

Changes in prevalence and characteristics of IgE-mediated food allergies in children referred to a tertiary care center in 2003 and 2008

Anik J. Amin, B.A., and Carla M. Davis, M.D.

ABSTRACT

Although epidemiological trends in peanut allergy have been determined, there are limited data for changes in prevalence and clinical characteristics for other common food allergens. This study was performed to determine the trends in prevalence and clinical characteristics of physician-diagnosed pediatric food allergy (FA) at a large urban-based tertiary care center from 2003 to 2008. The electronic medical record system was searched to identify all unique patients with FA as a diagnosis for 2003 and 2008. Included patients had either a definite clinical reaction on ingestion and (1) a positive specific IgE or skin-prick test or (2) food-specific IgE of >90% specificity. Patients with allergies to cow's milk, eggs, fish, peanuts, sesame, shellfish, soy, tree nuts, and wheat were included. The percentage of FA clinic patients increased from 3 to 8% over 5 years. The severity of initial reactions to food also increased from 2003 to 2008 ($p < 0.05$). Mean initial food-specific IgE decreased from 52 kU/L in 2003 to 40 kU/L in 2008 ($p = 0.002$). The age at diagnosis decreased from 2003 to 2008 for cow's milk (2.64–1.36 years; $p < 0.05$) and fish (5.10–2.86 years; $p < 0.05$) allergies. Peanuts and shellfish were associated with anaphylaxis and severe symptoms in 2008. Clinical characteristics of food-allergic reactions in this large tertiary care center worsened in severity over 5 years and reactions were associated with a lower specific IgE at presentation for peanut and shellfish allergy. Clinical presentation of FA may change over time and this phenomenon warrants study to determine contributory factors.

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Food allergies (FAs) are a significant disease in children with a self-report prevalence in children of ~12% and prevalence with food challenge confirmation in ~3% of children and adults.¹ Several studies have documented a rise in FAs over the past 10 years.^{2,3} It is the third most common cause of allergy/immunology (A&I) outpatient consultation.⁴ FAs can lead to life-threatening anaphylaxis, complicate other chronic allergic conditions such as atopic dermatitis and asthma, and affect nutrition management. Over 90% of all FAs in the United States are from eight food types: milk, eggs, peanuts, tree nuts, fish, shellfish, soy, and wheat.⁵ Sesame has been considered the ninth major food allergen in some centers because of the increasing internationalization of food.⁶

Studies examining food-specific trends have focused primarily on peanuts. A random-digit dial telephone survey found that the prevalence of peanut and/or tree nut allergy doubled from 1997 to 2002.³ Ages of first peanut reaction have declined over the past 10 years, and more peanut-allergic patients are also allergic to other foods.⁶ However, changes regarding clinical

characteristics of other FAs has not been extensively examined.

Recently, the National Health and Nutrition Examination Survey 2005–2006 was used to determine the prevalence of clinical FAs in the United States with criteria including both clinical symptoms and IgE sensitization.⁷ Mutually exclusive risk categories for clinical FA were determined based on the level of food-specific IgE.⁷ Recent National Institutes of Health (NIH) Guidelines for the Diagnosis and Management of Food Allergy in the United States express, “Food allergy should be considered in individuals presenting with anaphylaxis or any combination of symptoms that occur within minutes to hours of ingesting food, especially in young children and/or if symptoms have followed the ingestion of a specific food on more than one occasion.”⁸ The guidelines also recommend allergen-specific serum IgE tests for identifying foods that potentially provoke IgE-mediated food-induced allergic reactions.⁸ It is unknown if there have been any recent changes in the serum-specific IgE associated with clinically likely FA for specific foods. Although epidemiological trends in clinical characteristics of peanut allergy have been studied,⁶ there is limited data on the patient laboratory and clinical characteristics for all food types in the allergist's office. In this retrospective, cross-sectional study, analysis of the characteristics of physician-diagnosed pediatric FA patients seen at a large A&I academic practice in a tertiary care urban

