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# Correlation of initial food reactions to observed reactions on challenges

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**Background:** Food allergies occur in 2% to 3% of the pediatric population. These reactions can vary from mild cutaneous manifestations to severe life-threatening reactions. Limited information is available on which specific factors may predict the severity of subsequent reactions.

**Objective:** To determine whether the organ system or the specific food involved in the initial allergic reaction predicts the outcome of subsequent food challenge.

**Methods:** Retrospective review of all food sensitive children who underwent food challenges at The Children's Hospital of Philadelphia, Philadelphia, PA, in a 5-year period (n = 998 challenges). The specific food, initial symptom on presentation, and reaction on open challenges were recorded.

**Results:** A total of 413 of 998 food challenges produced positive results. Milk, egg, and peanut were the most common foods to be associated with a positive challenge result. The most common presentation of food allergy was cutaneous followed by multiorgan reactions. Peanut, milk, and egg sensitivities were more likely to cause a multiple-organ system reaction on challenge than wheat or other foods. Patients with egg allergy were more likely to have a different reaction on rechallenge than other foods.

**Conclusions:** Milk, egg, and peanut are the most common foods associated with food challenges. Patients will typically experience similar reaction on re-exposure to the initial reaction. However, multiple-organ system reactions can occur after any initial clinical presentation, with milk, egg, and peanut having more multiple-organ reactions than other foods.

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## INTRODUCTION

Food allergies occur in 6% to 8% of the pediatric population younger than 3 years and 2% to 3% of the general pediatric population.<sup>1</sup> These reactions cause significant concern and anxiety in the families and patients as exemplified in quality-of-life surveys.<sup>2</sup> Reaction to foods can vary from an isolated hive to life-threatening and potentially fatal anaphylaxis. Because of these extreme variations in reaction severity, one of the major concerns for both physicians and families is whether a subsequent allergic reaction to a specific food will be similar to the child's initial reaction or if a subsequent reaction will be more severe and potentially life-threatening. This concern also has implication for the practitioners in the decision to prescribe an injectable epinephrine device.

Studies have identified the most common food allergies in patients with atopic dermatitis by double-blind, placebo-controlled food challenges (DBPCFCs)<sup>3</sup> as milk, egg, and peanut.<sup>4</sup> These studies have found that patients with atopic dermatitis can have varied reaction on challenge, ranging from a mild cutaneous reaction to reactions involving multiple-organ systems. Milk, peanut, and egg were noted to be the most common foods to cause a multiple-organ system reaction in a study of 198 children with atopic dermatitis.<sup>5</sup>

Limited work has been done to examine the specific factors that might influence a subsequent reaction. Previous studies have not defined a relationship between IgE levels on Immuno-CAP (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden) tests with the severity of reaction.<sup>5</sup> For those patients with peanut allergy, initial reactions had a degree of correlation with subsequent reaction. Patients with milder initial reactions were more likely to either tolerate subsequent exposure or experience a single-system reaction on subsequent exposure when compared with patients who presented with life-threatening reactions on first exposure.<sup>6,7</sup> This retrospective medical record review will examine whether the clinical presentation of specific food allergies can predict subsequent reactions.

## METHODS

We undertook a retrospective medical record review of all patients seen in the Allergy Section at The Children's Hospital of Philadelphia, Philadelphia, PA, for food allergy during a 5-year period. The individual characteristics of the patients were compared, which also included the results of open food challenges, which were performed to confirm clinical sensitivity. All patients with previous food allergic reactions were offered an open challenge to confirm their diagnosis.

### *Food Challenges*

Open food challenges were performed by starting with a dose of 0.1 mL, followed by 0.5, 1, 2.5, 5, 10, 30, and 60 mL for liquid foods (milk, soy, or pasteurized liquid egg). For solid

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foods (peanut, wheat, chicken, and others), the challenge doses were  $\frac{1}{32}$  tsp,  $\frac{1}{16}$  tsp,  $\frac{1}{8}$  tsp,  $\frac{1}{4}$  tsp,  $\frac{1}{2}$  tsp, 1 tsp, 2 tsp, and ad lib (minimum of 2 tsp). For differing clinical scenarios, the starting dose was adjusted, occasionally omitting the first challenge dose. On these occasions, no patients reacted on the first dose. Each dose was administered with an interval of 15 to 20 minutes until 60 mL or 2 tsp of food was ingested or the patient experienced a reaction. The positive end points were defined as symptoms consistent with an allergic reaction within 2 hours of the last dose. Hives secondary to direct contact with the food, such as those on the face or hands, were not considered positive reactions. Ambiguous reactions (17 total) were not included in this review.<sup>6</sup> In patients with underlying atopic dermatitis, the skin was in good control at the time of challenge; patients' skin was cleared with aggressive topical therapy and antibiotics if necessary.

