

Clinical aspects of allergic disease

Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents

Hugh A. Sampson, MD, and Deborah G. Ho, BS *Baltimore, Md.*

Background: The double-blind, placebo-controlled food challenge (DBPCFC) is the "gold standard" for diagnosis of food hypersensitivity. Skin prick tests and RASTs are sensitive indicators of food-specific IgE antibodies but poor predictors of clinical reactivity. Previous studies suggested that high concentrations of food-specific IgE antibody were predictive of food-induced clinical symptoms. Because the CAP System FEIA (Pharmacia Diagnostics, Uppsala, Sweden) provides a quantitative assessment of allergen-specific IgE antibody, this study was undertaken to determine the potential utility of the CAP System FEIA in diagnosis of IgE-mediated food hypersensitivity.

Methods: Sera from 196 patients with food allergy were analyzed for specific IgE antibodies to egg, milk, peanut, soy, wheat, and fish by CAP System FEIA. Sera were randomly selected from 300 stored samples of children and adolescents who had been evaluated by history, skin prick tests, and DBPCFCs. The study population was highly atopic; all patients had atopic dermatitis, and approximately 50% had asthma and allergic rhinitis at the time of initial evaluation. The performance characteristics of the CAP System FEIA were compared with those of skin prick tests and the outcome of DBPCFCs or "convincing" histories of anaphylactic reactions.

Results: The prevalence of specific food allergies in the study population varied from 22% for wheat to 73% for egg. Allergy to egg, milk, peanut, and soy accounted for 87% of confirmed reactions. The performance characteristics of skin prick tests and CAP System FEIA (egg, milk, peanut, fish) were comparable, with excellent sensitivity and negative predictive accuracy but poor specificity and positive predictive accuracy. The performance characteristics of the CAP System FEIA for soy and wheat were poor. For egg, milk, peanut, and fish allergy, diagnostic levels of IgE, which could predict clinical reactivity in this population with greater than 95% certainty, were identified: egg, 6 kilounits of allergen-specific IgE per liter (kU_A/L); milk, 32 kU_A/L; peanut, 15 kU_A/L; and fish, 20 kU_A/L.

Conclusions: When compared with the outcome of DBPCFCs, results of CAP System FEIA are generally comparable to those of skin prick tests in predicting symptomatic food hypersensitivity. Furthermore, by measuring the concentrations of food-specific IgE antibodies with the CAP System FEIA, it is possible to identify a subset of patients who are highly likely (>95%) to experience clinical reactions to egg, milk,

peanut, or fish. This could eliminate the need to perform DBPCFCs in a significant number of patients suspected of having IgE-mediated food allergy. (*J Allergy Clin Immunol* 1997;100:444-51.)

Key words: Food hypersensitivity, skin prick test, RAST, CAP System FEIA, double-blind, placebo-controlled food challenge, predictive values

Adverse reactions to foods are common among young children, affecting 6% to 8% of infants in the first 3 years of life.¹ The majority of children "outgrow" their food allergy, but two large surveys suggest that about 1.5% to 2% of adults are reactive to food.^{2,3} Using double-blind, placebo-controlled food challenges (DBPCFCs) to confirm patients' reports, Young et al.² conducted a survey in the United Kingdom and found adverse food reactions in 1.4% to 1.8% of adults. A comparable study in the Netherlands concluded that about 2% of the adult Dutch population is affected by adverse food reactions.³ Individuals with atopic disorders are more likely to have food allergy as compared with the general population. The highest prevalence of food allergy may be found in children with moderate to severe atopic dermatitis; up to one third of children with atopic eczema have skin symptoms provoked by food hypersensitivity.⁴ In children with asthma followed up in respiratory clinics, 6% to 16% have been found to experience food-induced wheezing.^{5,6}

IgE-mediated reactions are the most well-characterized food hypersensitivity disorders and account for a variety of allergic symptoms. Skin prick tests and/or various in vitro tests (e.g., RAST) are used to determine whether a patient has IgE antibodies to specific foods. However, previous studies have shown that only 30% to 40% of patients with food-specific IgE antibodies experience clinical symptoms when the food is ingested.^{7,8} In previous studies of children with atopic dermatitis and cow's milk, egg, or peanut allergy, we noted that high concentrations of allergen-specific IgE antibody were predictive of food-induced clinical symptoms.^{9,10} The development of the CAP System FEIA (Pharmacia Diagnostics, Uppsala, Sweden), which provides a more quantitative evaluation of allergen-specific IgE, presented an opportunity to determine the potential utility of quantitative food-specific IgE values in the diagnosis of IgE-mediated food hypersensitivity.