From the Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas

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Address correspondence and reprint requests to Carla McGuire Davis, M.D., 1102 Bates Avenue, MC 330.01, Houston, TX 77030

E-mail address: cmdavis@texaschildrenshospital.org

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center between 2003 and 2008 was performed. Patients with allergy to the eight major food allergens and sesame were included. The study selection criteria included clinical symptoms of FA as defined by the recent NIH guidelines and evidence of elevated food-specific IgE to limit the study population to those with likely IgE-mediated food-allergic disease. Presenting characteristics of food-allergic children, initial reactions to food- and allergen-specific IgE were determined over this relatively recent time frame to better characterize this population.

PATIENTS AND METHODS

This study was approved by the Baylor College of Medicine Institutional Review Board, under protocol H-23905.

Patient Selection

A search query of the electronic medical record (EMR) system at Texas Children's Hospital (TCH) identified all patients diagnosed with "FA" (ICD-9 Code 693.1) in the A&I Department in 2003 and 2008. The EMR-based study inclusion criteria were as follows: (1) patients with a diagnosis of cow's milk, egg, fish, peanut, sesame, shellfish, soy, tree nut, and/or wheat allergy from the medical record and (2) patients had either a definite clinical reaction on ingestion and (a) a positive food-specific IgE (≥ 0.35 kU/L) or skin-prick test (if serum-specific IgE not available) or (b) food-specific IgE greater than either the 90% specificity decision point⁹ or the general class III cutoff for food types without established 90% specificity values (specific IgE > 3.51 kU/L). The included subjects were required to have the inclusion criteria from both criteria 1 and 2.¹⁰ The ImmunoCAP-FEIA method (Phadia AB, Uppsala, Sweden) was used for specific IgE testing, and Greer Laboratories (Lenoir, NC) commercial extracts were used for skin-prick tests. These methods for testing were identical in 2003 and 2008. Patients with multiple FAs satisfying the inclusion criteria had separate recordings for each food type. Patients satisfying the criteria in both 2003 and 2008 were only recorded in the 2003 database.

Variables Recorded

For both the 2003 and the 2008 databases, a single recording represented an individual's allergy to a single food type. There were some individuals with multiple FAs so multiple food allergens or types were recorded for one distinct patient. In addition to food type, several variables were recorded based on review of the electronic medical chart: gender, ethnicity, age at diagnosis, specific IgE at diagnosis, skin-prick wheal and flare (if available), symptoms of the reaction before diagnosis, and symptom severity for this reaction. If

ethnicity was not known, "unknown" was recorded. Age at diagnosis was defined as the earliest confirmed date when the previously mentioned inclusion criteria were met. For statistical analysis, specific IgE results of >100 kU/L were recorded as 100. Wheal and flare measurements were recorded as the net increase above negative control. The presence of symptoms was recorded under the following categories: eye and nasal (grouped together as mucosal), gastrointestinal, respiratory, vascular, anaphylaxis, eczema related, and urticaria/angioedema. Vascular symptoms included flushing, headache, and hypotension. Anaphylaxis was defined based on current literature.⁹ For patients with known symptoms, symptom severity was classified as either mild, moderate, or severe. If the patient had anaphylaxis, vascular symptoms, or symptoms in at least four categories, the reaction was defined as "severe." Reactions in nonsevere patients were classified as "moderate" if they had gastrointestinal symptoms, respiratory symptoms, or symptoms in three categories. The remaining patients with known symptoms were classified as "mild." Eosinophilic esophagitis and/or other atypical allergic disorders presenting with food-specific IgE were specifically excluded from the FA diagnosis. Only patients with classic symptoms of FA as listed previously were included.

