

The Food Challenge Risk Index: Predicting Positive Open Food Challenges to Milk, Egg, and Peanuts in Children

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ABSTRACT

Suspected food allergy is commonly encountered. Diagnosis requires skin testing, food-specific immunoglobulin E (IgE), and ultimately a food challenge. Previous studies determined food-specific IgE threshold levels predicting greater than 95% of the patients with a positive food challenge. However, if the food-specific IgE level is less than the threshold, a food challenge is required. Oral food challenges are time consuming, and they subject patients to allergic reactions. The aim of this study was to develop a food challenge risk index (FCRI) to predict positive food challenges. Fifty-five open food challenges were reviewed retrospectively. Skin prick tests, food-specific IgE levels, and time since last reaction were employed to develop a formula. The FCRI = $[3 \times \text{skin prick test wheal (mm)} + 10 \times \text{food-specific IgE level} - \text{time since last reaction (months)}]$. The FCRI value was compared to the food challenge results. Threshold levels chosen were 15, 20, and 25 for milk, egg, and peanut, respectively. Comparison of the FCRI to the actual food challenges across all groups revealed a sensitivity of 0.842 and a specificity of 0.861. We have derived a simple and accurate formula that uses readily available clinical data to predict positive food challenges. The FCRI may be used in a prospective fashion to reduce number of food challenges necessary for diagnosis of milk, egg, and peanut allergies in children.

INTRODUCTION

ALLERGIC REACTIONS TO FOODS are commonly encountered in allergy and immunology practice. Food allergy affects about 8% of children less than 3 years old and 40% of those with atopic dermatitis.¹⁻³ In children, the most common allergenic foods are milk, egg, and peanut.^{1,2,4,5} Fortunately, most children lose their sensitivity to milk and egg; however, only 20% lose their sensitivity to peanut.^{1,6-8} Because food allergy is often outgrown, it requires frequent reevaluation.

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The food allergy evaluation begins with a detailed history and physical examination. The subjective history is usually inaccurate, and only 40% of these histories are verified by food challenge.⁹⁻¹¹ Therefore, the diagnosis requires skin testing, blood testing, elimination diets, and often a food challenge.

The skin prick test is usually the first objective test in the food allergy evaluation. A negative skin test, if done properly, confirms the absence of food allergy whereas a positive skin prick test only suggests the possibility of food allergy and must be verified by an unequivocal history, further testing, or food challenge.^{2,3,9,12}

The next step and now often the first step in the food allergy evaluation is the measurement of food-specific immunoglobulin E (IgE) antibodies using the CAP System fluorescent-enzyme immunoassay (FEIA). Multiple studies used the food-specific IgE antibodies to determine food-specific IgE levels at which greater than 95% of patients will have a positive food challenge, thus eliminating the need for over 40% of all food challenges.^{3,5,6,9} If the patient's serum food allergic-specific IgE level is less than the 95% predictive value, the patient may react to the food and a food challenge is necessary.

The double-blind-placebo-controlled food challenge (DBPCFC) is the "gold" standard and has a positive and negative predictive accuracy of 95%.^{2,6,9} Food challenges are time consuming, require trained staff, are costly, and subject patients to allergic symptoms and anaphylaxis.^{3,8,11} A reaction during the challenge disrupts the allergist's office. Therefore, reducing the number of food challenges and the number of positive reactions is desirable.

The goal of this study was to develop a diagnostic strategy to predict positive food challenges, thus decreasing the number of food challenges even further than by using the CAP system FEIA alone. In this retrospective study, we employed the commonly gathered data in the food allergy workup, including the results of the skin prick test, the food-specific IgE level, and the time since last food reaction. These data were then used to derive a food challenge risk index. The food challenge risk index could accurately predict positive food challenges to milk, egg, and peanut in children. It may be used in a prospective fashion to predict positive food challenges which could ultimately decrease the number of necessary challenges.

