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The effect of age, sex, race/ethnicity, health insurance, and food specific serum immunoglobulin E on outcomes of oral food challenges

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ABSTRACT

Background: Although oral food challenge (OFC) is an important clinical procedure for diagnosing food allergy, there is a paucity of literature on the outcome of the procedure and specifically the patients on whom the procedure is performed from the aspects of their age, sex, race/ethnicity, health insurance status, and serum specific IgE to the food tested.

Objective: We aimed to review results of OFC and determine the impact of patient age, sex, race/ethnicity, insurance status, private or public, and food specific serum IgE on the outcome of OFC.

Methods: A retrospective chart review was performed of patients undergoing OFCs at a children's hospital outpatient allergy clinic over a two-year period. The outcome of OFC was allergic or non-allergic based on determination and documentation by the treating physician. A logistic regression model was built to determine the association between the OFC outcomes, age, and symptoms at the time of OFC. A Chi-square analysis was performed to check for any significant relationship between the OFC outcome and age when stratified by insurance status.

Results: Five hundred and eight children underwent 641 OFCs. Twenty nine percent of OFCs had an allergic outcome with the most commonly challenged foods being peanuts, eggs, and milk. Patient age and gender, when stratified by insurance status, did not have a significant effect on OFC outcomes. Serum IgE to peanuts and egg was significantly different between allergic OFC and non-allergic outcome. Vomiting and urticaria/angioedema correlated with an allergic OFC outcome.

Conclusion: OFCs confirm the food allergy diagnosis in about one-third of patients tested, and they should continue to be used when possible for an accurate diagnosis. Age, sex, and insurance status do not have a significant association with the outcome of OFC and cannot be added as predictive factors.

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Institutional review board: The study received approval from the Institutional Review Board of Cincinnati Children's Hospital Medical Center. The approval number and title are: 2015-4861: Factors affecting oral food challenge outcomes in children. Due to the retrospective chart review nature of the study, the approval did not require that subjects sign consent or assent forms.

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BACKGROUND

The prevalence of childhood food allergy within the United States is approximately 8%, and among these individuals, 38.7% have a history of severe reactions.[1] Immunoglobulin E- (IgE) mediated food reactions typically occur within 2 hours of consumption and may involve the skin, gastrointestinal, respiratory, and cardiovascular systems.[2] The clinical history is a cornerstone of the diagnosis of food allergy and can be supported to some extent with skin prick testing and food-specific serum IgE testing. Oral food challenge (OFC) is a clinical procedure that is performed, when possible, to confirm or refute the diagnosis of food allergy. Because OFC involves feeding the patient the food they may be allergic to, it carries the risk of an allergic reaction. OFC is thus a procedure that patients and health care providers might be hesitant to undertake.[3–5] This may result in a delay in performing an OFC, reasoning that the older the patient, the more likely they are to be able to express symptoms of a start of a reaction. There may also be differences in the racial and socioeconomic class attitudes towards risk taking, especially when there is an alternative of continuing to avoid the food.

Scant data exist regarding the influence of patient factors on food allergy and its diagnosis.[6,7] Regarding factors associated with the development of food allergy or allergic diseases, low socioeconomic class seemed to be protective in a Canadian study.[8] A United States based study found higher odds of food allergy in African American and Asian children compared to Caucasian children, but lower odds of having the allergy diagnosed. The study found that those with food allergies from a lower socioeconomic class are at a disadvantage when it comes to provision of care.[1,8,9] Racial differences were reported among Caucasians, African Americans, and Hispanics in the prevalence of food allergy, the food allergens, and the co-morbidities of food allergy, with the latter ethnic groups showing shorter periods of follow up by their allergists.[10] A recent study examined the epidemiology of multicenter clinic-based OFCs and found that anaphylaxis occurrence was higher in the Northeast, Midwest, and North Midwest regions of the United States, and that males were more likely than females to have anaphylaxis.[11] In the United States, insurance type, Medicaid vs non-Medicaid, distinguishes low vs high socioeconomic class. Medicaid is an insurance that is provided by state governments to adults and children with low incomes and limited resources. The term non-Medicaid lumps commercial insurances that are carried by parents who are employed or pay for the insurance by other means. Thus, children insured by Medicaid would be of low socioeconomic class, while children who are insured by a non-Medicaid insurance would be of a higher socioeconomic class. Given the previously listed factors that may impact the outcome of OFC, we examined the outcome of OFC conducted in our outpatient clinics in the population as stratified by race/ethnicity, insurance type, age, and gender and the effect of food specific serum IgE.