#### *Classification of Reactions*

Reactions on presentation and challenges were classified as cutaneous, respiratory, gastrointestinal, multiple-organ system, and anaphylaxis. Cutaneous reactions were hives, urticaria, erythematous flushing, cutaneous angioedema, or flaring of atopic dermatitis. Patients with severe atopic dermatitis without clear clinical history of food reaction were also included in this category. Respiratory reactions included rhinitis, sneezing, voice change, throat tightness, cough, wheeze, shortness of breath, or tachypnea. Gastrointestinal reactions were emesis or diarrhea. Multiple-organ system reactions included reactions with symptoms in more than one organ system but not anaphylaxis. Finally, anaphylaxis was a life-threatening reaction that involved more than 1 organ system plus 1 or more of the following: hypotension or rescue mediations (intravenous fluids, multiple doses of albuterol, or epinephrine).

#### *Skin Testing*

Skin testing was performed by the prick method using commercial extracts (Bayer Laboratories, Spokane, WA; Greer Laboratories, Lenoir, NC) and bifurcated needles. All skin tests were performed at the initial evaluation of the patient. Reactions of wheal and flare were recorded after 20 minutes by measuring the maximal longitudinal diameter of the wheal and the diameter orthogonal to it. Mean wheal diameters were calculated as  $(a + b)/2$ . A wheal of 3 mm greater than the negative control, accompanied by a flare, was considered positive. The positive control was 10 mg/mL of histamine dihydrochloride.

#### *Statistical Analysis*

The Mann-Whitney *U* test was used to compare wheal-and-flare diameter between groups, assuming skin tests are not normally distributed. The  $\chi^2$  analysis of independent variables was used to compare the initial reaction to the reaction observed on challenge and each food allergen to the reaction seen on challenge. Although the expected number of reactions in several cells is less than 5, the small expectation cells (less than 5) are rare, meeting the Cochran method for  $\chi^2$

analysis. Contingent tables for the  $\chi^2$  tests were based on all foods in 5 categories (cutaneous, gastrointestinal, respiratory, anaphylaxis, and multiple-organ system). Because of the small number of patients in the soy and wheat reaction groups, these patients were combined to gain statistical significance by the Cochran method for a  $\chi^2$  analysis.<sup>8</sup> The Monte Carlo simulation for the contingency tables (Tables 2 and 3) had similar *P* values to  $\chi^2$  analysis. Collection of patient data was in compliance with the Institutional Review Board of The Children's Hospital of Philadelphia. For comparison of the quantification of the reaction dose, solid measurements were converted to milliliters (1 tsp was equivalent to 5 mL).

## **RESULTS**

### *Demographics*

Approximately 3,000 patients were seen for evaluation of food allergy, with 1,769 patients having a convincing history and positive confirmatory skin test results. For the 1,769 patients, 1,119 were boys and 650 were girls, ranging from 7 days to 18 year of age. Only 110 (6%) of the 1,769 patients did not have a history of asthma, allergic rhinitis, or atopic dermatitis. Half (878) of the patients had a history of asthma, 866 patients (49%) had a history of atopic dermatitis, and 523 patients (30%) had a history of allergic rhinitis. Approximately one third (637, 36%) of the patients manifested at least 2 of the following: asthma, atopic dermatitis, or allergic rhinitis.