MATERIALS AND METHODS

We retrospectively reviewed food challenges performed in an outpatient allergy office from January 1, 1998, until March 26, 2003. A total of 156 food challenges were performed. Challenges to foods other than milk, egg, and peanut were excluded. Cases were included if there was a thorough history and physical exam, food skin prick test results, specific IgE levels using the CAP System FEIA technique, and a documented food challenge. A total of 55 (35%) of 156 charts met this criteria.

Children with suspected food allergy or atopic dermatitis underwent skin prick testing with commercially prepared extracts of the relevant foods. The skin tests were performed on the backs of infants and on the forearm of older children using the Multi-test (Lincoln Diagnostics). The skin weal diameter (mm) was measured after 20 minutes and compared to a positive control (histamine 10 mg/mL) and a negative control solution (50% glycerinated saline). The skin prick test was read by 1 of 2 physicians and considered positive if the weal diameter was 3 mm greater than the negative control. The majority of skin prick tests were performed within 3 months of the food challenge.

Children with suspected food allergy or atopic dermatitis were evaluated with food-specific IgE levels. The results were included in this study if they were done by Quest Diagnostic Laboratories using the CAP System FEIA technique. The majority of food-specific IgE levels were obtained within 4 months of the food challenge.

Children with a diagnosis of food allergy or atopic dermatitis underwent open food challenges under the supervision of 1 of 2 physicians in the outpatient allergy office. For at least 2 weeks prior to the open challenge, all patients were on a diet free from the food in question and were without symptoms. On the day of the open food challenge, increasing amounts of food were administered every 30 minutes until symptoms were noted or a normal portion sized amount of food was tolerated. The following amounts of food were administered: small amount of food touched to lips, 1/8 of a teaspoon, 1/4 of a teaspoon, 1/2 of a teaspoon, 1 teaspoon, 2 teaspoons, 3 teaspoons, and a regular serving of the food. The open food challenge

ceased at the first sign of any adverse reaction and was considered positive if one of the following symptoms was noted: erythema, wheezing, rhinitis, sneezing, coughing, pruritus, urticaria, diarrhea, vomiting, abdominal pain, or anaphylaxis. The challenge was considered negative if the child could tolerate a regular-sized serving of the food.

Two physicians developed the FCRI formula by using the results of skin prick test, food-specific IgE levels, and time since last reaction. The skin prick test size and food-specific IgE level were multiplied by a factor that reflected what the physicians felt were their relative importance. The time since last reaction was subtracted, as the longer the time since last reaction, the more likely a decrease in clinical sensitivity. The derived formula was $3 \times \text{wheal (mm)} + 10 \times \text{food specific IgE level (kU}_A\text{/L)} - \text{time since last reaction (months)}$. The FCRI formula was then retrospectively applied and compared to the food challenges. For each food, positive food challenges were more often seen when the FCRI result was a high number, whereas negative food challenges were more often seen when the FCRI result was a lower number. Different threshold levels were used for statistical analysis and we selected the statistically significant FCRI threshold level for each specific food. The FCRI threshold levels selected for each food were 15 for milk, 20 for egg, and 25 for peanut. Once threshold levels were determined, the FCRI results were compared to the 55 food challenge outcomes.

SPSS software was used to generate receiver operating characteristic (ROC) curves, correlations, and descriptive statistics. A positive food challenge was determined to be the “gold” standard and indicative of food allergy. Sensitivity, specificity, and predictive values of the FCRI versus food challenge results were manually computed.

RESULTS

Results of previously performed open food challenges were reviewed versus results of the proposed food challenge risk index calculated for each of the 55 patients. Twenty-five (45%) of the challenges were performed for suspected milk hypersensitivity, sixteen (29%) for suspected egg hypersensitivity and fourteen (25.5%) for suspected peanut hypersensitivity. Baseline characteristics by food hypersensitivity are summarized in Tables 1–3. Patients ranged in age from 14 months to 144 months, with a mean of 44.4 (± 27.18) months. Forty (72%) were male and 15 (27.3%) female. Forty (73%) had a history of atopic disease, 21 (38%) of the patients had eczema, 18 (33%) had the diagnosis of asthma, and 19 (35%) allergic rhinitis. Nineteen (34.5%) demonstrated a positive food challenge.

