

Utility of food-specific IgE concentrations in predicting symptomatic food allergy

Hugh A. Sampson, MD *New York, NY*

Background: The double-blind, placebo-controlled food challenge is considered the gold standard for diagnosing food allergy. However, in a retrospective analysis of children and adolescents with atopic dermatitis and food allergy, discrete food-specific IgE concentrations were established that could predict clinical reactivity to egg, milk, peanut, and fish with greater than 95% certainty.

Objective: The purpose of this investigation was to determine the utility of these 95% predictive decision points in a prospective evaluation of food allergy.

Methods: Sera from 100 consecutive children and adolescents referred for evaluation of food allergy were analyzed for specific IgE antibodies to egg, milk, peanut, soy, wheat, and fish by using the Pharmacia CAP System FEIA. Food-specific IgE values were compared with history and the results of skin prick tests and food challenges to determine the efficacy of previously established 95% predictive decision points in identifying patients with increased probability of reacting during a specific food challenge.

Results: One hundred children (62% male; median age, 3.8 years; range, 0.4-14.3 years) were evaluated for food allergy. The diagnosis of food allergy was established by means of history or oral food challenge. On the basis of the previously established 95% predictive decision points for egg, milk, peanut, and fish allergy, greater than 95% of food allergies diagnosed in this prospective study were correctly identified by quantifying serum food-specific IgE concentrations.

Conclusion: In a prospective study of children and adolescents referred for evaluation of food allergy, previously established 95% predictive decision points of food-specific IgE antibody concentrations for 4 major food allergens were effective in predicting clinical reactivity. Quantification of food-specific IgE is a useful test for diagnosing symptomatic allergy to egg, milk, peanut, and fish in the pediatric population and could eliminate the need to perform double-blind, placebo-controlled food challenges in a significant number of children. (*J Allergy Clin Immunol* 2001;107:891-6.)

Key words: Food allergy (hypersensitivity); symptomatic food allergy; double-blind, placebo-controlled food challenge; Pharmacia CAP System FEIA; food-specific IgE concentration; IgE antibodies

Although definitive surveys are lacking, many pediatricians and allergists dealing with children believe that the prevalence of food allergy is increasing in the pediatric population. Certainly the public's awareness of this problem is growing, and physicians are increasingly being asked to evaluate patients for possible food allergy. Recent studies from several westernized countries indicate that food allergy affects a significant portion of the pediatric population. Cow's milk allergy affects about 2.5% of newborn infants in the first year of life,¹⁻⁴ with IgE-mediated reactions accounting for about 60% of milk allergy-related disorders (1.5% of infants). Although most infants with cow's milk allergy outgrow their sensitivity by the third year of life,¹ 15% of infants with IgE-mediated cow's milk allergy retain their sensitivity into the second decade, and 35% have allergic reactions to other foods.⁵ IgE-mediated allergic reactions to egg occur in about 1.3% of young children⁶ and to peanut in 0.5% of children in the United Kingdom⁷ and United States.⁸ In addition, children with atopic disorders tend to have a higher prevalence of food allergy. About 40% of children with moderate-to-severe atopic dermatitis have food allergies,⁹ and about 6% of asthmatic children attending a general pulmonary clinic will have food-induced wheezing.¹⁰

In 1976, May¹¹ introduced the use of double-blind, placebo-controlled oral food challenges (DBPCFCs) to diagnose food allergy, a protocol now considered the gold standard for the diagnosis of food allergy-related disorders. However, many physicians find the DBPCFC impractical in the busy practice setting and continue to rely on patient history, results of skin tests, results of RASTs, and elimination diets to make the diagnosis, a practice that may lead to misdiagnosis in as many as one half the cases.¹² A laboratory test that could accurately diagnose symptomatic food allergy would greatly facilitate clinical practice. In a recent retrospective study,¹³ we found that absolute values of food-specific IgE antibody concentrations appeared to accurately identify a subset of patients allergic to egg, milk, peanut, or fish. In that study approximately 90% of patients had atopic dermatitis. The purpose of this study was to determine, in a prospective fashion, whether these previously established values are

From The Mount Sinai School of Medicine, New York.