Analysis of Data

Descriptive statistics were determined for each variable by year. Percents of total patient population were performed for categorical variables (food type, gender, ethnicity, symptoms, and symptom severity). Numeric variables (age at diagnosis, specific IgE, and skin-prick results) are presented as means $\pm$ SD. For age and specific IgE at diagnosis, mean values were calculated by food type per year. Chi-square and Fischer's exact test (for small sample sizes) compared 2003 with 2008 values for categorical variables. Cases with unknown ethnicity and symptom recordings were excluded. The Mann-Whitney test (for nonparametric data) was used for the numeric variables. For the 2008 group only, age at diagnosis by food type was compared using the Kruskal-Wallis test (multivariable and nonparametric), and odds ratios (ORs) were performed to determine the risk of anaphylaxis and the presence of severe symptoms (more than four systems involved) for each food type. For all tests, two-sided value of $p < 0.05$ was considered statistically significant.

RESULTS

Patient Demographics

The food allergens for each patient were recorded as well as the number of patients. The distinct food allergens increased from 148 in 2003 to 379 in 2008 and the number of distinct patients increased from 57 in 2003 to

Table 1 Demographic characteristics of 2003 vs 2008 food allergy groups

	2003	2008
Total no. of A&I patients	1852	2364
No. of food allergies	148	379
Distinct patients, no. (%)	57 (3%)	191 (8%)
Male, no. (%)	106 (72%)	242 (64%)
Ethnicity		
White, no. (%)	43 (41%)	92 (36%)
Black, no. (%)	29 (27%)	72 (28%)
Hispanic, no. (%)	19 (18%)	57 (22%)
Asian, no. (%)	15 (14%)	28 (11%)
Other, no. (%)	0 (0%)	7 (3%)
Total known ethnicity, no.	106	256

A&I = allergy and immunology.

191 in 2008 (Table 1). Because some patients had more than one FA, the number of recordings of food allergens was higher than the number of distinct patients. The number of total patients in the A&I Clinic increased from 1852 to 2364, a 27% increase, over these 5 years. Although there was an increase in the total number of patients seen in the clinic, the percentage of total clinic patients that were food allergic still increased over this 5-year period from 3 to 8%. There was a male predominance both years, but no significant difference between the gender distribution in 2003 and 2008 ($p = 0.09$). Although, there was a significant difference ($p < 0.001$) between the ethnicity distributions of the two groups, with a shift from white to Hispanic patients from 2003 to 2008, this shift mirrored an increase in Hispanic patients in the total TCH population (34% in 2003 to 40% in 2008). Eighty percent of our Hispanic population was male patients, which was significantly higher than our non-Hispanic patients ($p < 0.01$) but there were no other significant differences in our Hispanic patients compared with the non-Hispanic patients. The proportion of black American patients remained relatively stable and the proportion of Asian patients only slightly decreased over the 5-year time frame (Table 1).

Comparison of Variables for the Entire Group, 2003 versus 2008

In both years, peanuts, eggs, and cow's milk were the most common food allergens (Fig. 1). The proportions were similar across both groups, and there was no significant difference in the food-type distribution in 2003 versus 2008 ($p > 0.05$). The percentage of peanut-allergic children in 2008 (29%) was slightly larger than in 2003 (26%) but this difference was not statistically significant.

The average ages at diagnosis in 2003 and 2008 were 3.05 (± 2.75 years) and 2.79 (± 2.87 years) years, respectively (Table 2). The mean food-specific IgE at diagnosis was 51.95 kU/L (± 39.82 kU/L) in 2003 and 40.32 kU/L (± 35.99 kU/L) in 2008 ($p < 0.005$; Table 2). The percentage of patients diagnosed by *in vitro* IgE levels was similar in 2003 and 2008 at 92 and 98%, respectively. There was no significant change in the age at diagnosis, skin-prick wheal, or skin-prick flare between the two years ($p > 0.05$).

For both years, the most common symptoms on ingestion were skin-related—eczema exacerbation, hives, or angioedema. Nonanaphylactic vascular symptoms were the least common in both groups. Hives/angioedema, mucosal, and gastrointestinal symptoms were significantly more prominent ($p < 0.001$, $p < 0.05$, $p \leq 0.005$, respectively) in 2008 compared with 2003. The severity of reactions before diagnosis of FA worsened ($p < 0.05$), with the percentage of severe allergic reactions doubling from 2003 to 2008 (Table 2).