All groups

Comparison of the proposed risk index to the actual food challenges across all groups revealed a sensitivity of 0.842 and a specificity of 0.861, resulting in a false-positive rate of 13.9% and a false-negative rate of 15.8%. An overall negative predictive value (NPV) indicated that the proposed risk index is accurate 91.2% of the time. The overall positive predictive value (PPV), or percent truly positive, was 0.762 (Table 4). Area under the ROC curve was 0.840 with a confidence interval (CI) between 0.727 and 0.953. This indicates an 84% probability that a randomly selected, positively challenged case will yield a formula value larger than a randomly selected negative case. A post-test probability of 77% was calculated based on a 6.06 positive likelihood ratio (LR^+) and baseline prevalence rate of 34.5% from the sample population.

Milk group

Comparison of the proposed risk index to the actual food challenge for the milk hypersensitivity group revealed a sensitivity of 1.00, resulting in a false-negative rate of 33.3% and a zero probability of a false-positive occurrence. This is in agreement with an NPV of 1.00. PPV for the milk group was 0.647 (Table 4). The area under the ROC curve was 0.838 and the CI between 0.676 and 1.00. A post-test probability of 75% was calculated on the basis of a 3.50 LR^+ and baseline prevalence rate of 44% found in the sample population.

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TABLE 1. MILK

	<i>Sex</i>	<i>Age (month)</i>	<i>Atopy^a</i>	<i>Wheal (mm)</i>	<i>Food- specific IgE (kU_A/L)</i>	<i>Last reaction (month)</i>	<i>Challenge</i>	<i>Formula result</i>
1	M	17	FA	11	0.11	5	Positive	29.1
2	M	14	FA, AS	5	0.21	8	Negative	9.1
3	M	32	FA	5	0.35	24	Negative	-5.5
4	M	51	FA,AD,AS	0	0.35	30	Negative	-26.5
5	M	49	FA,AD,AS	6	0.35	37	Negative	-15.5
6	M	32	FA,AD	5	0.35	24	Negative	-5.5
7	M	22	FA	4	0.35	14	Negative	1.5
8	M	33	FA,AD	7	0.68	10	Positive	17.8
9	M	25	FA	8	0.7	33	Negative	-2
10	F	37	AD	13	0.77	37	Negative	9.7
11	M	29	FA,AS	16	0.98	17	Positive	40.8
12	M	40	FA,AS,AR	5	1.66	18	Negative	13.6
13	M	52	FA,AS	10	1.92	28	Positive	21.2
14	M	17	FA,AD	16	2.26	10	Negative	60.6
15	F	25	FA,AS,AR	15	2.36	7	Positive	61.6
16	F	77	FA	12	3.04	10	Positive	56.4
17	M	90	FA,AS,AR	13	3.3	66	Negative	6
18	M	66	FA,AR	12	4.31	9	Positive	70.1
19	F	61	FA,AS,AD	16	4.7	49	Positive	46
20	F	53	AD	10	5.68	16	Negative	70.8
21	M	53	FA	0	8.1	44	Negative	37
22	F	56	FA	33	8.44	32	Positive	151.4
23	F	30	FA	15	8.71	12	Positive	120.1
24	M	46	FA,AR	8	8.89	36	Negative	76.9
25	M	21	FA,AS,AR	12	15.1	10	Positive	177

^aAD, atopic dermatitis; AR, allergic rhinitis; AS, asthma; FA, food allergy.

Egg group

Comparison of the proposed risk index formula results to the actual food challenge results for the egg hypersensitivity group revealed a sensitivity of 0.60 and specificity of 0.91. This results in a false-positive rate of 9% and a higher false-negative rate of 40%. The PPV was 0.75 with a NPV of 0.83 (Table 4). The area under the ROC curve was 0.764, with a CI between 0.495 and 1.00. A post-test probability of 74% was calculated on the basis of a 6.67 LR⁺ and 31.25% prevalence rate found in the sample population.