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Reprint requests: Hugh A. Sampson, MD, Department of Pediatrics; Box 1090, The Jaffe Institute of Food Allergy, The Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029-6574.

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Abbreviations used

DBPCFC: Double-blind, placebo-controlled food challenge
NPA: Negative predictive accuracy
PPA: Positive predictive accuracy

indeed useful in diagnosing symptomatic food allergy in a less-selected population.

METHODS**Study population**

One hundred consecutive children and adolescents referred to the Johns Hopkins Pediatric Allergy Clinic for evaluation of suspected IgE-mediated food hypersensitivity were enrolled in the study. Patients ranged in age from 3 months to 14 years (median, 3.8 years), and the majority were boys (male/female = 62:38). Sixty-one percent of patients had atopic dermatitis, approximately one half had asthma, and about 90% came from atopic families. Evaluation consisted of an extensive history, physical examination, and skin prick testing to suspected foods. If history and skin testing suggested food hypersensitivity, patients returned to the Pediatric Clinical Research Center for blinded food challenges to establish the diagnosis of food allergy. Sera was obtained at the time of the initial visit for quantification of food-specific IgE antibodies to the 6 major food allergens (ie, egg, milk, peanut, fish, soy, and wheat).

Laboratory studies

Serum samples from all patients were analyzed for food allergen-specific IgE antibodies by using the Pharmacia CAP System FEIA (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden), as previously described.¹³ Briefly, venous blood samples were obtained at the time of initial evaluation and analyzed with the automated Pharmacia CAP System. Fifty microliters of standards or patient sera were added to the solid matrix, ImmunoCAP, and incubated for 30 minutes. After appropriate washing, enzyme-labeled anti-IgE was added to the ImmunoCAP, incubated for 2.5 hours, and washed, and then 50 μ L of developing solution was added to each sample. After a 10-minute incubation, stopping solution was added, and fluorescence was determined and compared with values from the standard curve. Before initiating the study, intra-assay and interassay coefficients of variation for the CAP System FEIA were shown to be less than 10%. The diagnoses made on the basis of food-specific IgE levels were compared with the outcome of physician-supervised food challenges, convincing histories of food allergic reactions, or highly suggestive histories of food allergic reactions.

Patients were considered definitely allergic if their food-specific IgE concentration was equal to or exceeded the 95% predictive decision points established in our earlier retrospective study, possibly allergic if food-specific IgE was less than the 95% of predictive value but was greater than 0.35 kU_A/L, or nonallergic if food-specific IgE was less than 0.35 kU_A/L.¹³

Skin prick tests

Skin prick tests were performed as described previously.¹⁴ Briefly, glycerinated food extracts (1:10 or 1:20; kindly provided by Greer Laboratories, Lenoir, NC) were applied by means of the prick technique, along with appropriate negative (saline) and positive (histamine) controls. Food allergens eliciting a mean wheal diameter of 3 mm or larger than that produced by the negative control were considered positive.