METHODS

Data collection

We conducted a retrospective chart review on patients who had OFCs at our allergy and immunology outpatient clinics from December 2013 through November 2015. Institutional Review Board (IRB) approval was obtained prior to chart review. OFCs that were part of a desensitization study and those that did not have the outcome clearly determined were excluded; all other OFCs were included. The following data were extracted: patient race/ethnicity, sex, age at OFC, insurance payor whether medicaid or non-medicaid, zip code, foods tested in the OFCs, outcomes of the OFCs as documented by a physician, symptoms documented during OFCs, and serum food specific IgE results dating back up to a year prior to the date of OFC. Age at OFC was stratified into 4 groups: 0–5, 6–10, 11–15, and 16 years and above.

Statistical analysis

Statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, North Carolina). Descriptive statistics were performed to analyze the outcome of OFCs by patient age, sex, race/ethnicity, and type of food challenged. A logistic regression model was used to determine if age at OFC, insurance type, symptoms at OFC, and food specific serum IgE results were associated with OFC

outcome. A Chi-Square test in SAS was performed to determine any associations. Food specific serum IgE results lower than 0.35 kUA/L were replaced by the level of detection/√2 and results ≥100 kUA/L were converted to 101.[12,13] Food specific serum IgE levels were not normally distributed and were therefore compared using Mann-Whitney *U* test.

RESULTS

A total of 641 OFCs performed during the period of study were included. They were performed on 508 children with ages ranging from 0 to 19 years old. All OFCs were performed as outpatient procedures and were open challenges. Zip code distribution showed that Medicaid patients were concentrated around the medical center, while non-medicaid patients came from a wider area including the suburbs (Fig. 1). Of note, our academic center provides health care to all children regardless of insurance status and their ability to pay for medical care, so there is no population of children that does not have access to medical care. When the data was stratified by age group, sex and insurance status, the majority of the OFCs (30.3%) were performed on non-medicaid males in the age group 0–5 years (Table 1a). Out of the 641 challenges, 188 (29%) were designated as patient is allergic to the challenge food, and the rest were non-allergic (Fig. 2). A majority of the patients tested (76%) were Non-Hispanic and Caucasian (Table 1b). The most common food allergens tested by OFC were peanut (32%), egg (29%), and milk (13%) followed by soy and mixed nuts (4% each). These foods accounted for 82% of the OFCs performed. The remainder were OFCs to individual tree nuts, fruits, wheat, fish, shellfish, sunflower, sesame, oats, poultry, coconut, beef, pork, peas, orange, corn, and chocolate (Table 2). Analysis of median specific IgE level (most recent value collected up to 1 year prior to OFC) of peanut, egg, and milk showed that median specific IgE associated with allergic OFC outcomes in all 3 food allergens was higher than that associated with non-allergic outcomes, though only the data for peanut and egg were statistically significant (Table 3).

A logistic regression model was built to determine if age at OFC, insurance type, food specific serum IgE values, and symptoms occurring at the OFC, had a significant effect on OFC outcome. A backward elimination selection method was