Food-Specific 2003 versus 2008 Comparisons

In 2008, there was a significant difference ($p < 0.001$) in the age at diagnosis based on food type compared with 2003, with a decrease for patients allergic to cow's milk (2.64 and 1.36 years, respectively; $p < 0.05$) and fish (5.10 and 2.86, respectively; $p < 0.05$; Table 3). Shellfish allergies were diagnosed in older children from 2003 to 2008, but this did not reach statistical significance. In 2003, soy-allergic patients had the earliest age at diagnosis, followed by eggs (2.09 and 2.32, respectively; Table 3). In 2008, cow's milk-allergic patients presented the earliest, followed by eggs (1.36 and 1.95, respectively; Table 3). Initial food-specific IgE (Table 4) was lower in 2008 than 2003 ($p < 0.05$) for peanuts (69.26 and 54.22 kU/L, respectively) and shellfish (49.02 and 28.34 kU/L, respectively).

The specific IgE levels in Hispanics, blacks, and whites were compared for peanuts and shellfish for 2003 and 2008. The peanut-specific IgE for Hispanics (84.8 kU/L in 2003 and 52.4 kU/L in 2008) and whites (82.3 kU/L in 2003 and 55.6 kU/L in 2008) was lower in 2008 compared with 2003, which may have influenced these overall findings. The shellfish-specific IgE in blacks was lower in 2008 compared with 2003 (43.2 kU/L in 2003 and 13.3 kU/L in 2008), which contributed to the decreased specific IgE in the total population.

Risk of Anaphylaxis and Severe Symptom Category (Four or More Systems Involved)

The risk of anaphylaxis as the initial reaction to a food in 2008 was highest for peanuts (OR = 1.76) and shellfish (OR = 1.54) and lowest for sesame, soy, and

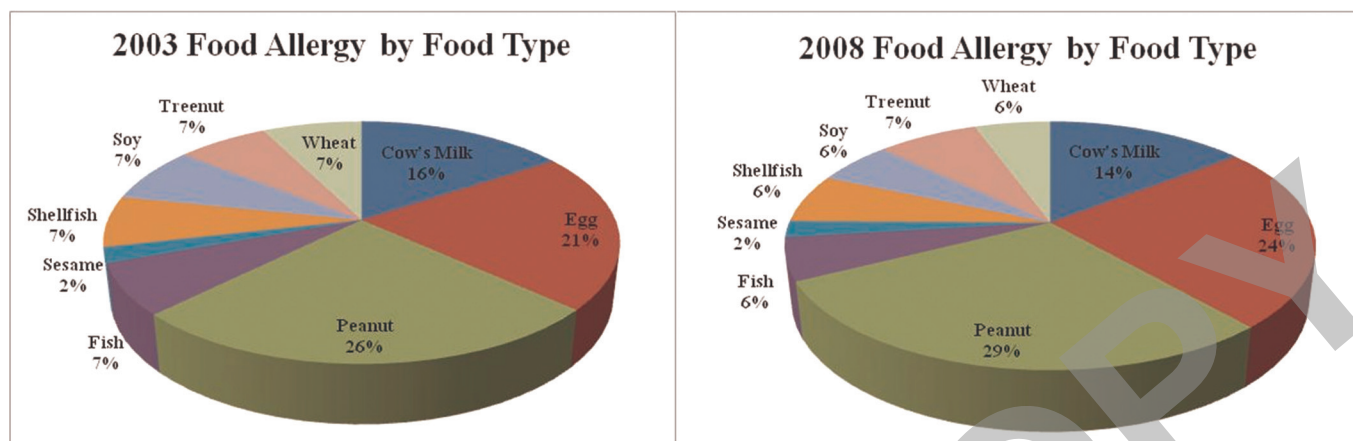


Figure 1. The 2003 and 2008 allergy recording distributions by food type.