Oral food challenges

In patients with positive skin prick test responses or food-specific

IgE levels of greater than 0.35 kU_A/L who were not suspected of having food allergy, single-blind challenges or open feedings were performed to assure lack of clinical reactivity. Suspected food hypersensitivity was confirmed by using DBPCFCs, as previously described.^{15,16} Over a 90-minute period, patients were given up to 10 g of dehydrated food camouflaged in juice, infant formula, or moist food (eg, rice cereal). Two challenges were performed each day separated by 3 to 4 hours; one contained the challenge food and one contained placebo. Research unit dietitians performed randomization and preparation of the challenges. All negative challenge results were confirmed by using open challenges. Open challenges consisted of feeding the test food in approximately twice the quantity of a normal portion for age. All reactions were scored as to type, time of onset, severity, and duration. DBPCFCs were not performed when a patient had a convincing history of a severe allergic reaction and evidence of IgE antibodies to a specific food. Convincing histories were defined as immediate allergic reactions to a food within the previous 2 years that developed after an isolated ingestion of the suspected food and required emergency management by a physician. For ethical reasons, as required by the Johns Hopkins University Institutional Review Board, all parents were informed of the previous study, which suggested that high levels of certain food-specific IgE antibodies correlated with clinical reactivity to a food,¹³ and the results of their child's food-specific IgE antibody concentrations. Consequently, many parents of children with suggestive histories of food allergy and high levels of food-specific IgE antibodies refused to have their children undergo DBPCFCs. A suggestive history consisted of an immediate allergic reaction that occurred after the ingestion of a food (not necessarily in isolation) on one or more occasions but did not require emergency management by a physician or a convincing reaction that occurred more than 2 years previously.

Statistics

All statistical tests were 2-sided, and comparisons were considered significant at a *P* value less than .05. Patients with food-specific IgE antibody levels exceeding the previously established levels for 95% probability of reacting to a specific food challenge (ie, decision points) for diagnosis were considered to have a positive test result. Performance characteristics of the 95% decision points were calculated for individual food antigens in the prospective study and compared with performance characteristics in the previous retrospective study.¹³

The study was approved by the Johns Hopkins' Joint Committee on Clinical Investigations (institutional review board).

RESULTS

One hundred children and adolescents with suspected food allergy were enrolled in the study. The diagnosis of food hypersensitivity was based on the outcome of DBPCFCs, a convincing history of clinical reactivity, or a suggestive history of reactivity with a food-specific IgE level that exceeded the previously established 95% decision points. As shown in Table I, the prevalence rates of allergic reactivity to individual foods in the prospective study compared with prevalence rates in the retrospective study were slightly higher for milk, peanut, soy, and wheat; about the same for egg; and slightly less for fish. The diagnosis of clinical reactivity was more often based on history in this study compared with the retrospective study because many parents refused a diagnostic challenge when they were informed that their child's food-

specific IgE concentration was greater than the previously established 95% decision point. As shown in Table II, in the present study only 33% of the diagnoses of egg or milk allergy, 2% of the diagnoses for peanut allergy, and none of the diagnoses of fish allergy were based on DBPCFC results. Because the previously established diagnostic predictability for soy- and wheat-specific IgE values were poor, most children underwent DBPCFCs to establish the diagnosis of wheat or soy allergy. Consequently, the diagnosis of soy or wheat allergy was established by means of DBPCFCs in 84% and 74% of patients, respectively. Symptoms elicited during the food challenges consisted of mild-to-moderate cutaneous, respiratory, and/or gastrointestinal symptoms. Skin symptoms were most frequent, developing during 22 of 25 egg challenges with positive results, 19 of 21 milk challenges with positive results, 14 of 21 soy challenges with positive results, and 16 of 17 wheat challenges with positive results. Respiratory symptoms occurred in 10 of 25 egg challenges with positive results, 5 of 21 milk challenges with positive results, 5 of 21 soy challenges with positive results, and 8 of 17 wheat challenges with positive results. Gastrointestinal symptoms developed in 14 of 21 egg challenges with positive results, 10 of 21 milk challenges with positive results, 13 of 21 soy challenges with positive results, and 9 of 17 wheat challenges with positive results. The majority of individuals studied were clinically allergic to 2 or more foods: 1 food, 18; 2 foods, 23; 3 foods, 27; 4 foods, 17; and 5 or more foods, 10. Only 5 of the children enrolled in the study had no evidence of symptomatic food hypersensitivity.