Peanut group

Comparison of the proposed risk index to the actual food challenge for the peanut hypersensitivity group revealed a sensitivity of 0.667 and specificity of 1.00, resulting in a false-positive rate of 28.6% and a zero probability of a false-negative occurrence. This is in agreement with a PPV of 1.0 and LR⁺ of 0. The NPV for the peanut group was 0.917 (Table 4). The area under the ROC curve was 0.879 with a CI between 0.649 and 1.00.

DISCUSSION

Suspected allergic reactions to food are commonly encountered, and egg, milk, and peanut are most frequently implicated in children.^{1,5} The initial food allergy evaluation relies on subjective symptoms experi-

TABLE 2. EGG

	<i>Sex</i>	<i>Age (month)</i>	<i>Atopy^a</i>	<i>Wheal (mm)</i>	<i>Food- specific IgE (kU_A/L)</i>	<i>Last reaction (month)</i>	<i>Challenge</i>	<i>Formula result</i>
26	M	16	FA	8	0.11	16	Negative	9.1
27	M	14	AS	5	0.21	14	Negative	3.1
28	M	33	AD	5	0.35	25	Negative	-6.5
29	F	15	AD	3	0.35	15	Positive	-2.5
30	M	144	FA	5	0.35	122	Negative	-103.5
31	M	31	FA,AS,AR	5	0.35	23	Negative	-4.5
32	M	90	FA,AD,AS,AR	4	0.35	24	Positive	-8.5
33	M	21	FA,AR	15	0.35	21	Positive	27.5
34	M	42	AS,AR,FA	7	0.88	42	Negative	-12.2
35	F	34	FA	6	1.01	22	Negative	6.1
36	F	36	FA,AD	10	1.13	36	Negative	5.3
37	M	89	FA,AS,AR,AD	10	1.41	65	Negative	-20.9
38	M	38	FA	10	2.41	2	Positive	52.1
39	M	51	AD	0	3.81	51	Negative	-12.9
40	F	31	FA,AD	25	4.54	31	Positive	89.4
41	F	25	FA,AD	4	4.89	12	Negative	48.9

^aAD, atopic dermatitis; AR, allergic rhinitis; AS, asthma; FA, food allergy.

enced and few suspected reactions are verified by food challenge.^{9,10} Therefore, the diagnosis of food allergy requires skin tests, blood tests, elimination diets, and ultimately a food challenge. In previous studies, the food-specific IgE antibodies using the CAP System FEIA have determined food-specific IgE levels in which greater than 95% of the patients will have a positive food challenge. These food-specific IgE levels have decreased the number of food challenges necessary to diagnose food hypersensitivity. However,

TABLE 3. PEANUT

	<i>Sex</i>	<i>Age (month)</i>	<i>Atopy^a</i>	<i>Wheal (mm)</i>	<i>Food- specific IgE (kU_A/L)</i>	<i>Last reaction (month)</i>	<i>Challenge</i>	<i>Formula result</i>
42	M	57	AD	5	0.35	21	Negative	-2.5
43	M	35	AS,AR	15	0.35	35	Negative	13.5
44	M	25	FA,AD	5	0.35	25	Negative	-6.5
45	M	36	FA,AR	4	0.35	36	Negative	-20.5
46	M	29	FA	5	0.35	29	Negative	-10.5
47	F	144	FA,AS,AD	4	0.35	114	Negative	-98.5
48	F	57	FA,AS,AR	8	0.35	24	Positive	3.5
49	M	28	AD	9	0.35	28	Negative	2.5
50	M	34	FA	15	0.4	24	Positive	25
51	F	64	AD	6	0.68	64	Negative	-39.2
52	M	46	FA,AR	10	1.63	36	Negative	10.3
53	M	62	FA,AS,AR	10	1.68	32	Negative	14.8
54	M	50	AS,AD,AR	3	3.44	26	Negative	17.4
55	M	39	AS,AR	15	4.01	39	Positive	46.1

^aAD, atopic dermatitis; AR, allergic rhinitis; AS, asthma; FA, food allergy.