The CAP System FEIA reportedly binds at least three

From Johns Hopkins University School of Medicine, Baltimore.
Received for publication Jan. 29, 1997; accepted for publication May 7, 1997.

Reprint requests: Hugh A. Sampson, MD, Johns Hopkins Hospital, CMSC 1102, 600 N. Wolfe St., Baltimore, MD 21287-3923.

Copyright © 1997 by Mosby-Year Book, Inc.

0091-6749/97 \$5.00 + 0 1/1/83344

Abbreviations used

DBPCFC: Double-blind, placebo-controlled food challenge
kU_A: Kilounits of allergen-specific IgE per liter
ROC: Receiver operating characteristic

times the amount of allergen in the solid phase as compared with the standard paper disk RAST. This CNBr-activated cellulose matrix was reported to provide a slight increase in sensitivity and a broader dynamic range (<0.35 kU/L to 100 kU/L IgE) compared with the standard RAST (Fig. 1).¹¹ The assay is calibrated against the World Health Organization standard for IgE, allowing for a quantitative assessment of allergen-specific IgE antibodies in kilounits of allergen-specific IgE per liter (kU_A/L). Given the quantitative capability of the CAP System FEIA, we sought to determine the efficacy of this test in the diagnosis of IgE-mediated food allergy in a group of children and adolescents referred for evaluation of atopic dermatitis. Results of the CAP System FEIA were compared with results of skin prick tests and the outcome of oral food challenges.

METHODS

Study population

Over a 10-year period, 300 children and adolescents were evaluated for food hypersensitivity by DBPCFCs. All subjects were highly atopic. All had atopic dermatitis; and approximately 50% had asthma and allergic rhinitis at the time of initial evaluation, 80% had elevated serum IgE concentrations, and 90% had a family history of atopic disease. After screening patients with history, physical examination, and skin prick tests and/or RASTs with food allergens, patients underwent DBPCFCs to establish the diagnosis of food hypersensitivity, as previously described.^{12, 13} Unless contraindicated by a history of a previous severe allergic reaction, patients were challenged with egg, milk, peanut, wheat, soy, fish, and other foods suspected of provoking skin symptoms. DBPCFCs were performed if history or skin testing suggested a possible sensitivity; otherwise, patients were challenged openly under observation in the Pediatric Clinical Research Center (RR-00052). From this group of 300 well-characterized patients, previously frozen sera from 196 patients were randomly selected for analysis by CAP System FEIA. Patients' history numbers were entered into a computer database, and then 100 subjects were randomly selected for entry into the study. To ensure adequate numbers of patients with wheat and soy allergy, 10 patients with wheat allergy and 10 patients with soy allergy were selected for inclusion, and then 80 more patients were randomly selected from the database. Four patients were removed from the study because they were older than 18 years of age. Sera were selected from patients ranging in age from 0.6 to 17.9 years (mean, 5.2 years); 117 were boys, and 79 were girls. A total of 434 allergic reactions had been attributed to the six foods studied in this cohort of patients. Egg (*n* = 123), milk (*n* = 106), and peanut (*n* = 89) were believed to be responsible for 73% of the allergic reactions to food in this group and accounted for 85% of the severe reactions described.

Slope of standard curves

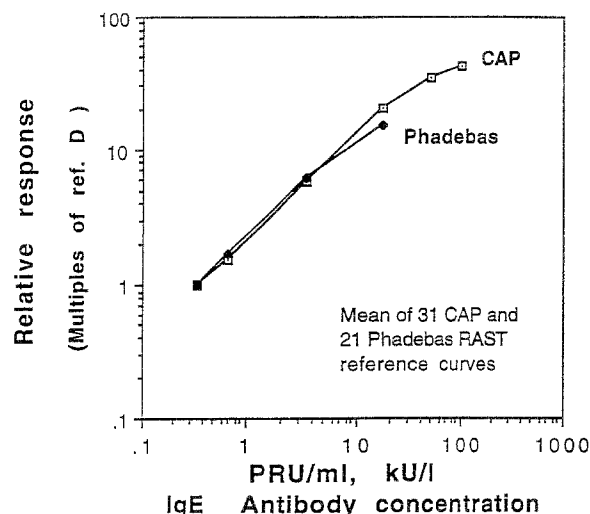


FIG. 1. Comparison of standard curves for CAP System FEIA and Phadebas RAST.¹¹ PRU, Phadebas RAST units.