The most common initial presentation was a multiple-organ system reaction to a food in 37% of the patients, with 28% of the patients reporting an urticarial reaction, 21% reporting a flare of their underlying atopic dermatitis, 11% reporting gastrointestinal symptoms as a reaction, and 4% reported respiratory symptoms. Patients were more likely to report multiple foods that trigger atopic dermatitis (average, 4.5 foods per patient) or cutaneous symptoms (average, 2.72 foods per patients) than respiratory (average, 1.3 foods per patient) or multiple-organ system reactions (average, 1.37 foods per patient). The maximum number of foods reported by history that elicited symptoms was 25 in 1 patient, with 13 of those foods eliciting positive reactions on skin test and 8 of those confirmed on food challenges.

The 12 most common positive skin test results were to peanut (816 patients), egg (800 patients), milk (654 patients), soy (391 patients), tree nuts (361 patients), wheat (261 patients), shellfish (210 patients), peas (193 patients), potato (150 patients), chicken (134 patients), beef (133 patients), and fish (130 patients).

### *Results of Open Challenges*

All patients with a history of food allergic reaction and positive skin test results were offered food challenges. If the initial reaction was thought to be significant, patients' challenges were recommended 1 year after their last reaction. If the history was equivocal, patients' challenges were performed at an earlier date. A total of 998 food challenges were

performed, excluding 17 challenges with equivocal results. A total of 413 challenge results were positive and 585 were negative. Milk, egg, and peanut accounted for 83% of the positive challenges; wheat, soy, and chicken accounted for 11% of the positive challenge results; and 10 other foods represented the remaining 6% (Table 1). We only performed 19 challenges for tree nuts, shellfish, and fish, with 1 challenge result being positive.

Milk, egg, peanut, wheat, and soy represent the most common foods implicated in childhood food allergy, which is consistent with previous reports.<sup>3,4</sup> Patients were challenged to an average of 1.2 foods, with a maximum of 8 foods in 1 patient. Eight patients were challenged to 4 or more foods, 9 patients were challenged to 3 foods, and 31 patients were challenged to 2 foods. More than 90% of the patients had fewer than 3 confirmed food allergies.

Patients with a positive food challenge result had significantly larger skin test reactivity than patients with negative food challenge results (Table 1). However, there was a significant overlap in the range of skin test wheal diameter in both groups (3 to 25 mm in the negative food challenge result group and 3 to 40 mm in the positive challenge result population).

Cutaneous reactions were the most common end point in our food challenges, with 43% of the patients experiencing such reactions (Table 2). Similar to previous studies,<sup>3</sup> isolated respiratory reactions were rare (5%). The rate (38%) of multiple-organ system reactions (the combination of anaphylaxis and multisystem reactions as defined in the "Methods" section) was nearly identical to reviews reported elsewhere.<sup>9</sup>

Patient age at the time of challenge was not statistically different in any reaction group except that the patients with respiratory reactions were older (Table 3). Patients with asthma were more likely to have a respiratory reaction or anaphylaxis than a patient with atopic dermatitis or a nonatopic patient (Table 4).

#### *Relationship of Food to Reaction on Food Challenge*

Milk, egg, and peanut were more likely to manifest with multiple-organ system reaction on challenge than soy or wheat (Table 2). Contingency tables that project each food trigger an equal proportion of subsequent reactions (43% cutaneous, 14% gastrointestinal, 5% respiratory, 14% anaphylaxis, and 24% multiple-organ system) were made. Wheat and soy showed statistically fewer multiple-organ system reactions than predicted, with wheat having more cutaneous reactions and soy more respiratory reactions. Peanut had statistically more multiple-organ system and anaphylaxis reactions and fewer cutaneous reactions than were predicted. Milk and egg were near the predicted values for cutaneous and multiple-organ system reactions. All of the 5 most common foods had at least 1 multiple-organ system reaction (Table 2).

We examined wheal size of each food compared with reaction size on challenge (Table 5). No statistical difference in wheal size based on foods or challenge reaction was found on food challenges.