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TABLE 4. SUMMARY

<i>Food allergen group</i>	<i>Cutoff value (group specific)</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>NPV</i>	<i>PPV</i>
All groups		0.84	0.86	0.91	0.76
Milk	15	1.00	0.71	1.00	0.65
Egg	20	0.60	0.91	0.83	0.75
Peanut	25	0.67	1.00	0.92	1.00

if the food-specific IgE levels are less than the threshold, a food challenge is still required to diagnose or exclude the food allergy and positive challenges are frequently encountered. However, as a child grows older, his or her clinical food sensitivity may decrease or disappear, so the family and the physician may want to know if the child is still food allergic. This would require a food challenge if the skin test and/or the specific IgE levels are still measurable. Oral food challenges are time-consuming procedures and subjects patients to potentially severe allergic reactions or anaphylaxis, which is not only dangerous but also disruptive to the allergy office.¹¹ Therefore, reducing the number of necessary food challenges is desirable.

More recent studies demonstrate an improved predictive accuracy of skin prick tests when employed in specific patient populations. Sporik et al. found that in children with a skin test wheal size above 8 mm for milk and peanut and 7 mm for egg accurately predicted positive open food challenges to milk, egg, and peanut.^{13,14} Eigenmann et al. studied atopic older children and found that using a skin prick test wheal size could predict positive challenges with a specificity of 92% for milk, 75% for egg, and 95% for peanut.¹⁵ The skin prick test remains a valuable tool in the evaluation of food allergy, and these studies suggest that the size of the skin prick test may correlate with food challenge result. Used alone, skin prick test results have limitations; however, it is easily obtained and assists in the diagnosis of food allergy. Because the size of the wheal may correlate with hypersensitivity to food, the skin prick wheal size was included in our FCRI formula.

Many researchers have correlated food-specific IgE levels with oral food challenge results. Sampson et al. prospectively and retrospectively correlated threshold levels of IgE with positive food challenge results. If a food-specific IgE level is greater than the threshold level, no food challenge is necessary because there is a greater than 95% probability that the challenge will be positive.⁵ One of our patients had a milk IgE level of 15.1 kU_A/L, which exceeds the published threshold level for milk, therefore a food challenge was unnecessary because it has a greater than 95% probability of being positive. The FCRI result, in this patient, was 177 which is much greater than our determined milk threshold of 15. This patient was challenged and, as expected, had a positive food challenge. Therefore, both the food-specific IgE threshold level and our FCRI threshold accurately predicted this positive food challenge.

Rance et al. used the combination of skin prick test results and food-specific IgE levels to predict positive food challenges. A skin prick wheal greater than 16 mm and the food-specific IgE greater than 57 kU_A/L predicted a positive food challenge with a positive predictive value of 100%.¹⁶ Garcia-Ara et al. found a milk threshold level of 2.5 kU_A/L in infants.¹⁷ Crespo et al. also investigated food-specific antibodies in predicting acute reactions to eggs, and found that as the level increased so did the likelihood of a positive food challenge.¹⁸ These studies have reduced the number of necessary food challenges. However, a patient with a food-specific IgE level less than the threshold must still be challenged for definitive diagnosis.⁵

The skin patch test has shown promise in the diagnosis of food allergy. In a study by Atkins et al., 55% of children with a positive atopy patch test were positive on food challenge.^{19,20} The atopy patch test is only valid in patients with atopic dermatitis and is not commonly used by practicing allergists; therefore, its role will be better defined in the future.

There is no perfect test to diagnose food allergy because these tests only support or refute the diagnosis. Ultimately a food challenge must be performed for accurate diagnosis, and the DBPCFC is the gold standard.

