate vicinity of a hospital. Stratification of the risk of OFC would be important for choosing the right location of OFC performance as well as to better counsel the family on risk associated with OFC. The value of the initial presentation as predictor of type of future outcome has also not proven a good parameter to predict severity of OFC [9,21].

In conclusion, we have developed a simple score, which for the first time can help clinicians to accurately identify oral food challenges that have an elevated risk of severe outcome and can help the clinician to decide on safe locations such as the hospital setting or lower starting doses for those challenges.

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SUPPLEMENTAL MATERIAL

STUDY POPULATION AND ORAL CHALLENGES

Informed consent was obtained from the participants, and the study was approved by the institutional review board of The Children's Hospital of Philadelphia (CHOP), Philadelphia, PA. Children were seen in clinics at either the main hospital or its associated satellites. As previously reported, initial or repeated open food challenges were performed when oral tolerance was suspected [1E]. Challenges were administered in escalating doses of the food allergen as tolerated every 20 minutes for a total age-appropriate serving by using an appropriate food or powdered protein (Barry Farm Enterprises, Wapakoneta, OH, USA) camouflaged with juice, or other moist food, such as applesauce or pudding [1E,2E]. Hives secondary to direct contact with the food, such as those on the face or hands, were not considered positive reactions. Ambiguous reactions (25 total) were not included in this review. In patients with underlying atopic dermatitis, the skin was in good control at the time of the challenge; patients' skin was cleared with aggressive topical therapy and antibiotics if necessary. Challenges were stopped if clear symptoms of an allergic reaction developed [3E]. Emergency medications, including diphenhydramine, epinephrine, albuterol, and prednisone were administered at the physician's discretion. Medication was prescribed for failed challenges on the basis of the type and severity of reaction. Short-acting antihistamine doses were oral diphenhydramine 1.5 to 2 mg/kg (maximum dose 50 mg). The same dose was repeated orally 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.

Negative or passed challenge was declared if patients ingested 100% of the intended dose without significant untoward effects. All patients were observed for a minimum of 2 hours or until signs of clinical reactivity subsided for those patients who failed the challenge. Patients were informed about late-phase reactions before discharge and instructed to contact the supervising physician immediately if symptoms recurred [3E]

SKIN TESTING

Reactions of wheal and flare were recorded after 20 minutes by measuring the maximal longitudinal diameter of the wheal and the diameter orthogonal to it. Mean wheal diameters were calculated as (a + b)/2. A wheal of ≥ 3 mm than the negative control, accompanied by a flare, was considered positive. The positive control was 10 mg/ml of histamine dihydrochloride. Food-specific IgE levels were measured and SPTs were performed within 6 to 12 months of OFCs.

STATISTICAL METHODS

The children were categorized (positive or negative) on the basis of any reaction, multi-organ system reaction after OFC, multi-organ system reaction after OFC after ingestion of a dose < 1 g, anaphylaxis, or anaphylaxis after ingestion of a dose < 1 g. Collection of patient data was in compliance with the internal review board of The Children's Hospital of Philadelphia.

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Table E1. Demographics of the study population

Characteristic	Study population (n=982)
Male gender	687 (68%)
Female gender	295 (32%)
Mean ± SD age (yrs)	5. 0 ± 2.6
Atopic history	
Asthma	540 (58%)
Eczema	476 (53%)
Prior reaction(s)	654 (74%)
Milk	248 (84%)
Egg	244 (70%)
Peanut	161 (62%)
Non-cutaneous previous reaction	465 (53%)
Milk	144 (50%)
Egg	190 (54%)
Peanut	130 (50%)
Prior ingestion	733 (76%)
Milk	262 (92%)
Egg	296 (74%)
Peanut	174 (62%)
Wheal mean size (mm ± SD)	
Milk	6.5 ± 3.9
Egg	5.7 ± 3.3
Peanut	6.4 ± 4.2
Serum IgE	
Milk	7.1 ± 14.8
Egg	4.8 ± 12.34
Peanut	6.8 ± 18.8

Table E2. Clinical characteristics in children with a positive and negative OFC

	Positive OFC	Negative OFC	*P*	Anaphylaxis	Non-anaphylaxis	*P*
Wheal (mm) (mean ± SE)						
Milk	8.15 ± 0.32	4.8 ± 0.26	$< 1x10^{-4}$	7.4 ± 0.7	6.3 ± 0.23	0.07
Egg	6.7 ± 0.25	4.7 ± 0.1	$< 1x10^{-4}$	7. ± 0.52	5.5 ± 0.16	$< 1x10^{-2}$
Peanut	8.8 ± 0.34	4.36 ± 0.27	$< 1x10^{-4}$	9.6 ± 0.47	5.7 ± 0.27	$< 1x10^{-4}$
sIgE kU/L (mean ± SE)						
Milk	10.08 ± 1.7	4.01 ± 0.98	$< 1x10^{-4}$	12.2 ± 3.7	6.3 ± 0.99	0.045
Egg	7.04 ± 1.3	2.93 ± 0.73	$< 1x10^{-4}$	16.5 ± 4.8	3.4 ± 0.52	$< 1x10^{-4}$
Peanut	13.41 ± 2.8	1.54 ± 0.25	$< 1x10^{-4}$	7.6 ± 2.5	2.5 ± 0.52	0.183
Male (%)	70.35	69.46	0.7	70	70	0.8
Age	5.1 ± 0.12	4.8 ± 0.11	0.056	5.7 ± 0.21	4.8 ± 0.09	$< 1x10^{-2}$
Asthma (%)	52	42	$< 1x10^{-4}$	64	57	0.11
Eczema (%)	47	47	0.90	55	51	0.2
Prior ingestion (%)	98	73	0.11	75	68	0.06
Any prior reaction (%)	80	70	$< 1x10^{-4}$	57	67	0.06
Non-cutaneous previous reaction (%)	53	41	$< 1x10^{-4}$	77	44	$< 1x10^{-4}$