#### *Relationship of Symptom on Presentation to Reaction on Food Challenge*

Patients were statistically more likely to experience symptoms similar to their initial symptom presentation than a change of symptoms when challenged to the offending food. For example, patients with cutaneous reactions on presentation of either atopic dermatitis or urticaria were more likely to have a cutaneous reaction on subsequent food challenge (Table 3). Assuming an equivalent distribution of reaction regardless of presentation, the predicted ratio would be 43% cutaneous, 14% gastrointestinal, 5% respiratory, 14% anaphylaxis, and 24% multiple-organ system reactions. Only patients who refused to eat the offending food on presentation had the anticipated ratio. Patients with initial gastrointestinal symptoms were statistically more likely to have gastroin-

Table 1. Food Challenge Results\*

| Food        | No. of challenges performed | Positive challenge result, no. (%) | Negative challenge result, no. (%) |
|-------------|-----------------------------|------------------------------------|------------------------------------|
| Egg         | 299                         | 150 (50)                           | 149 (50)                           |
| Milk        | 271                         | 111 (41)                           | 160 (59)                           |
| Peanut      | 136                         | 82 (60)                            | 54 (40)                            |
| Soy         | 115                         | 22 (19)                            | 93 (81)                            |
| Wheat       | 58                          | 19 (33)                            | 39 (67)                            |
| Chicken     | 14                          | 4 (29)                             | 10 (71)                            |
| Barley      | 14                          | 4 (29)                             | 10 (71)                            |
| Peas        | 10                          | 3 (30)                             | 7 (70)                             |
| Beef        | 11                          | 2 (18)                             | 9 (72)                             |
| Rice        | 5                           | 2 (40)                             | 3 (60)                             |
| Turkey      | 4                           | 1 (25)                             | 3 (75)                             |
| Other foods | 61                          | 13 (21)                            | 48 (79)                            |
| Total       | 998                         | 413                                | 585                                |

\* Wheal size was  $8.7 \pm 0.31$  mm for those with a positive challenge result and  $5.16 \pm 0.21$  mm for those with a negative challenge result;  $P < .001$  by Mann-Whitney  $U$  test.

Table 2. Reaction Rate on Food Challenges\*

| Food                | No. (%) of patients |                  |             |             |                       |
|---------------------|---------------------|------------------|-------------|-------------|-----------------------|
|                     | Cutaneous           | Gastrointestinal | Anaphylaxis | Respiratory | Multiple-organ system |
| Milk (n = 111)      | 51 (46)             | 14 (13)          | 17 (15)     | 6 (5)       | 23 (21)               |
| Egg (n = 150)       | 63 (42)             | 22 (15)          | 15 (10)     | 9 (4)       | 41 (28)               |
| Peanut (n = 82)     | 27 (33)             | 11 (13)          | 21 (26)     | 2 (2)       | 21 (26)               |
| Soy (n = 22)        | 10 (45)             | 7 (8)            | 1 (5)       | 2 (9)       | 2 (9)                 |
| Wheat (n = 19)      | 14 (74)             | 1 (5)            | 1 (5)       | 1 (5)       | 2 (11)                |
| All foods (n = 413) | 176 (43)            | 58 (14)          | 56 (14)     | 22 (5)      | 101 (24)              |

\* Cutaneous reactions are defined as urticaria or flares of atopic dermatitis; gastrointestinal reactions are defined as vomiting or diarrhea; respiratory reactions are defined as wheezing or rhinitis; multiple-organ system reactions are defined as non-life-threatening symptoms in more than 1 category; and anaphylaxis was a life-threatening reaction ( $\chi^2_{24} = 12$ ,  $P = .02$ ).

Table 3. Reaction of Presentation to Reaction of Challenge\*

| Initial reaction on presentation      | Reaction on food challenge |                 |                  |                  |                       |
|---------------------------------------|----------------------------|-----------------|------------------|------------------|-----------------------|
|                                       | Anaphylaxis                | Cutaneous       | Gastrointestinal | Respiratory      | Multiple-organ system |
| Cutaneous, % (n = 218)                | 12                         | 56              | 8                | 6                | 17                    |
| Gastrointestinal, % (n = 35)          | 6                          | 11              | 49               | 3                | 31                    |
| Refusal to eat, % (n = 37)            | 14                         | 35              | 14               | 3                | 35                    |
| Anaphylaxis, % (n = 69)               | 22                         | 33              | 14               | 6                | 25                    |
| Multiple-organ system, % (n = 40)     | 12                         | 30              | 18               | 5                | 35                    |
| Wheal size, mean $\pm$ SEM, mm        | 10.1 $\pm$ 0.69            | 8.21 $\pm$ 0.35 | 8.67 $\pm$ 0.94  | 7.95 $\pm$ 1.5   | 9.53 $\pm$ 0.49       |
| Dose on challenge, mean $\pm$ SEM, mL | 4.16 $\pm$ 1.13†           | 7.76 $\pm$ 1.08 | 11.2 $\pm$ 1.93† | 10.8 $\pm$ 3.1†  | 7.82 $\pm$ 1.54       |
| Age at challenge, mean $\pm$ SEM, y   | 2.7 $\pm$ 0.25             | 2.8 $\pm$ 0.14  | 3.0 $\pm$ 0.26   | 4.59 $\pm$ 0.56‡ | 1.8 $\pm$ 0.20        |