Laboratory studies

CAP System FEIA. Serum samples from all patients were analyzed for total and antigen-specific IgE antibodies by using the Pharmacia System CAP System FEIA as detailed by the manufacturer. Briefly, venous blood samples were obtained at the time of initial evaluation, and sera were stored frozen at -20°C until analyzed. With the automated Pharmacia CAP System, 50 μL of standards and patient samples were added to the solid matrix (ImmunoCAP) and incubated for 30 minutes. After appropriate washing, 50 μL of enzyme-labeled anti-IgE was added to the ImmunoCAP and incubated for 150 minutes. After a washing step, 50 μL of developing solution was added and incubated for 10 minutes; stop solution was added, and fluorescence was determined and compared with the standard curve. In a preliminary study both intraassay and interassay coefficients of variation for the method were found to be less than 10%. Sera from all patients were analyzed for the following food allergens: egg, milk, peanut, soy, wheat, and fish; and 147 of 196 sera were analyzed for the following inhalant allergens: *Dermatophagoides pteronyssinus*, *D. farinae*, cat dander, and dog dander. The results of the CAP System FEIA studies for foods were compared with the results of the DBPCFCs or physician-confirmed histories of reactions after the isolated ingestion of the food in question, and for inhalant allergens, with the clinical diagnosis on the basis of patient history and results of skin prick tests.

Skin prick tests. Skin prick tests were performed as previously described.^{7, 14} Briefly, glycerinated food extracts (1:10 or 1:20; Greer Laboratories; Lenoir, N.C.), and appropriate positive (histamine) and negative (saline) controls were applied by the prick technique. Food allergens eliciting a mean wheal diameter of 3 mm or greater than the negative control were considered positive.

DBPCFCs. DBPCFCs were performed as previously described.^{12, 15} Up to 10 gm of dehydrated food was camouflaged in juice, infant formula, or moist food (e.g., cream of rice cereal) and administered over 90 minutes. Two challenges

TABLE I. Symptoms provoked by DBPCFC

Antigen	Cutaneous		Gastrointestinal		Respiratory		Total positive	
	No.	%	No.	%	No.	%	No./Total	%
Egg	80	87	74	80	39	42	92/126	73
Milk	50	93	35	65	26	48	54/109	50
Peanut	19	95	13	65	7	35	20/41	49
Soy	21	68	24	77	7	23	31/111	28
Wheat	15	79	9	47	6	32	19/87	22
Fish	10	91	7	64	1	9	11/20	55

separated by about 4 hours were performed each day; one challenge food contained placebo, and one contained the suspected food antigen. Randomization and preparation of the challenges were performed by dietitians in the clinical research unit. All negative challenge results were confirmed by open challenge. Open challenges consisted of feeding the test food in approximately twice the quantity normally consumed at a meal on the basis of the age of the child. All reactions were scored as to type, time of onset, severity, and duration. DBPCFCs were not performed when a patient with evidence of food-specific IgE antibody had a "convincing" history of a severe allergic reaction to food. A convincing history was defined as an immediate allergic reaction to food, which developed after the isolated ingestion of the suspected food and required emergency management by a physician within the previous 2 years.

Statistics

All statistical tests were two-sided, and a level of significance less than 5% ($\alpha = 0.05$) was considered significant. For each food, the median of specific IgE (kU_A/L) with 95% confidence interval was calculated. The Wilcoxon rank-sum test was used to compare median levels of specific IgE to different foods between nonreactors and reactors. Performance characteristics of the CAP System FEIA were calculated for individual food antigens as previously detailed¹⁶ (i.e., efficiency, sensitivity, specificity, positive and negative predictive accuracies, and 95% and 90% predictive values). Performance characteristics were calculated for a "cutoff value" of 0.35 kU_A/L , the limit of detectable antigen-specific IgE measured by the assay, and the "optimal decision point" on a receiver operating characteristic (ROC) curve, a calculated value that maximizes "true positives" (sensitivity) and minimizes "false positives" ($1 - \text{specificity}$). Because the prevalence of a disorder has a direct impact on its predictive value and because the prevalence of allergic reactions to food in this study population is considerably higher than would be expected in children and adolescents typically evaluated for food allergy, predictive values are also presented as "corrected values" for a food allergy prevalence of 10%.

RESULTS

Overall, 494 DBPCFCs were performed in the 196 children and adolescents selected for this study. Table I lists the symptoms provoked during DBPCFCs. Cutaneous symptoms included a pruritic, erythematous morbiliform rash or urticaria; gastrointestinal symptoms included nausea, abdominal pain, vomiting, and diarrhea; and respiratory symptoms involved the upper airway (nasal pruritus, congestion, rhinorrhea, and/or sneezing) and the lower airway (dyspnea, cough, and/or wheezing).