SE = standard error, OFV = oral food challenge, anaphylaxis = OFC resulting in anaphylaxis, non-anaphylaxis = OFC with no anaphylaxis

Table E3. Univariate logistic regression of factors associated with a positive OFC or OFC with anaphylaxis

	Positive OFC		Anaphylaxis	
	Odds ratio	*P*	Odds ratio	*P*
Wheal	1.32	$< 1x10^{-4}$	1.14	$< 1x10^{-4}$
sIgE	1.06	$< 1x10^{-4}$	1.04	$< 1x10^{-2}$
Age	1.05	0.058	1.12	$< 1x10^{-4}$
Male	1.04	0.762	1.01	0.948
Asthma	1.63	$< 1x10^{-4}$	1.36	0.11
Eczema	1.02	0.86	1.77	0.404
Prior ingestion	0.98	0.885	0.73	0.11
Previous reaction	1.60	$< 1x10^{-4}$	1.15	$< 1x10^{-4}$
Non-cutaneous previous reaction	1.32	$< 1x10^{-4}$	4.44	$< 1x10^{-4}$

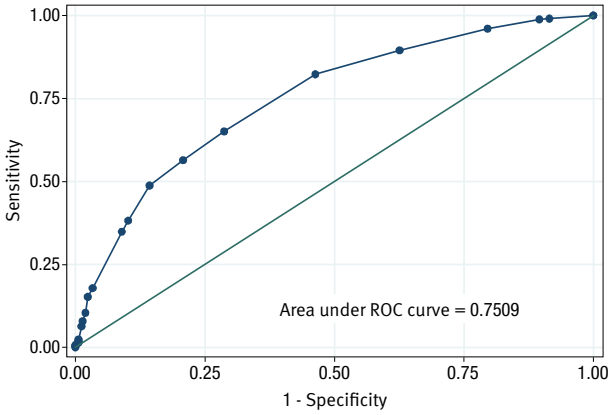
Table E4. Food challenge score

	Score
Wheal > 9 mm	1
sIgE > 6 kU/L	1
Age ≥ 5 yrs	1
Initial reaction not cutaneous	1
Max total	4

Figure E1. ROC curve wheal size and prediction of positive OFC

[A] ROC output was used to determine the positive/negative cutoff points for wheal size (mm) to predict positive OFC. **[B]** The sensitivity, specificity, efficiency, positive predictive value and negative predictive value (NPV) of different cutoff points

A



B

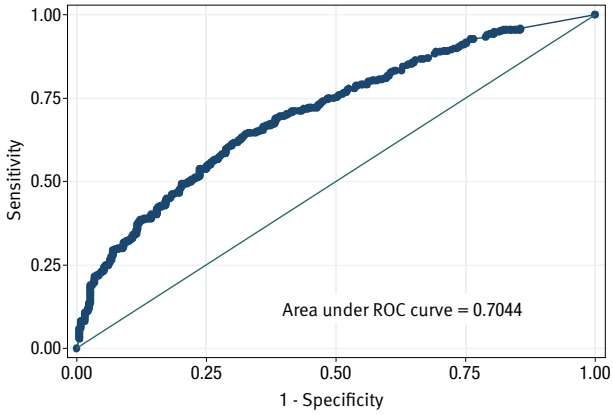
OFC positive	Specificity	Sensitivity	Efficiency	PPV	NPV
Wheal › 0	99	8	51	48	91
Wheal › 1	99	10	52	50	91
Wheal › 2	96	20	56	51	85
Wheal › 3	90	37	62	56	80
Wheal › 4	82	54	67	61	77
Wheal › 5	82	53	63	65	69
Wheal › 6	65	71	68	71	66
Wheal › 7	56	79	68	74	65
Wheal › 8	49	85	68	77	61
Wheal › 9	38	90	65	78	59
Wheal › 10	34	91	64	86	57
Wheal › 11	18	97	59	85	56

PPV = positive predictive value, NPV = negative predictive value

Figure 2E. ROC curve sIgE and prediction of positive OFC

[A] ROC output was used to determine the positive/negative cutoff points for sIgE (kU/L) to predict positive OFC. **[B]** The sensitivity, specificity, efficiency, positive predictive value (PPV) and negative predictive value (NPV) of different cutoff points

A



B

OFC positive	Specificity	Sensitivity	Efficiency	PPV	NPV
IgE › 0	93	17	54	51	72
IgE › 1	70	55	62	59	66
IgE › 2	57	70	63	64	63
IgE › 3	44	89	69	67	61
IgE › 4	48	78	63	70	60
IgE › 5	41	84	63	73	58
IgE › 6	34	88	62	76	58
IgE › 7	31	91	62	77	56
IgE › 9	28	92	61	79	56