When using a test of allergic disease, the physician is most interested in knowing whether his or her patient will have symptoms when exposed to the allergen under investigation. In our previous retrospective study,¹³ food-specific IgE antibody levels representing a 95% probability of reacting to a challenge (ie, 95% predictive decision points) were established for 4 major food allergens, and lesser predictive points were established for soy and wheat. Table III depicts the performance characteristics of the previously established decision points in predicting clinical food hypersensitivity in children and adolescents prospectively evaluated for food allergy in this study. For example, the IgE antibody level indicating a 95% probability of a patient reacting to an egg challenge (95% predictive decision point) in the retrospective study was 6 kU_A/L. Using 6 kU_A/L as the diagnostic decision point in the prospective study appropriately predicted egg reactivity in 96% of patients (ie, positive predictive value of 96%). The positive predictive values for the 4 major food allergens (egg, milk, peanut, and fish) ranged from 96% to 100%. As expected, the sensitivities of the 95% diagnostic decision points were low in this prospective study, indicating that these decision points should only be used as a means of confirming a specific symptomatic food allergy and not as a means of excluding a food allergy. By using decision points of 100 kU_A/L for wheat and 65 kU_A/L for soy, the positive predictive accuracies in this prospective study were 100% and 86%, respectively.

TABLE I. Prevalence of food hypersensitivity in the previous retrospective study¹³ and the current prospective study

Food	Retrospective study	Prospective study	Comparison between studies*
Egg	74%	80%	<i>P</i> = .28
Milk	49%	66%	<i>P</i> = .005
Peanut	69%	81%	<i>P</i> = .05
Fish	27%	15%	<i>P</i> = .07
Soybean	17%	27%	<i>P</i> = .06
Wheat	12%	27%	<i>P</i> = .002

*Significance of differences in prevalence of specific food allergies between the retrospective and prospective studies (χ^2 test).

TABLE II. Diagnoses of food hypersensitivity on the basis of DBPCFCs, convincing histories, or suggestive histories

Food	Challenge (%)	Convincing history (%)	Suggestive history (%)
Egg (n = 75)	33	40	27
Milk (n = 62)	34	30	46
Peanut (n = 68)	2	85	13
Fish (n = 8)	12	88	0
Soybean (n = 25)	84	16	0
Wheat (n = 23)	74	20	10

Because sensitivity and specificity are inherent properties of a test and predictive values reflect the inherent properties of the test plus the prevalence of disease in the population under investigation, an alternative approach to minimize the effect of disease prevalence uses the 95% or 90% specificity values to establish diagnostic decision points. Table IV depicts the performance characteristics of the 90% specificity decision points established in our previous retrospective study¹³ to diagnose food allergy in the prospective study. As seen in Table IV, the positive predictive values for egg, milk, and peanut on the basis of the 90% specificity values are excellent (ie, 98%-100%) but are less predictive for fish, wheat, and soy (ie, 56%, 73%, and 74%, respectively).

DISCUSSION

A number of studies have confirmed the poor positive predictive value of patient history and skin prick test and RAST results in the diagnosis of symptomatic IgE-mediated food hypersensitivity.^{2,12,15,17,18} However, a number of studies have confirmed that negative skin prick test responses have excellent negative predictive values for excluding the presence of IgE-mediated food allergy.^{11,14,17} Consequently, the DBPCFC has become the gold standard for the diagnosis of food allergy, with positive and negative predictive accuracies exceeding 95%.^{12,15,19} However, the DBPCFC requires several hours of physician and patient (and patient's family) time, is relatively expensive to administer, subjects the patient to the discomfort of allergic symptoms when challenge results

TABLE III. Performance characteristics of the 95% predictive decision points established in the retrospective study¹³ in diagnosing 100 consecutive children and adolescents with food allergy referred for evaluation of food hypersensitivity

Allergen	Decision point (kU _A /L)	Sensitivity	Specificity	Efficiency	PPV	NPV
Egg	6	64	90	69	96	39
Milk	32	34	100	56	100	44
Peanut	15	57	100	66	100	36
Fish	20	25	100	89	100	89
Soybean	65	24	99	79	86	78
Wheat	100	13	100	77	100	76

PPV, Positive predictive value; NPV, negative predictive value.