Table 2 Food allergy clinical features, 2003 vs 2008

	2003	2008	P Value
Average age at diagnosis, yr	3.05	2.79	0.192
Average specific IgE at diagnosis, kU/L	51.95	40.32	0.002
Average skin-prick wheal, mm	21	10	0.437
Average skin-prick flare, mm	20	22	0.648
Symptoms			
Mucosal, no. (%)	10 (10%)	62 (20%)	0.03
Gastrointestinal, no. (%)	8 (8%)	64 (21%)	0.005
Respiratory, no. (%)	25 (26%)	58 (19%)	0.141
Vascular, no. (%)	2 (2%)	16 (5%)	0.191
Anaphylaxis, no. (%)	7 (7%)	40 (13%)	0.122
Eczema-related, no. (%)	70 (71%)	205 (66%)	0.311
Hives or angioedema, no. (%)	27 (28%)	153 (49%)	<0.001
Symptom Constellation			0.049
Mild, no. (%)	66 (67%)	187 (60%)	
Moderate, no. (%)	22 (23%)	58 (19%)	
Severe, no. (%)	10 (10%)	66 (21%)	
Total no. of classified cases	98	311	

Note: Percentages are based on number of distinct cases.

wheat (OR = 0.87, 0.37, and 0.37, respectively). Tree nut allergy had the third highest OR for anaphylaxis (OR = 1.16; Table 5).

DISCUSSION

The results of this investigation of food-allergic patients at a large tertiary center suggest that certain clinical characteristics of physician-diagnosed food-allergic patients have changed from 2003 to 2008. Over this recent 5-year time frame, characteristics have changed both across and within the nine major food allergens. The number and percentage of food-allergic patients increased over 5 years, which is consistent with reports in peanut allergy in the United States.³ This also could be partly explained by the increase in patient referrals and patient referral pattern in our

center given that the number of physicians in the section increased from seven to nine.

Our total patient population saw a large increase in Hispanic patients, which mirrors a recent study using national health surveys.⁷ An increasing Hispanic food-allergic population in the United States was documented in the U.S. Census. Although there were no significant differences in our Hispanic food-allergic population and other races besides male predominance, differences in the Hispanic diet, genetic factors, or risk factors in the Hispanic culture could affect FA outcomes in children. More information is needed to further define the characteristics of FAs in this population.

Patients in our clinic presented at younger ages in 2008 compared with 2003. Clinical symptoms experi-

Table 3 The 2003 vs 2008 mean age at diagnosis by food type

	2003 yr (range)	2008 yr (range)	<i>p</i> Value
Cow's milk	2.64 (0–11)	1.36 (0–12)	0.02
Eggs	2.32 (0–11)	1.95 (0–13)	0.62
Fish	5.1 (1–11)	2.86 (1–12)	0.02
Peanuts	3.58 (0–11)	3.00 (0–13)	0.45
Sesame seed	3.33 (2–5)	3.88 (1–7)	0.76
Shellfish	3.00 (1–8)	5.46 (0–15)	0.07
Soy	2.09 (0–5)	2.43 (0–12)	0.97
Tree nuts	3.60 (1–8)	5.07 (1–12)	0.20
Wheat	2.83 (0–11)	2.81 (0–13)	0.67

Table 4 The 2003 vs 2008 specific IgE at diagnosis by food type

	2003 IgE kU/L (range)	2008 IgE kU/L (range)	<i>p</i> Value
Cow's milk	47.58 (1.57–100)	32.61 (0.97–100)	0.11
Eggs	33.71 (1.06–100)	29.67 (0.35–100)	0.63
Fish	45.53 (5.09–100)	26.21 (0.88–89.60)	0.16
Peanuts	69.26 (0.35–100)	54.22 (0.55–100)	0.048
Sesame seed	12.52 (5.47–21.7)	20.20 (2.03–57.3)	0.76
Shellfish	49.02 (13.80–100)	28.34 (0.38–100)	0.04
Soy	64.61 (0.85–100)	61.82 (1.53–100)	0.85
Tree nuts	50.12 (0.51–100)	38.46 (0.35–100)	0.42
Wheat	67.59 (21.30–100)	54.58 (2.38–100)	0.36