\* Cutaneous reactions are defined as urticaria or flares of atopic dermatitis; gastrointestinal reactions are defined as vomiting or diarrhea; respiratory reactions are defined as wheezing or rhinitis; multiple-organ system reactions are defined as symptoms in more than 1 category without life-threatening reaction; and anaphylaxis was a life-threatening reaction ( $\chi^2_{71.7} = 16$ ,  $P < .001$ ).

†  $P < .05$  for age at challenge for respiratory reaction vs other reactions.

‡  $P < .05$  for dose of challenge for anaphylaxis vs gastrointestinal or respiratory reactions.

Table 4. Atopic Background vs Reaction on Food Challenge\*

| Patient's atopic background                           | No. of patients with positive challenge results |           |                  |             |                       |
|-------------------------------------------------------|-------------------------------------------------|-----------|------------------|-------------|-----------------------|
|                                                       | Anaphylaxis                                     | Cutaneous | Gastrointestinal | Respiratory | Multiple-organ system |
| Atopic dermatitis                                     | 7                                               | 41        | 14               | 5           | 20                    |
| Asthma                                                | 7                                               | 13        | 5                | 0           | 8                     |
| Allergic rhinitis                                     | 2                                               | 0         | 1                | 1           | 0                     |
| Atopic dermatitis and allergic rhinitis               | 4                                               | 0         | 3                | 0           | 1                     |
| Asthma and atopic dermatitis and/or allergic rhinitis | 32                                              | 81        | 31               | 14          | 49                    |
| None                                                  | 3                                               | 28        | 4                | 2           | 20                    |

\* Cutaneous reactions are defined as urticaria or flares of atopic dermatitis; gastrointestinal reactions are defined as vomiting or diarrhea; respiratory reactions are defined as wheezing or rhinitis; multiple-organ system reactions are defined as symptoms in more than 1 category without life-threatening reaction; and anaphylaxis was a life-threatening reaction ( $\chi^2_{74.5} = 20$ ,  $P < .001$ ).

testinal than cutaneous symptoms based on this model but had the predicted amount of multiple-organ system reactions. Patients with multiple-organ system reactions on presentation had more multiple-organ system reaction and fewer cutaneous reactions on challenge than the model predicted. However, multiple-organ system reactions on challenge can occur in patients with all types of reactions on presentation (Table 3).

To further define whether initial reactions were similar to subsequent reactions, we examined patients who had multiple positive challenge results. Seventy repeated challenges were performed with 51 patients. Egg and milk were the most common food to have repeated challenges (Table 6). Among patients challenged to egg, there were different organ system involvements in 12 of 33 repeated challenges. Patients reacting to other foods on subsequent challenges had the same