TABLE IV. Performance characteristics of 90% specificity diagnostic decision points generated in the retrospective study¹³ in diagnosing food allergy in 100 consecutive children and adolescents referred for evaluation of food hypersensitivity

Allergen	Decision point (kU _A /L)	Sensitivity	Specificity	Efficiency	PPV	NPV
Egg	7	61	95	68	98	38
Milk	15	57	94	69	95	53
Peanut	14	57	100	84	100	36
Fish	3	63	91	87	56	93
Soybean	30	44	94	81	73	82
Wheat	26	61	92	84	74	87

PPV, Positive predictive value; NPV, negative predictive value.

are positive, and places the patient at risk for a severe anaphylactic reaction. Nevertheless, the consequences of misdiagnosis are well described²⁰ and generally outweigh the expense and risk of performing DBPCFCs. Despite the excellent predictability of the DBPCFC, laboratory tests that could provide similar predictive values at less risk and expense would be extremely useful.

Earlier studies suggested that high concentrations of food allergen-specific IgE antibodies to milk and egg were predictive of clinical reactivity.^{21,22} By using the Pharmacia CAP System FEIA to quantify food-specific IgE antibody concentrations in patients previously diagnosed with food allergy, we were able to establish diagnostic decision points that were at least 95% predictive of clinical reactivity to egg, milk, peanut, and fish.¹³ In the current study we intended to validate the previously established diagnostic decision points by determining their ability to correctly predict the outcome of DBPCFCs in children undergoing prospective evaluation for food hypersensitivity. However, for ethical reasons, it was necessary to inform the children's parents of their food-specific IgE levels before challenge. Consequently, many parents elected not to have their children challenged when their child had a suggestive history of food allergy and a level of food allergen-specific IgE that greatly exceeded the 95% predictive decision points. A few children who lacked a suggestive history of a food-allergic reaction, despite having a food-specific IgE value exceeding the 95% predictive value, were challenged, and all but one reacted. Although it is likely that the vast majority of children not challenged in the prospective study were allergic to the food in question on the basis of their suggestive or convincing histories, the paucity of DBPCFCs clearly impaired our ability to val-

idate the 95% diagnostic decision points for egg, milk, peanut, and fish generated in the previous study. Because the previous predictive decision points for soy and wheat were not definitive, all children without convincing histories of food-allergic reactions were challenged. Although the predictive values for these foods appear to have performed better than anticipated in this prospective study, this may in part reflect the greater prevalence of soy and wheat allergy in the prospective study compared with that found in the previous retrospective study.

The sensitivity, specificity, and efficiency of a test provide information about the ability of the test to identify a specific condition or trait within a population.²³ In practice, clinicians are less interested in knowing how well the test can identify certain traits (eg, food allergy) in a population than in how well the test predicts whether their patients have a certain condition (ie, the positive predictive accuracy [PPA] and negative predictive accuracy [NPA]). Sensitivity and specificity reflect inherent properties of the test and are largely unaffected by the population being evaluated. As denoted in the formulas below, the composition of the population investigated affects the PPA and NPA values:

$$PPA = \frac{sP}{SP + (1-f)(1-P)} \quad \text{and} \quad NPA = \frac{f(1-P)}{f(1-P) + (1-s)P}$$

where *s* is defined as sensitivity, *f* is defined as specificity, and *P* is defined as prevalence of the condition in the population being studied. Consequently, universal predictive accuracies are difficult to establish because they vary with the prevalence of disease in the population under investigation. Because the prevalence of food allergies in the subjects enrolled in this prospective study was similar to that in children enrolled in our retrospective study, the 95%