The FCRI was developed to help practicing allergists decide when to challenge or rechallenge a potentially food allergic patient. In this study, the FCRI was retrospectively applied to previously performed food challenges. For each food, positive food challenges were more often seen when the FCRI result was a high number, whereas negative food challenges were more often seen when the FCRI result was a lower number. Various FCRI numbers were statistically analyzed, and we selected the most statistically significant FCRI threshold level for each specific food. The FCRI threshold levels selected for each food were 15 for milk, 20 for egg, and 25 for peanut. FCRI results greater than these thresholds were more likely to predict a positive food challenge, whereas FCRI results lower than these thresholds were more likely to predict a negative food challenge. Using our thresholds, the FCRI had a negative predictive value of 91% and a positive predictive value of 76%. At first glance, the statistics appear less robust than other studies. The peanut and egg thresholds had a better specificity than the milk threshold; however, the negative and positive predictive values are acceptable. This is not a failure to identify the diagnosis because the FCRI only helps to categorize patients previously requiring food challenge into those more likely or less likely to react. This could obviate the need for challenge in those patients at higher risk for a positive outcome.

If the FCRI for milk, egg, and peanut were used prospectively in these patients, challenges would be avoided in 21 of the 55 food challenges because the FCRI was predictive of positive food challenges. Thus, in this study, the total number of food challenges would have been reduced by 38%. Of the 34 food challenges deemed necessary by the formula, only 9% (3 of 34) would have been positive, therefore reducing the number of potentially severe allergic reactions or anaphylaxis.

Children often outgrow food allergy, and it is recommended that patients be rechallenged every few years.^{13,21} Multiple authors describe features that can help determine if the child will outgrow food sensitivity.^{13,21} A lower food-specific IgE, smaller wheal on skin prick testing, and longer time on the elimination diet improve the chance that the food allergy has been lost.^{7,8,11,22–24} These factors are included in the FCRI formula, so the FCRI may be used to follow patients and determine when they may have lost food sensitivity.

This study must be interpreted within the limits of the methodology. This is a small retrospective pilot study that attempted to devise a future means of reducing the number of necessary challenges and of those challenged, limiting the number of high probable positives. The FCRI must be validated in a prospective fashion.

This study reviewed the results of open food challenges and it would have been optimal to perform DBPCFC. The open challenges may have led to an observer bias; however, we feel bias is limited because it is our practice to define a positive challenge when an objective acute reaction is observed by the physician. Delayed reactions were not included in this study. If patient bias was suspected, we performed single blind studies and if necessary referred patients to tertiary care centers for DBPCFC.

There could also be some selection bias favoring less sensitive subjects because only the data of those who actually underwent food challenge was analyzed. Patients with high food-specific IgE results were not challenged. Therefore, the children that underwent food challenge would be expected to have lower FCRI than children who may be highly allergic; thus, our thresholds may be too low. However, we feel that the data and patients in this study are typical of patients who undergo food challenges administered by a practicing allergist.

If our thresholds are too low, our calculated FCRI might yield a bias toward too few food challenges. In this patient group, 9% (5 of 55) of our patients would have been falsely labeled as food allergic, would not have undergone challenge, and would have unnecessary food restrictions. However, we suspect that if we reassess food allergy and FCRI annually, these patients would have a lower FCRI and eventually undergo challenge and be correctly diagnosed. Monitoring the FCRI every year may be useful in determining when to rechallenge patients. Even though our calculated FCRI might yield too few challenges, our primary goal was to avoid the risk of a positive challenge, even at the cost of erroneously labeling some children who would have a negative challenge. The results of future studies may adjust the cutoff points to separate more adequately children at a high probability of having a positive challenge result from those with a high probability of a negative food challenge.

We have derived a simple and accurate FCRI to identify patients at increased risk for positive food challenges. The FCRI uses readily available clinical data to predict food challenge results. In this study, the

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food challenge risk index was derived, retrospectively applied, and compared with the food challenge results for milk, egg, and peanuts. The FCRI should now be studied prospectively to predict food challenge results for milk, egg, and peanut in children. Ultimately this may yield a clinical tool that reduces the number of food challenges necessary for the diagnosis of milk, egg, and peanut allergy in children.

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