Table 5. Wheal Size for Individual Foods vs Reactions on Food Challenges\*

| Food      | Wheal size, mean $\pm$ SEM, mm |                 |                  |                 |                       |
|-----------|--------------------------------|-----------------|------------------|-----------------|-----------------------|
|           | Anaphylaxis                    | Cutaneous       | Gastrointestinal | Respiratory     | Multiple-organ system |
| Milk      | 9.14 $\pm$ 0.61                | 8.38 $\pm$ 0.78 | 5.57 $\pm$ 1.38  | 7.25 $\pm$ 1.65 | 8.04 $\pm$ 0.74       |
| Egg       | 9.93 $\pm$ 0.69                | 8.63 $\pm$ 0.66 | 8.67 $\pm$ 0.93  | 8.29 $\pm$ 1.78 | 8.14 $\pm$ 0.73       |
| Peanut    | 11.8 $\pm$ 1.25                | 9.48 $\pm$ 1.06 | 15.8 $\pm$ 3.53  | 12.5 $\pm$ 7.5  | 9.24 $\pm$ 1.02       |
| Soy       | 8.0 $\pm$ 0                    | 4.1 $\pm$ 1.08  | 4.8 $\pm$ 0.71   | 5.0 $\pm$ 1.0   | 4.0 $\pm$ 2.0         |
| Wheat     | 9.0 $\pm$ 0                    | 5.8 $\pm$ 0.63  | 4.5 $\pm$ 1.06   | 3.0 $\pm$ 0     | 5.0 $\pm$ 1.0         |
| All foods | 10.1 $\pm$ 0.69                | 8.21 $\pm$ 0.35 | 8.67 $\pm$ 0.94  | 7.95 $\pm$ 1.5  | 9.53 $\pm$ 0.49       |

\* There is no statistically significant difference between skin tests and reaction for each food ( $P < .05$ ).

Table 6. Subsequent Reactions on Second and Third Challenges to Identical Foods

| Food (total number) | Subsequent reaction |                        |                            |                            |
|---------------------|---------------------|------------------------|----------------------------|----------------------------|
|                     | Same organ system   | Different organ system | More organ system involved | Less organ system involved |
| Egg (33)            | 16                  | 12                     | 1                          | 4                          |
| Milk (24)           | 18                  | 0                      | 3                          | 3                          |
| Other foods (13)    | 9                   | 0                      | 1                          | 3                          |

organ system or less organ system involvement in subsequent challenges at equal or lower quantities of food. When more organ systems were involved on subsequent challenges to foods than other eggs, patients were reacting to higher doses.

#### *Relationship of Dose to Reaction on Challenge*

Patients with anaphylaxis on challenge reacted to a lower dose of food compared with patients with other symptoms. The dose of food that caused anaphylaxis was significantly smaller compared with respiratory ( $P = .02$ ) and gastrointestinal reactions ( $P = .004$ ) and close to statistical significance for skin and multiple-system reactions ( $P < .07$  and  $P < .11$ , respectively). Patients with respiratory or gastrointestinal reactions react to higher doses of food compared with other reactions on challenges (Table 3). We did not correlate initial reactions because of variability and inherent difficult in quantifying the amount by history only.

## DISCUSSION

The Children's Hospital of Philadelphia has performed approximately 1,000 food challenges in the last 5 years. Milk, egg, and peanut were the predominant food allergens in children.<sup>3,9,10</sup> These 3 foods also accounted for most multiple-organ system reactions on food challenges, which is similar to previous studies.<sup>3,9,10</sup> We have noted that an initial presentation of mild symptoms of food allergy does not rule out a severe reaction on subsequent challenges.

One limiting factor in the study is that the challenges were performed by open method rather than DBPCFCs. However, the incidence of each organ system reaction and the most common foods identified indicates that this method is valid. DBPCFCs are necessary for evaluation of subjective changes due to foods or equivocal open challenge. In our experience, food allergies do not cause subjective reactions. The only

behavioral change we noted during the challenges was anxiety due to the symptom of the reaction. There were only 17 challenges with equivocal results. Most of these challenges had to be prematurely stopped due to the patient's refusal to take a higher enough dose to reach a final end point.

Another variable factor of this study is that the quantity of food was carefully monitored during the challenges, whereas the quantity ingested at presentation was variable. It is possible that reactions with more organ system involvement could have occurred if increasing doses of food were given. Also, it is difficult to compare initial reaction in the community to the reaction under controlled circumstances. To address this specific concern, we also examined patients who had multiple challenges to the same food. In these 51 patients, reactions were similar to the previous reaction on challenge in most cases. However, 5 of the 70 repeat challenges had more significant reaction on subsequent challenges. All of these reactions were at greater amount of ingested foods. This indicates that large doses of food allergen could lead to more severe reactions or more organ system involvement. Interestingly, only patients who had egg allergy had different organ system involvement on subsequent challenges compared with reactions on initial challenge.