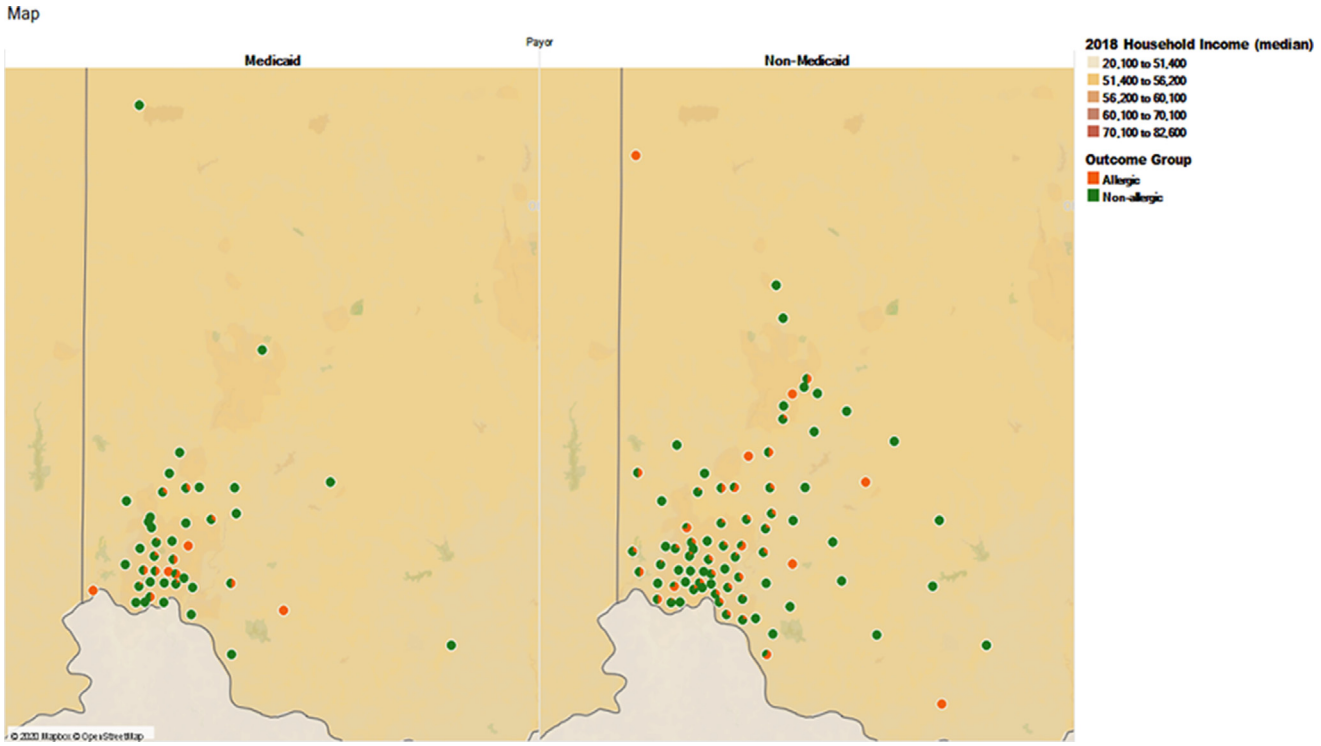

Fig. 1 Map of zip codes of patients who had OFCs divided by insurance type: Medicaid and non-Medicaid

Age Group	Gender	Insurance Type	Number of OFCs	% OFCs	Median age in years	Inter-Quartile range
0–5yrs	Female	Medicaid	34	5.3%	4	2–5
		Non-Medicaid	75	11.7%	3	2–5
	Male	Medicaid	36	5.6%	3	2–4
		Non-Medicaid	194	30.3%	3	2–4
6–10 yrs	Female	Medicaid	21	3.3%	8	6–9
		Non-Medicaid	69	10.8%	7	6–8
	Male	Medicaid	23	3.6%	7	7–7
		Non-Medicaid	101	15.8%	8	6–9
11–15 yrs	Female	Medicaid	3	0.5%	11	11–12
		Non-Medicaid	16	2.5%	13.5	11.5–15
	Male	Medicaid	10	1.6%	12.5	11–14
		Non-Medicaid	38	5.9%	13	12–14
16 & Above	Female	Medicaid	2	0.3%	17.5	17–18
		Non-Medicaid	6	0.9%	18	16–18
	Male	Medicaid	5	0.8%	18	17–18
		Non-Medicaid	8	1.2%	17.5	16–18

Table 1a. Number of oral food challenges stratified by age, sex and insurance type

deployed to remove factors that were not significant. The following symptoms were found to have a significant effect on OFC outcome: erythematous rash ($P < 0.0001$), pruritis ($P = 0.0003$), urticaria/angioedema ($P < 0.0001$), rhinorrhea ($P = 0.003$), cough ($P < 0.0049$), nausea ($P < 0.0049$), vomiting ($P < 0.0006$), or other complaints ($P < 0.0001$). A frequency distribution of the symptoms that are associated with OFC outcomes are listed in Table 4.