Symptoms developed within minutes to 2 hours of the food challenge. Egg, milk, peanut, and soy were responsible for 87% of the positive DBPCFC results and 88% of the severe reactions (i.e., cutaneous and/or gastrointestinal symptoms with significant laryngeal or lower respiratory component). The majority of the individuals reacted to three or fewer foods (1 food, 21%; 2 foods, 30%; 3 foods, 27%), which included some foods other than the six tested by CAP System FEIA. Cutaneous symptoms were seen most frequently, which was not unexpected in this group of patients referred for evaluation of atopic dermatitis. Challenges were not performed when there was a clear history of a severe immediate reaction after the isolated ingestion of a food and a positive skin prick test result. Most positive responses to egg (87%), milk (84%), soy (93%), and wheat (90%) were based on positive food challenge results; whereas a substantial number of positive responses to peanut and fish were based on convincing histories (43% and 33%, respectively). However, because loss of reactivity to these foods is very rare and because diagnoses of allergic reactions were based on isolated ingestions of the food, were relatively severe in nature, generally occurred on more than one occasion, and were confirmed by a physician, it is highly probable that these reactions represent "true-positive" reactions.

The patient cohort studied also had a high rate of sensitivity to indoor inhalant allergens. Of the 147 patients evaluated for inhalant allergen sensitivity, about 75% were believed to be allergic to dust mites, 65% to cats, and 62% to dogs on the basis of history and skin prick test results. Significant IgE antibodies were found to *D. pteronyssinus* in 79% of patients, to *D. farinae* in 74%, to cat in 78%, and to dog in 93%.

Table II lists the efficiency, sensitivity, and specificity of skin prick tests with food antigens when compared with DBPCFCs in the study population. As previously published,¹⁶ the sensitivities (except for soy) and negative predictive accuracies of skin prick tests are excellent for the six foods studied, whereas the specificities and positive predictive accuracies are very poor. When corrected for a "hypothetical, normalized" population (see Discussion) with a 10% prevalence of specific food allergies, all antigens had a positive predictive accuracy of less than 20%, whereas the negative predictive accuracies were 95% or greater.

TABLE II. Performance characteristics of skin prick test with cutoff level at 3 mm compared with DBPCFC

	Egg	Milk	Peanut	Soy	Wheat	Fish
No. of patients positive/negative	90/34	53/53	20/21	29/78	19/65	11/7
Efficiency (%)	86	74	59	55	60	78
Sensitivity (%)	98	96	90	76	90	90
Specificity (%)	53	51	29	47	51	57
Predictive value based on study population						
Positive	85	66	55	35	35	77
Negative	90	93	75	84	94	80
Predictive value based on "hypothetical, normalized" population (prevalence = 10%)						
Positive	19	18	12	14	17	19
Negative	99	99	96	95	98	98

TABLE III. Performance characteristics of CAP System FEIA at the cutoff level of 0.35 kU/L

	Egg	Milk	Peanut	Soy	Wheat	Fish
No. of patients positive/negative	145/51	95/101	136/60	34/162	23/173	52/144
Efficiency (%)	84	64	79	37	29	72
Sensitivity (%)	98	100	97	94	96	94
Specificity (%)	45	30	38	25	20	65
Predictive value based on study population						
Positive	84	57	78	21	14	49
Negative	88	100	85	95	97	97
Predictive value based on "hypothetical, normalized" population (prevalence = 10%)						
Positive	17	2	15	12	15	30
Negative	99	100	99	97	98	99

When the median concentrations of food-specific serum IgE concentrations were compared, patients with positive DBPCFC results had significantly higher levels of specific antibody than patients with negative challenge results: egg, 9.8 kU_A/L versus 1.0 kU_A/L ($p < 0.0001$); milk, 33.6 kU_A/L versus 1.7 kU_A/L ($p < 0.0001$); peanut, 47.2 kU_A/L versus 2.0 kU_A/L ($p < 0.0002$); and fish, 9.9 kU_A/L versus 1.6 kU_A/L ($p < 0.02$). Among the six foods studied, the 75th percentile levels of food-specific IgE antibodies were highest for peanut (82 kU_A/L), milk (29 kU_A/L), and egg (23 kU_A/L). The highest 75th percentile levels of serum IgE to inhaled allergens were to *D. farinae* (95 kU_A/L), *D. pteronyssinus* (89 kU_A/L), and dog (59 kU_A/L). The median serum IgE concentration for the study group was 3000 IU/ml, ranging from less than 100 IU/ml to greater than 40,000 IU/ml, although the total serum IgE concentration did not appear to correlate with the likelihood of reacting to the various foods.