Table 5 Odds ratios for the risk of anaphylaxis and severe symptoms (more than four systems)

Food Allergy	Anaphylaxis	95% CI	Severe Symptoms	95% CI
Cow's milk	1.04	0.44–2.49	0.98	0.47–2.02
Eggs	0.6	0.26–1.42	1.17	0.63–2.16
Peanuts	1.76	0.90–3.45	1.15	0.65–2.05
Sesame	0.87	0.83–0.90	0.78	0.73–0.83
Shellfish	1.54	0.42–5.64	1.67	0.56–5.0
Soy	0.37	0.05–2.84	0.43	0.10–1.91
Tree nuts	1.16	0.32–4.14	1.2	0.42–3.44
Wheat	0.37	0.05–2.84	0.7	0.197–2.49

enced by patients after food ingestion before diagnosis in our clinic increased to include more systems. There were increases in patients with mucosal symptoms, gastrointestinal symptoms, hives, and angioedema. Severe food-allergic reactions to food doubled in this time period. In 2000, the American Academy Committee on Nutrition recommended a restricted diet for allergenic foods for breastfeeding mothers of high-risk infants and delayed introduction of solid foods into the diet of high-risk infants until 6 months of age, with dairy products delayed until 1 year; eggs until 2 years; and peanuts, nuts, and fish until 3 years of age.^{8,11} In 2008, these recommendations were changed to allow solid food introduction of all foods after 6 months of age because of insufficient data to support a protective

effect of any dietary intervention.¹² There is evidence that early introduction of food is associated with a decrease in the incidence of peanut and milk allergy.^{13,14} This evidence, along with the recent demonstration through several clinical trials that desensitization to milk, eggs, fish, and peanuts is possible in food-allergic patients through careful slow introduction of the food,¹⁵ suggests that avoidance does not protect from atopic disease. From 2003 through 2008, the delayed food introduction guidelines were recommended, so it is possible that the institution of these guidelines, based on best practices at that time, may have contributed to an increase in prevalence and severity of FA in our cohort. Further study would be required with follow-up investigation to determine the importance of this effect.

The increase in the severity of food-allergic reactions was accompanied by a decrease in the level of food-specific IgE in our cohort, as initial food-specific IgEs decreased over the 5-year period. The decreases were most pronounced for peanuts and shellfish, foods that have been considered more likely to be associated with severe food-allergic reactions in children.^{16,17} These decreases were largest in Hispanic and white populations for peanuts and black populations for shellfish. Therefore, shifting demographics may play a role in the changes in FAs in the future. Delayed introduction of foods may also play a role. However, without a prospective study regarding the food introduction habits of this population, this can not be stated definitively. The finding of increased symptomatology may also be partly explained by increased awareness of patients and physicians regarding the definition of anaphylaxis given the clarified definition in 2004.⁹

According to the NIH Guidelines for the Diagnosis and Management of Food Allergy in the United States, an important part of the natural history of FA is determining the likelihood of FA and the actual time of resolution of disease.⁸ A high initial level of specific IgE is associated with a lower rate of resolution of clinical allergy over time.^{8,18,19} Ho *et al.* showed lower peanut-specific IgE to be a predictor of peanut allergy resolution.¹⁸ Shek *et al.* have also shown decreasing food-specific IgE levels to be predictive of the development of tolerance in cow's milk and egg allergies.¹⁹ Although the average peanut IgE at diagnosis decreased from 2003 to 2008 in our study, it will be interesting to see whether this will result in a larger percentage of our peanut-allergic patients developing tolerance over time. Currently, only 20% of peanut-allergic patients outgrow their allergy.²⁰