Age at the time of OFC and food specific serum IgE values were non-significant and consequently removed from the final model.

The Chi-square results showed no significant relationship between OFCs outcomes i.e. allergic ($p = 0.40$) and non-allergic ($p = 0.74$) and age, sex, and insurance status.

DISCUSSION

In this study, conducted to examine patient factors that may impact the outcome of OFCs, 508 children underwent 641 OFCs. Twenty nine percent of OFCs had an allergic outcome with the most commonly challenged foods being peanuts, eggs, and milk.

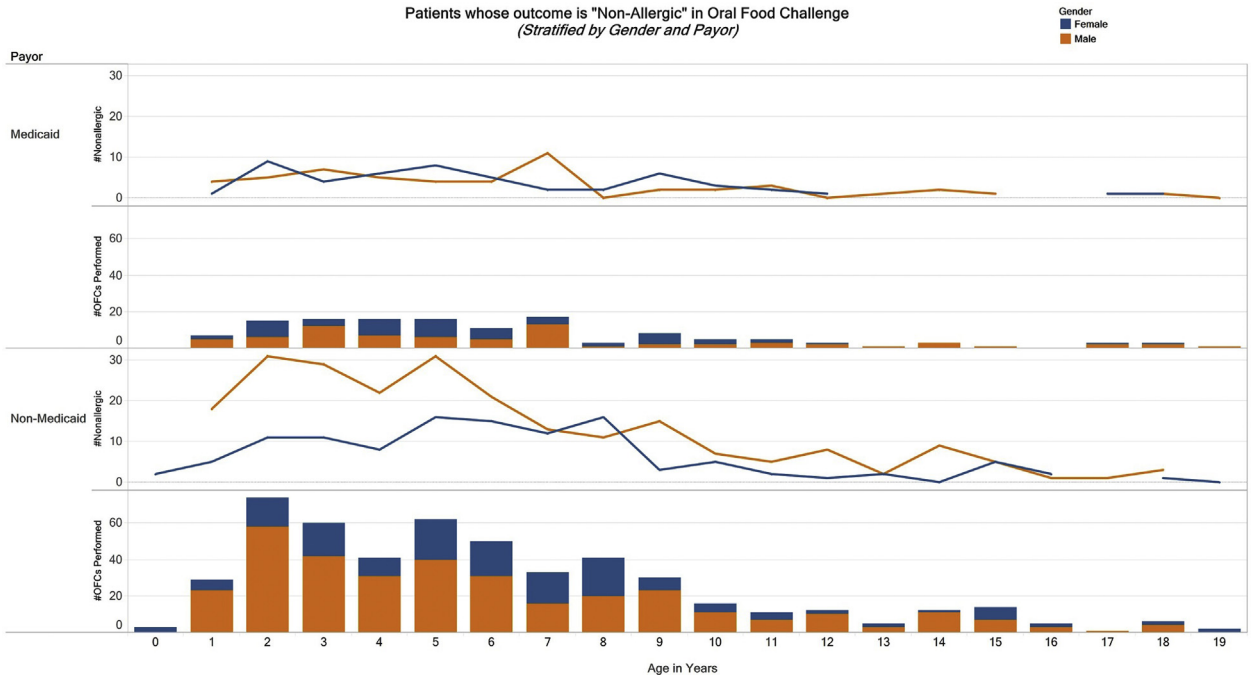

Fig. 2 Outcome of food challenges as non-allergic by age, sex and insurance type as Medicaid or non-Medicaid

Patient age and sex, when stratified by insurance status, did not have a significant effect on OFC outcomes. Serum IgE to peanuts and egg was significantly different between allergic OFC and non-allergic outcome. Vomiting and urticaria/angioedema correlated with an allergic OFC outcome.