The performance characteristics of the CAP System FEIA were established on the basis of the positive DBPCFC results and convincing histories of allergic

reactions. Table III lists the performance characteristics of the test for each food when the cutoff value for a positive result is set at 0.35 kU_A/L of antigen-specific IgE antibodies. Predictive accuracies are given for both the study cohort and a hypothetical, normalized patient population in which the prevalence of specific food allergies is 10%. As can be seen, sensitivities were excellent, ranging from 94% to 100%; and "corrected" negative predictive accuracies were 97% or greater for each food, comparable to the values found with skin prick tests. However, both the specificities (range, 25% to 65%) and corrected positive predictive accuracies were very poor (range, 2% to 30%), perhaps slightly inferior to the values found for skin prick tests shown in Table II.

An alternative way to establish a cutoff value for a test is to determine the "optimal decision point" from an ROC curve. When this procedure is used, equal weight is given to sensitivity and specificity of the test. Table IV lists the optimal decision points (cutoffs) for the six food antigens studied and the performance characteristics of the test when these values are used. Excluding wheat and

TABLE IV. Performance characteristics of CAP System FEIA at the optimal decision point selected from an ROC curve

	Egg	Milk	Peanut	Soy	Wheat	Fish
No. of patients positive/negative	145/51	95/101	136/60	34/162	24/172	52/144
ODP (kU _A /L)	3.4	5.8	10.7	5.0	8.1	1.8
Efficiency (%)	83	81	80	64	73	87
Sensitivity (%)	82	80	76	68	70	85
Specificity (%)	84	81	88	63	73	88
Predictive value based on study population						
Positive	94	80	94	28	25	71
Negative	62	81	62	90	95	94
Predictive value based on "hypothetical, normalized" population (prevalence = 10%)						
Positive	36	32	41	17	22	39
Negative	98	97	99	94	96	98

ODP, Optimal decision point.

soy, the efficiency of these ROC curve-derived cutoffs are quite good, exceeding 80%, with specificities superior to skin prick test results but sensitivities falling significantly below those of skin prick test results shown in Table II.

From the physician's point of view, cutoffs that provide high positive and negative predictive values would be most useful in the clinical setting, because this would indicate which patients are likely to have symptoms in response to a certain food and which are probably nonreactive. Table V shows cutoff values that provide greater than 95% and 90% predictive values, based on foods studied in this population, and their respective sensitivities and specificities. For example, if a patient has an IgE antibody level to egg of 6 kU_A/L or greater, it is greater than 95% likely that the patient will experience an allergic reaction if he or she ingests egg protein. However, only when a patient suspected of having egg allergy has 0.6 kU_A/L or less IgE egg antibodies, it is greater than 90% likely that the patient will not react if egg is ingested. As expected, the sensitivities of the tests when using the 95% predictive diagnostic values are poor, and so it cannot be assumed that a patient will not experience an allergic reaction unless the value falls below the 95% negative predictive value. On the basis of data from the population studied, it can be assumed that patients will experience allergic reactions to food if they have serum IgE levels exceeding the following 95% predictive diagnostic values: egg ≥ 6 kU_A/L, milk ≥ 32 kU_A/L, peanut ≥ 15 kU_A/L, and fish ≥ 20 kU_A/L. The soy and wheat CAP System FEIAs were too nonspecific and never reached a 90% predictive value (soy, 50% at 65 kU_A/L and wheat, 75% at 100 kU_A/L). The negative predictive accuracies for egg and peanut never reached 95% in the cohort studied; the best negative predictive accuracy for egg was 90% (at 0.6 kU_A/L) and for peanut

at 85% (0.35 kU_A/L). The 95% negative predictive values for milk and fish were 0.8 kU_A/L and 0.9 kU_A/L, respectively.

On the basis of our previously published scoring system,^{12, 15} allergic reactions to food were categorized as mild, moderate, or severe. Table VI provides the median antigen-specific IgE value for each response group. As can be seen, there is no correlation between the level of food allergen-specific IgE and the severity of the allergic reaction.

DISCUSSION

Since first reported by May¹⁷ in the mid 1970s, the DBPCFC has provided the "gold standard" for diagnosis of food hypersensitivity. Patient history, skin prick tests, and/or in vitro tests such as the RAST may suggest IgE-mediated food hypersensitivity. In general, however, less than one half of positive histories can be validated by DBPCFC,¹ and overall positive predictive accuracies for food skin test results are less than 50%. On the other hand, negative skin test results are extremely useful for confirming the absence of IgE-mediated reactions, with negative predictive accuracies exceeding 95% if good quality food extracts are used.^{7, 8, 14, 18, 19} Consequently, the skin prick test may be considered an excellent means of ruling out IgE-mediated food allergies but only suggestive of the presence of clinical food allergies. Intradermal skin tests are more sensitive than skin prick tests but are much less specific and have an even lower positive predictive accuracy than skin prick tests for detecting symptomatic food allergy when compared with the outcome of DBPCFCs.¹⁸ Although it provides a highly reliable indicator of clinical food hypersensitivity, the DBPCFC is time-consuming for both the patient and physician and is not without risk. Consequently, attempts have been made to develop laboratory tests that