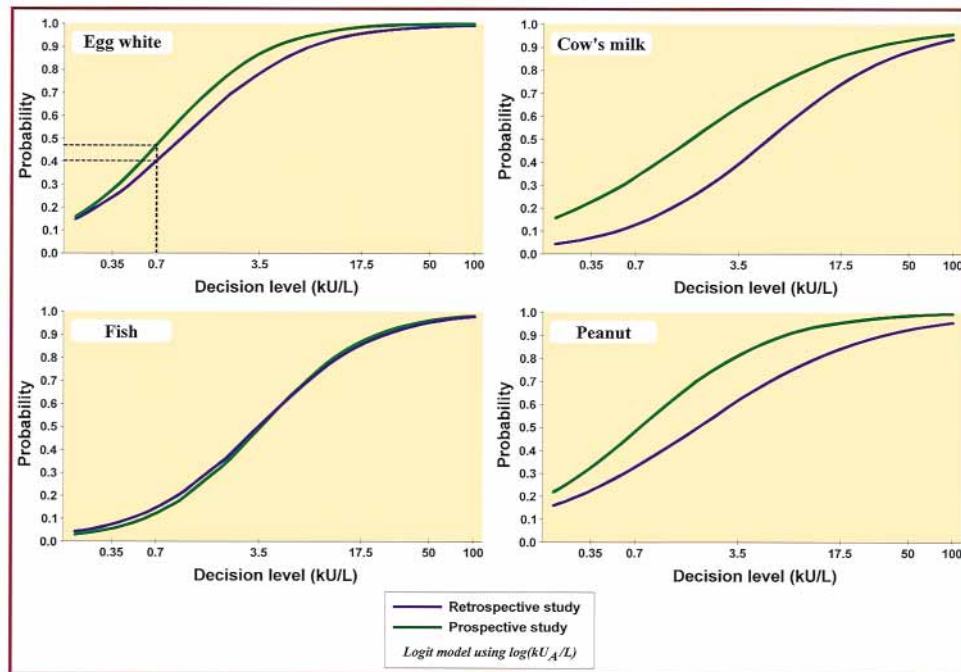


FIG 1. Probability of reacting to a food at a given IgE value.

TABLE V. Recommended interpretation of food allergen-specific IgE levels (kU_A/L) in the diagnosis of food allergy

	Egg	Milk	Peanut	Fish	Soy	Wheat	
Reactive if $\geq$ (no challenge necessary)	7	15	14	20	65	80	Probability of reaction
Possibly reactive (physician challenge*)					30 [†]	26 [†]	
Unlikely reactive if $<$ (home challenge*)	0.35	0.35	0.35	0.35	0.35	0.35	

*In patients with a strongly suggestive history of an IgE-mediated food allergic reaction, food challenges should be performed with physician supervision, regardless of food-specific IgE value. If the food-specific IgE level is less than 0.35 kU_A/L and the skin prick test response is negative, the food challenge can be performed at home unless there is a compelling history of reactivity.

predictive decision points previously established proved highly efficient in diagnosing symptomatic food hypersensitivity. Because these 95% predictive decision points were generated from a population of children with atopic dermatitis, a patient group that typically has the most elevated IgE levels, patients without atopic dermatitis (who typically have much lower IgE antibody levels than patients with atopic dermatitis) would be quite likely to experience a positive food challenge result if their food-specific IgE levels exceeded these 95% decision points. The generally lower levels of IgE antibodies in patients without atopic dermatitis at least partially compensates for the lower prevalence of food allergy in the patients without atopic dermatitis compared with the population with atopic dermatitis. However, it must be appreciated that predictive values are significantly affected by disease prevalence within the population under investigation.