This study was conducted in an academic center that serves a mix of Medicaid and non-Medicaid insured pediatric populations. The center is unique in the community in its ability to service Medicaid insured populations. By the same token this study is unique in examining the effect of insurance type on the result of OFC. Medicaid insurance is more common in the inner city population, which was demonstrated in the results where the challenges for the Medicaid population were from the area surrounding the medical

Ethnicity	Race	Number of OFCs (n)	Percent of all OFCs
Hispanic	White or Caucasian	5	0.8%
	Other	22	3.4%
	Asian	1	2.0%
Non-Hispanic	White or Caucasian	487	76.1%
	Black or African American	82	12.8%
	Other	12	1.9%
	Asian	20	3.1%
	Unknown	4	0.6%
Unknown	White or Caucasian	3	0.5%
	Other	2	0.3%
	Unknown	2	0.3%

Table 1b. Number of oral food challenges stratified by ethnicity and race *OFC = oral food challenge*

Type of Food	Performed OFC (n)	Percent Allergic
Peanut	200	35%
Egg	181	33%
Milk	81	32%
Mixed nuts	23	39%
Soy	22	14%
Almond	18	6%
Fruit	12	8%
Wheat	11	27%
Fish	10	10%
Walnut	9	56%
Hazelnut	6	0%
Cashew	6	50%
Shellfish	6	0%
Pistachio	6	17%
Pecan	3	33%
Sesame	3	0%
Chicken	3	0%
Sunflower	3	0%
Oat	3	0%
Turkey	2	50%
Coconut	2	0%
Beef	2	0%
Pork	1	0%
Chocolate	1	0%
Brazil Nut	1	0%
Corn	1	0%
Orange	1	0%
Pea	1	0%
Other	23	17%

Table 2. Food allergens tested by an oral food challenge and outcome

center, where people of low socioeconomic status reside, while the non-Medicaid were spread in the suburbs, where people of high socioeconomic status reside. Despite this insurance mix, the majority of the population was non-Hispanic Caucasian, so a difference by race/ethnicity was not noted in the analysis. The race/ethnicity, however, mirrors the population of the county which is 65.2% Caucasian alone, 25.3% African American alone, and 3.27% Hispanic or Latino.[14] The reason for conducting the challenges were clinical indications, which were either to confirm the allergy or to determine whether the food allergy has resolved. In the 641 OFCs on 508 children, ages 0–19 years-old, 29% of OFCs had an allergic outcome with the foods most commonly challenged being peanuts (32% of OFCs performed), eggs (29%), and milk (13%). Our data is similar to prior studies which found egg, milk, and peanut to be among the most commonly challenged foods.[15,16] Spergel et al. did a retrospective chart review of 998 oral food challenges with egg, milk, and peanut accounting for 30%, 27%, and 14% of OFCs performed, respectively.[15] Lieberman et al. performed a retrospective chart review of 701 OFCs and reported peanut, tree nuts, egg, and milk accounting for 18%, 17%, 16%, and 7.8% of OFCs, respectively.[16]

Serum IgE to food allergens has previously been studied for its predictive value in determining outcomes of OFCs. Our data found that the median sIgEs for peanut, egg, and milk are higher in patients with allergic OFC outcomes to the respective foods, compared to patients with non-allergic OFC outcomes, but this was only statistically significant for peanut and eggs. Comparing to other studies, food-specific serum IgE have been shown to predict allergic OFC outcomes, with age of patients acting as a confounding variable in the predicted probabilities between these studies.[17-19] Rolinck-Werninghaus et al. found food specific serum IgE level, young age, and history of eczema were predictors of allergic outcome of OFC to milk and egg.[20] Cortot et al. found skin prick tests, food-specific serum IgE levels, and age were not good predictors of OFC results to baked egg.[21] Cianferoni et al. found that age was not, but food-specific serum IgE and skin prick test wheal size were associated with allergic outcome of OFC.[22] Ahrens et al. found that younger age was a

	% Non-allergic OFC	Median IgE Level in KAU/L, Non-allergic OFCs	Interquartile Range, Non-allergic OFCs	Median IgE level in KAU/L, Allergic OFCs	Interquartile Range, Allergic OFCs	P-Value
Peanut (n = 102)	71%	0.29	0.07–0.96	1.03	0.48–2.85	<0.0001
Egg (n = 141)	67%	0.71	0.27–2.02	2.73	1.2–6.23	<0.0001
Milk (n = 61)	70%	0.83	0.18–4.09	1.46	0.26–5.13	0.092