The third limitation of the study was that the severity of reaction could not be graded and compared, except for anaphylaxis. For example, a patient with wheezing and vomiting and another patient with hives and rhinorrhea would both be classified as multiple-organ system reaction. Adding to the complexity of evaluation, severity in challenges is a dose-dependent reaction, because we stopped at the first sign of clinical symptoms. It would be ideal to know the quantity of foods that caused the initial reaction or an unintentional

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reaction. However, this quantification is not available or inaccurate. Therefore, we did not include it in our study.

Our results are similar to those reported from other centers; approximately 41% of our food challenge results were positive, with milk, peanut, and egg being the predominant allergens.<sup>3,11</sup> The positive response rate on food challenge varied from 24% to 55%. These differences most likely reflect differences in referral populations. The Children's Hospital of Philadelphia is a tertiary referral center, where we may have a higher rate of clinical severity and sensitivity disease than a more general population. Also, our patients were preselected carefully by history and skin testing for challenges, which may account for our positive challenge result rate being on the higher end of the range reported.

Most food allergic patients are not allergic to multiple foods. Our data are much in the line with previous studies that found 21% of patients reacted to 1 food, 30% to 2 foods, and 27% to 3 foods.<sup>5</sup> In our patient population, the rate of multiple food allergies was even lower, with 70% having 2 or fewer food allergies and 90% having 3 or fewer food allergies.

IgE-mediated reactions to foods can vary from mild to life-threatening reactions. We separated our reactions into 5 general categories similar to previous studies.<sup>12</sup> Reaction could be localized to the skin (hives, angioedema, or atopic dermatitis flare), gastrointestinal tract (emesis or diarrhea), respiratory tract (either upper [rhinorrhea, sneezing] or lower<sup>13</sup>), multiple-organ system involving 2 or more of these reactions, and anaphylaxis. Studies using DBPCFCs have demonstrated that a variety of clinical reactions can occur in patients with atopic dermatitis. Niggemann et al<sup>9</sup> in open challenges found similar results to ours, with 64% of the challenges involving 1 organ system and 36% involving 2 or more organ systems, with skin only (55%) and skin and gastrointestinal (23%) being the 2 most common reactions. Sampson and Ho<sup>5</sup> found that 71% of the challenges had gastrointestinal symptoms, 86% had cutaneous symptoms, and 38% had respiratory symptoms by DBPCFCs. These well-controlled studies have limitations in that they only examined children with moderate-to-severe atopic dermatitis. However, their overall rates of reaction were nearly identical to our review. We examined all patients with food allergy and found that 43% experienced cutaneous reactions and 24% experienced multiple-organ system reactions. Similarly, in 2 studies<sup>3,14</sup> that examined food challenges in patients referred for general food allergies, the most common reaction was cutaneous, followed by gastrointestinal and respiratory. These rates of organ system reactions were similar to our observed rate of 43% cutaneous, 14% gastrointestinal, 14% anaphylaxis, 5% respiratory, and 24% multiple-organ system. In all of the studies, isolated respiratory symptoms ranged from 2% to 4%, whereas isolated cutaneous symptoms are the most common, ranging from 35% to 55%.

Our data demonstrated that milk, egg, and peanut were the most likely allergens responsible for multiple-organ involvement or anaphylaxis, which is similar to previously reported

studies (Table 2).<sup>3,5,12,14</sup> Niggemann et al<sup>9</sup> also found that wheat was less likely to cause a multiple-organ system reaction (12%) compared with soy (28%), milk (36%), and egg (42%). These rates of multiple-organ reactions are nearly identical to our results, except for a lower rate for soy: milk (25%), egg (36%), peanut (27%), wheat (2%), and soy (2%). These studies seem to indicate that certain foods are more likely to be associated with a multiple-organ system reaction when compared with other foods. One possible origin is due to the allergenic potential of the epitope based on its stability and structure. Evidence for this hypothesis is derived from the observation that patients with persistent milk allergy have antibodies to the linear epitope, whereas patients who become tolerant to milk have antibodies to only the native structure.<sup>15</sup> Similarly, patients who can tolerate egg on ingestion but develop contact reactions have antibodies to enzymatically unstable epitope. Patients with symptoms on ingestion of egg have antibodies to enzymatically stable epitope.<sup>16</sup> Although these are promising leads, the cause of multiple-organ system reaction remains to be elucidated. It is important to remember that host factors probably play a role.