An alternative approach that minimizes the influence of disease prevalence when establishing decision points among different populations is to establish the diagnostic decision points from specificity values (eg, 95% or 90%). With such an approach, one accepts that 5% or 10% of nondiseased individuals may be erroneously labeled as

clinically reactive (ie, allergic). Applying diagnostic decision points on the basis of 90% specificity values in our retrospective study (Table IV), the positive predictive values for the 3 major food allergens (ie, egg, milk, and peanut) were 95% or greater in the prospective study. As noted with the 95% predictive diagnostic decision points generated in the retrospective study, the 90% specificity diagnostic decision points have poor sensitivity, and therefore physicians cannot assume that a patient with a food-specific IgE value less than the diagnostic decision point will not have a clinical reaction to that food. Only a physician-supervised food challenge can clearly establish clinical reactivity.

Because the Pharmacia CAP System FEIA uses standardized allergens and is calibrated against the World Health Organization IgE standard, the predictive values that are reported in this study should be useful for the diagnosis of food allergy throughout the world. Table V presents the diagnostic decision points (ie, the food-specific IgE antibody levels recommended for identifying patients with $>95\%$ probability of reacting to a food challenge). For example, a physician would not need to perform an oral milk challenge on a child without atopic dermatitis if the milk-specific IgE level was 15 kU_A/L or

greater because it is greater than 95% likely that the child would experience a positive reaction. If the milk-specific IgE level was less than 15 kU_A/L but 0.35 kU_A/L or greater, the physician would need to perform some form of milk challenge to determine whether the child is truly reactive to milk. If the milk-specific IgE level was less than 0.35 kU_A/L and there was no compelling history of milk allergy, milk could be introduced at home. However, if there is any suspicion of milk allergy, it would be necessary to confirm that the child had a negative skin prick test response to milk as well before suggesting that milk be added without some physician supervision. In addition, reintroduction (or challenge) of a food should be done under physician supervision any time there is a strongly suggestive history of a food allergy, regardless of the outcome of the food-specific IgE or skin prick test.

By using data from the retrospective and prospective studies, it is possible to generate probability curves that depict the likelihood of patients with a particular food-specific IgE level reacting during a food challenge (Fig 1). Assuming that an individual patient is positive with a certain probability of π or negative with a certain probability of $1 - \pi$, it is possible to estimate the P value as a function of the specific IgE antibody levels by using a simple logistic model:

$$P = \frac{1}{e^{-\alpha - \beta x} + 1}$$

where x is defined as $\ln(\text{kU}_A/\text{L})$. Fig 1 depicts the probabilities of individuals reacting to egg, milk, peanut, or fish at given food-specific serum IgE levels. These curves indicate that even low levels of food-specific IgE antibodies are associated with a certain risk of clinical reactivity. For example, a patient with an egg-specific IgE level of 0.7 kU_A/L has a 40% to 45% chance of experiencing an allergic reaction if egg is ingested. Comparing a patient's food-specific IgE value against the appropriate probability curve could provide the physician with a better idea of the likelihood of his or her patient reacting to a particular food. However, more patients need to be studied in each group to confirm the predictability of these probability curves. Until more patients are studied, physicians should consider challenging any patient in cases in which the predictability is less than 90%, unless there is a strong history to support clinical reactivity.

Because egg, milk, and peanut account for about 85% of the documented food allergy in children and adolescents, use of food allergen-specific IgE values have enabled us to reduce the number of DBPCFCs we need to perform by 40% to 50%. As discussed in the previous study,¹³ we are continuing to explore the utility of monitoring food-specific IgE concentrations for predicting the likelihood of outgrowing a food allergy. On the basis of preliminary observations, we are routinely rechallenging children when their food-specific IgE level decreases to about one fourth the diagnostic decision point (eg, egg, 1.5 kU_A/L; milk, 8 kU_A/L; except peanut and fish), unless they have experienced a recent allergic reaction. Studies are ongoing to determine whether these values prove useful in a larger cohort of patients. Studies also

are underway to establish diagnostic decision points for other foods and to develop recombinant protein-based assays to improve the specificity of the assay for soy and wheat. The final proof of using food allergen-specific IgE levels for the diagnosis of symptomatic food allergy awaits confirmation by other investigators.

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