TABLE V. Levels of specific IgE antibodies yielding positive predictive values of 95% and 90%

Food	PPV		NPV	
	>95%	>90%	>95%	>90%
Egg				
Diagnostic value	6*	2	—	0.6
Sensitivity	72%	89%	—	98%
Specificity	90%	73%	—	57%
Milk				
Diagnostic value	32	23	0.8	1.0
Sensitivity	51%	58%	98%	95%
Specificity	98%	94%	41%	48%
Peanut			Best NPV = 85% at 0.35 IU/ml	
Diagnostic value	15	9		
Sensitivity	73%	77%		
Specificity	92%	82%	—	—
Fish				
Diagnostic value	20	9.5	0.9	5
Sensitivity	40%	56%	89%	71%
Specificity	99%	98%	82%	96%
Soy				
Diagnostic value	Best PPV = 50% at 65 IU/ml		2	5
Sensitivity			88%	68%
Specificity			50%	63%
Wheat				
Diagnostic value	Best PPV = 75% at 100 IU/ml		5	79
Sensitivity			78%	17%
Specificity			62%	99%

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

*kU_A/L of IgE/ml.

are highly predictive of clinical hypersensitivity. For IgE-mediated food hypersensitivity, the RAST and similar in vitro assays (including ELISA) have been studied for their utility in predicting IgE-mediated food allergies. In an earlier study comparing skin prick tests and Phadebas RAST with DBPCFCs, skin prick test and RAST results were found to have similar sensitivities and specificities when a Phadebas score of 3 or greater was considered positive.⁷ A similar study in which Phadebas scores of 2⁺ or greater were used demonstrated slightly improved sensitivity but a drastic reduction in the specificity and positive predictive accuracy of the test.²⁰ Other more recent studies comparing the outcome of food challenges with RAST results (or similar tests to identify food-specific IgE antibodies) have reached similar conclusions.²¹⁻²³

The sensitivity, specificity, and efficiency of a diagnostic test provide information about its ability to identify a known condition and thus provide some insight into the utility of the test in clinical practice. However, in practice the physician is more interested in knowing how likely it is that the patient has the disorder if the diagnostic test result is positive (positive predictive accuracy) or how likely it is that the patient does not have the disorder if the test result is negative (negative predictive accuracy). The predictive accuracies are much more difficult to establish than the sensitivity and specificity because they are heavily impacted by the preva-

lence of the disorder in the population being studied,²⁴ as denoted by the following formulas:

$$PPA = \frac{sP}{sP + (1 - f)(1 - P)}$$

$$NPA = \frac{f(1 - P)}{f(1 - P) + (1 - s)P}$$

where PPA = positive predictive accuracy, NPA = negative predictive accuracy, *s* = sensitivity, *f* = specificity, and *P* = prevalence of the condition in the population under study. Consequently, if the prevalence of food allergy in the patient population to be studied is not the same as that found in the population that was used to establish predictive rates, a correction must be made to determine the expected accuracy of the test. Without such a correction, one might erroneously conclude that the positive predictive value of a test is sufficient to predict reactivity.²⁵

In our study the prevalence of food allergy in the 196 subjects varied from 22% for wheat to 73% for egg, prevalence rates considerably higher than would be anticipated in a more general population being evaluated for food allergy. Therefore to get a better appreciation for the utility of skin prick tests and the CAP System FEIA, the predictive accuracies were corrected to reflect a hypothetical, normalized population in which

TABLE VI. Comparison of median allergen-specific IgE and severity of food-induced allergic reaction

	Egg	Milk	Peanut	Soy	Wheat
Median allergen-specific IgE					
Mild	11.2	55.4	47.2	12.0	4.8
Moderate	8.7	29.0	50.5	9.3	37.0
Severe	12.5	57.2	61.7	3.9	41.8

about 10% of the patients evaluated would be expected to have a food allergy (Tables II to IV). Although about 1.5% of the general population reportedly experience adverse reactions to foods,^{2,3} the practicing physician is unlikely to perform the test without some suspicion of a food allergy. Therefore it was assumed that about 10% of the patients initially suspected of having a food allergy by the physician would actually have clinical reactivity. The performance characteristics for the CAP System FEIA were comparable to those of the skin prick test. As is evident from Tables III and IV, the negative predictive accuracies for the CAP System FEIA performed in the hypothetical, normalized population are excellent, but the positive predictive accuracies are quite poor, even when the optimal cutoff point derived from the ROC curve is used.