Table 3. OFC outcome and serum specific IgE levels for peanut, egg, and milk

predictor of an allergic outcome of OFC.[23] Horimukai et al. found that age did not affect OFC outcome.[24]

Looking at adverse symptoms occurring in relation to OFC outcome in our study, patients with vomiting had much greater odds ratio of being diagnosed as allergic to the OFC food (OR = 41.2, 95%CI = 7.0–786.7, P < 0.0006), followed by urticaria/angioedema (OR = 27.4, 95%CI = 12.7–65.0, P < 0.0001). Previous studies have reported cutaneous system complaints being the most common symptom during OFCs.[15,16,25-27] Spergel et al. found cutaneous reactions to be most common during OFCs, followed by multi-organ reactions.[15] Similarly, Ahrens et al. and Mankad et al. reported that the majority of clinical reactions were cutaneous, followed by gastrointestinal symptoms.[25,26] All of these studies found that positive OFCs were mostly to egg and cow's milk. Likewise, Lieberman et al. reported that cutaneous reactions were the most common during OFCs, and cow's milk was the most common food to be associated with an allergic OFC result.[16] Yanagida et al. and Gupta et al. retrospectively evaluated 393 and 2304 OFCs, respectively.[28,29] Similar to our results, they found that gastrointestinal symptoms were the most common OFC-provoked reaction. This may be a reflection of peanut and egg being the most commonly challenged foods in our study, which differs from other OFC studies where cow's milk and egg are challenged more frequently. Recent studies have shown the development of gastrointestinal symptoms more likely in OFC with egg and peanut compared to OFC with cow's milk, soy and wheat.[25,29]

Symptom	Allergic (n = 188)	Non-Allergic (n = 453)
Vomiting	11% (n = 20)	0.2% (n = 1)
Urticaria/ Angioedema	51% (n = 96)	8% (n = 36)
Nausea	10% (n = 18)	1% (n = 4)
Cough	8% (n = 15)	1% (n = 6)
Erythematous rash	38% (n = 71)	11% (n = 48)
Rhinorrhea	16% (n = 30)	2% (n = 9)
Pruritis	30% (n = 56)	6% (n = 27)
Other Complaints	30% (n = 57)	7% (n = 31)

Table 4. Frequency distribution of significant symptoms associated with OFC outcome

Age did not have a significant effect on OFC outcome in our data, similar to previous studies.[21,22,24] Moreover, stratifying OFC outcomes by age, sex, and insurance type did not result in any significant association with outcome of OFC.

This study examined the outcome of OFC as allergic or non-allergic in children based on their serum IgE to the food, but in the context of the patients' age at the time of the OFC, gender, race/ethnicity, and the socio-economic statuses, determined by the patient insurance with Medicaid and non-Medicaid insurances representing low and high socio-economic statuses, respectively. There is a potential limitation in the study. While the various races/ethnicities and socio-economic statuses are all represented in the study population, the patient population who attend our clinics are skewed towards a majority Caucasian, non-Hispanic, and high socio-economic status. This may have impacted the analysis showing no association of these factors with the outcome of OFC. The serum IgE continued to be associated with the

outcome of OFC, specifically for peanut and egg. Future studies should recruit minority populations with low socio-economic status.

In conclusion, our study found that: 1) out of 641 OFCs, 29% of OFCs had an allergic outcome; 2) the most commonly challenged foods were peanuts, eggs, and milk; 3) higher median sIgE for peanut and egg was associated with allergic OFC outcome; 4) vomiting and urticaria/angioedema were highly associated with allergic OFC outcome; and 5) Age, sex, and insurance type were not associated with OFC outcome.

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Declaration of Competing Interest

I, Andrew Dang, do not have any conflicts of interest to disclose.
I, Pavan Chundi, do not have any conflicts of interest to disclose.
I, Nadeem Mousa, do not have any conflict of interest to disclose.
I, Amanda Beyer, do not have any conflicts of interest to disclose.
I, Somboon Chansakulporn, do not have any conflicts of interest to disclose.
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I, Tesfaye B. Mersha, do not have any conflicts of interest to disclose.
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