Limited work is published on which specific clinical factors may predict future reactions. Most of the work has been done for the most severe type of reactions (fatalities) and tolerance (outgrowing food allergies). Studies by Bock et al<sup>17</sup> have examined the clinical factors that might predispose patients to a fatal reaction. They identified peanut and tree nut allergy, history of asthma, and age (adolescence and young adulthood) as risk factors. In our patients, age of challenge was a risk factor for respiratory reactions but not for anaphylaxis (Table 3). Similar to the finding of Bock et al, asthma was a risk factor for anaphylaxis (Table 4).

Numerous studies have indicated that patients can become tolerant of food antigens, since most patients outgrow their milk allergies by the age of 3 years and egg allergies by the age of 5 years. Recent reports<sup>6,7,18,19</sup> confirmed that patients can also become tolerant to peanut allergies; even selected patients with serious initial reactions can develop tolerance to the food, although this is much less likely for peanut compared with milk and egg.<sup>20–23</sup>

Data suggest that subsequent reactions tend to be similar to initial reactions to the food. However, Vander Leek et al<sup>7</sup> found that for peanut an initial single-system reaction did not predict a subsequent single-system reaction, since only 37% of the skin reactive patients had isolated skin symptoms on subsequent reactions. They also noted that patients with previous multiple-system reactions were more likely to have similar subsequent reactions on re-exposure.

We compared all patients' initial reaction to their subsequent reaction on challenge. Patients were more likely to have a similar reaction on re-exposure. For example, if a patient presented with cutaneous symptoms (urticaria or atopic dermatitis), 56% of the reactions were cutaneous compared with the predicted rate of 43%. Similarly, in a patient who presented with gastrointestinal symptoms, 49% had similar reactions compared with 13% predicted from our model.

However, even if a patient presented only with a cutaneous reaction, it did not rule out the possibility of having a multiple-organ system reaction on subsequent exposure. This finding is similar to the results of Vander Leek et al on peanut-allergic patients and previous studies on patients with atopic dermatitis, whereby patients had different reactions on subsequent doses in the community or challenges in a physician office.<sup>5,7</sup>

One unanswered question is whether one food is more likely to have similar-type reactions on subsequent challenges or have different reactions. To control for the variability of the dose of the initial reaction or challenge, we examined the patients who had undergone multiple challenges. Interestingly, patients with egg allergy were more likely to have variable reactions on challenge compared with patients who were challenged to other foods in the limited number of multiple challenges (70; Table 6).

The essential question is whether a predictive test or specific factor correlates with subsequent type of reaction. We found that the size of skin test reactivity did not correlate with the location or severity of the reaction. Similar, Sampson and Ho<sup>5</sup> did not find any relationship of quantitative Immuno-CAP levels to the severity of reactions for milk, egg, peanut, and soy, and Niggemann et al<sup>9</sup> did not find a relationship between Immuno-CAP levels and titrated dose of food that caused a clinical reaction. This would seem to indicate that the level of IgE measured by either skin test or Immuno-CAP cannot predict the severity or the location of subsequent reactions.

We also examined patient demographics and found that patients who had respiratory reactions were older than the patients with other reactions. Possible explanations include the fact that older patients were able to identify respiratory symptoms better than younger patients or simply that older patients are more likely to have asthma symptoms than younger patients. The latter reason was not supported by the fact that patients with asthma were not more likely to have respiratory reactions than patients without asthma (Table 4). Patients with asthma, regardless of whether they have atopic dermatitis or allergic rhinitis, were more likely to have anaphylaxis on challenge than patients without asthma.

Therefore, there is no conclusive method or specific test that can predict the location of subsequent reactions. Patients can present with a diffuse spectrum of reaction with potential for subsequent reactions of varying severity. Therefore, it would be prudent for all patients with food allergies, regardless of their presentation, to be taught emergency use of epinephrine in an effort to prevent food-related fatalities. Previous studies have indicated that a number of those fatalities from food allergic reactions were related to delayed use or failure to use epinephrine.<sup>17</sup> Additionally, information regarding the use of epinephrine in potential emergency situations needs to be reviewed not only with families but also with school and medical personnel.

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