Because previous studies of children with atopic dermatitis and food hypersensitivities had suggested that high serum concentrations of allergen-specific IgE antibody were predictive of food-induced clinical symptoms,^{9,10} IgE antibody levels creating 95% and 90% positive and negative predictive accuracies were calculated (Table V). Patients with food-specific IgE antibody levels greater than the 95% predictive value for egg, milk, peanut, and fish are extremely likely to experience an allergic reaction if they ingest the food and therefore do not need to be challenged to establish a diagnosis of symptomatic food hypersensitivity. In the patient population studied, this would eliminate the need for about 40% of the DBPCFCs performed. When reactions were classified as mild, moderate, or severe, there was no correlation between the level of food-specific IgE antibody and the severity of symptoms reported by history or recorded during the DBPCFCs. Depending on the clinical situation, a greater than 90% predictive value may be considered sufficient to make the diagnosis of food allergy without oral challenge, but this should not be considered adequate for research studies. As may be surmised by the sensitivities calculated for the 95% predictive diagnostic values, there will be a significant number of patients with food-specific IgE antibody values less than the 95% predictive values who will experience symptoms of allergy if they eat the food. For patients with food-specific IgE values greater than the 95% negative predictive diagnostic values but less than the 95% positive predictive diagnostic values, supervised oral food challenges are necessary to establish clinical reactivity. Patients with values less than the 95% negative predictive diagnostic values could be challenged at

home, unless there is a strong suspicion that they may have experienced an allergic reaction.

The CAP System FEIA for soy and wheat were not sufficiently specific to provide greater than 95% predictive diagnostic values. This is probably due to extensive IgE cross-reactivity with other legumes and cereal grains/grass pollens, respectively. However, immunoblots of various legumes and cereal grains indicate that soybeans and wheat have distinct protein fractions that distinguish them from other members of their botanical families, and these could be exploited to develop more specific diagnostic tests.^{26,27} Eventual characterization of these protein fractions and generation of recombinant proteins could lead to highly specific tests for these foods and others. Nevertheless, egg, milk, peanut, and fish allergy account for about 80% of food hypersensitivity in children with allergy validated by DBPCFC,^{4,8,28} so the correct identification of clinical reactivity to these foods in a subset of patients should greatly reduce the risk, time, and expense involved in the diagnosis of food allergy.

At least two factors may affect the utility of the 95% predictive diagnostic values for use in general populations. All patients in this study have atopic dermatitis, a group of patients who tend to have the highest levels of IgE antibodies. In addition, the group of patients studied had a much higher prevalence of food hypersensitivity than is seen in most populations to be evaluated. Both factors would tend to increase the positive and negative predictive diagnostic values; that is, in a more general population with food-specific IgE values exceeding the positive predictive diagnostic value, it is even more likely that the patient would react to the food, whereas if the patient had a value below the negative predictive diagnostic value, it is even less likely that the patient would react compared with patients in this study. Therefore the diagnostic values established should provide a "margin of safety" for making an accurate clinical diagnosis, although future prospective studies are necessary to confirm this.

The CAP System FEIA provides standardized measurements of food-specific IgE antibodies, which may be used to diagnose food allergy in a portion of patients with IgE-mediated disease. In addition, the "absolute" values of specific IgE to individual foods may provide some information about the natural history of the food allergy. For example, preliminary data suggest that patients with symptoms of food allergy and lower levels of food-specific IgE antibody are more likely to "outgrow"

their reactivity in a few years, whereas patients with high levels of IgE antibodies (i.e., three to four times the 95% predictive diagnostic value) are unlikely to lose their reactivity for many years (i.e., 5⁺ years). Monitoring food-specific IgE antibody levels every 1 to 2 years may be useful in determining when to rechallenge patients. For example, when IgE antibody concentrations to egg or milk fall to one third of the 95% predictive value, a rechallenge is probably warranted. Future studies should be directed toward improving the specificity of CAP System FEIA antigens (e.g., wheat and soy), determining the 95% predictive diagnostic values for other foods, and assessing the utility of monitoring CAP System FEIA values for predicting when allergic reactions to food are outgrown.