Previous studies support our finding that the age at diagnosis varies by food type, with patients allergic to cow's milk most prevalent at early ages.⁸ Patients allergic to cow's milk and fish presented at earlier ages in 2008 compared with 2003 at our institution. There is no consensus on why patients may be presenting at younger ages to these foods. A recent study of peanut-allergic patients in one center found an earlier age of reaction to peanuts if they were born between 2000 and 2005 compared with those born between 1989 and 1999. Timing of exposure to peanuts was attributed as a potential contributing factor.⁶ There is the possibility that a change in timing of exposure to cow's milk and fish in our patients may have contributed to a change in presenting ages of cow's milk and fish allergy. Other potential factors contributing to earlier presentation of FA include reduced immune system stimuli from infections ("hygiene hypothesis") and nonfood-specific dietary changes.⁵

Shellfish is a significant cause of emergency room visits in children aged 6–18 years by a recent survey

of food-allergic reactions and anaphylactic events through the National Electronic Injury Surveillance System.¹⁷ Shellfish was associated with an increase in age of presentation in our cohort. The regional differences in shellfish consumption with more consumption of shellfish in states bordering the Gulf of Mexico, such as Texas,²¹ may explain this observation.

The higher anaphylaxis and severe symptom ORs for children with peanut and shellfish allergies compared with other food types are consistent with reports indicating clinical symptoms are worse for patients allergic to these two food types.²² Tree nuts were the third food more likely to cause severe symptoms, which is consistent with reports of tree nut allergy as a risk factor for anaphylaxis.^{20,22} Sesame, soy, and wheat were not as likely to be associated with anaphylaxis in our center.

The primary limitation of this study is its retrospective and cross-sectional nature. The study can not explain why the trends and changes in FA characteristics between 2003 and 2008 occurred. The various clinical characteristics for each FA recording are based on reviewing an EMR, so data quality relies on the quality of information recorded into the EMR. Other limitations include a small number of observations for less common FAs (*e.g.*, sesame). Finally, a FA diagnosis was less certain for patients allergic to sesame and certain tree nuts because of a lack of established specific IgE 90% confidence levels. However, recent studies have started to establish 95% predictive values for various foods, particularly tree nuts.⁵ The class III cutoff values for sesame seed (specific IgE > 3.51 kU/L) are similar to values that have been recently determined to have a >90% specificity.²³

Strengths of this study include the fact that all patients in 2003 and 2008 were seen at the A&I Clinic at TCH in Houston, TX, a large tertiary care center in a diverse city. Our pediatric population is more diverse compared with the national pediatric population. Also, all of the eight common food allergens were assessed and compared with one another in the same cohort. Important trends were seen in the decreased age of diagnosis for cow's milk and fish, an increased age of diagnosis for shellfish allergy, an increase in the number of systems involved and severity of food-allergic reactions in children and decreased food-specific IgE at diagnosis.

These findings may have implications for the development of tolerance in our center. Another tertiary care center has reported a longer time to development of tolerance to peanuts, soy, wheat, and eggs in food-allergic children than was previously thought.^{24–27} If lower initial specific IgE is associated with development of tolerance, one would expect for our 2008 patients to outgrow their FAs sooner than the 2003 group. Given the changing landscape of food introduction in

the United States, the evolving demographics, and the progress in the development of protocols for desensitization, characteristics of clinical food-allergic disease may continue to shift with time. In this study from a large tertiary center, the trend is toward increased symptom severity and decreased specific IgE.

CONCLUSION

FAs are a significant and growing issue in the pediatric population. Based on physician-diagnosed clinical data and selection criteria for true IgE-mediated FAs, this study indicates an increased prevalence of nine major FAs in this tertiary care center across a recent 5-year span. In addition, patients are experiencing worsening symptoms for their initial food-allergic reactions and presenting at an earlier age for cow's milk and fish allergy. Their initial food-specific IgE values have decreased over 5 years, which may be related to changing demographics. Clinical characteristics of FAs in this cohort have changed over a relatively short period of time and may continue to evolve secondary to possible genetic and environmental factors.

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