REFERENCES

1. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987;79:683-8.
2. Young E, Stoneham MD, Petrukevitch A, Barton J, Rona R. A population study of food intolerance. *Lancet* 1994;343:1127-30.
3. Niestijl Jansen JJ, Kardinaal AFM, Huijbers GH, Vlieg-Boerstra BJ, Martens BPM, et al. Prevalence of food allergy and intolerance in the adult Dutch population. *J Allergy Clin Immunol* 1994;93:446-56.
4. Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr* 1988;113:447-51.
5. Novembre E, de Martino M, Vierucci A. Foods and respiratory allergy. *J Allergy Clin Immunol* 1988;81:1059-65.
6. Bock SA. Respiratory reactions induced by food challenges in children with pulmonary disease. *Pediatr Allergy Immunol* 1992;3:188-94.
7. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 1984;74:26-33.
8. Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990;117:561-7.
9. James JM, Sampson HA. Immunologic changes associated with the development of tolerance in children with cow milk allergy. *J Pediatr* 1992;121:371-7.
10. Bernhisel-Broadbent J, Dintzis HM, Dintzis RZ, Sampson HA. Allergenicity and antigenicity of chicken egg ovomucoid (*Gal d III*) compared with ovalbumin (*Gal d I*) in children with egg allergy and in mice. *J Allergy Clin Immunol* 1994;93:1047-59.
11. Axen R, Drevin H, Kober A, Yman L. A new laboratory diagnostic system applied to allergy testing. In: Johansson SGO, editor. *Clinical workshop: IgE antibodies and the Pharmacia CAP system in allergy diagnosis*. Uppsala, Sweden: Pharmacia Diagnostics AB; 1988. p. 3-4.
12. Sampson HA. Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol* 1983;71:473-80.
13. Sampson HA. Immunologically mediated food allergy: the importance of food challenge procedures. *Ann Allergy* 1988;60:262-9.
14. Sampson HA. Comparative study of commercial food antigen extracts for the diagnosis of food hypersensitivity. *J Allergy Clin Immunol* 1988;82:718-26.
15. Sampson HA. Diagnosing food allergy. In: Spector SL, editor. *Provocation testing in clinical practice*. New York: Marcel Dekker, Inc; 1995. p. 623-46.
16. Sampson HA. Managing peanut allergy. *Br Med J* 1996;312:1050-1.
17. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to food in asthmatic children. *J Allergy Clin Immunol* 1976;58:500-15.
18. Bock S, Buckley J, Holst A, May C. Proper use of skin tests with food extracts in diagnosis of food hypersensitivity. *Clin Allergy* 1978;8:559-64.
19. Atkins FM, Steinberg SS, Metcalfe DD. Evaluation of immediate adverse reactions to foods in adult patients. I. Correlation of demographic, laboratory, and prick skin test data with response to controlled oral food challenges. *J Allergy Clin Immunol* 1985;75:348-55.
20. Wraith K, Merret J, Roth A, Yman L, Merrett TG. Recognition of food-allergic patients and their allergens by the RAST technique and clinical investigation. *Clin Allergy* 1979;9:25-36.
21. Roger A, Pena M, Botey J, Eserverri JL, Marin A. The prick test and specific IgE (RAST and MAST-CLA) compared with the oral challenge test with milk, eggs and nuts. *J Invest Allergol Clin Immunol* 1994;4:178-81.
22. Tang RB, Chen BS, Wu KG, Hwang B. Comparison of food specific IgE antibody test (RAST) and skin tests in children with atopic dermatitis. *Chinese Med J* 1993;52:161-5.
23. Bircher AJ, Van Melle G, Haller E, Curty B, Frei PC. IgE to food allergens are highly prevalent in patients allergic to pollens, with and without symptoms of food allergy. *Clin Exp Allergy* 1994;24:367-74.
24. Feinstein AR. On the sensitivity, specificity and discrimination of diagnostic tests in clinical biostatistics. In: Feinstein AR, editor. *St. Louis: CV Mosby Co; 1977. p. 214-26.*
25. Caffarelli C, Cavagni G, Giordano S, Stapano I, Rossi C. Relationship between oral challenges with previously uningested egg and egg-specific IgE antibodies and skin prick tests in infants with food allergy. *J Allergy Clin Immunol* 1995;95:1215-20.
26. Eigenmann PA, Burks AW, Bannon GA, Sampson HA. Identification of unique peanut and soy allergens in sera adsorbed with cross-reacting antibodies. *J Allergy Clin Immunol* 1996;98:969-78.
27. Jones SM, Magnolfi CF, Cooke SK, Sampson HA. Immunologic cross-reactivity among cereal grains and grasses in children with food hypersensitivity. *J Allergy Clin Immunol* 1995;96:341-51.
28. James JM, Sampson HA. An overview of food hypersensitivity. *Pediatr Allergy Immunol* 1992;3:67-78.