

Oral food challenge failures among foods restricted because of atopic dermatitis



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ABSTRACT

Background: Recent studies have suggested that removing foods from the diet to manage atopic dermatitis (AD), based on positive allergy test results, may lead to immediate allergic reactions on reintroduction of that food.

Objective: To examine the frequency of oral food challenge (OFC) failures among foods removed from the diet as suspected AD triggers, focusing on the 5 major food allergens in the United States.

Methods: OFCs to egg, milk, peanut, soy, and wheat, performed from 2008 to 2014, at a children's hospital's allergy clinics, were reviewed. OFCs were offered based on history and laboratory values. Reasons for food avoidance were classified as food allergy (IgE-mediated reaction occurring within 2 hours); sensitization only (lack of introduction because of positive test results); and removal because of test results during AD evaluation.

Results: There were 442 OFCs performed, with 89 failures (20.1%). Reasons for OFCs included a history of food allergy (320 of 442 [72.4%]), food sensitization without any introduction (77 of 442 [17.4%]), and AD (45 of 442 [10.2%]). OFC failures among those who had food allergy (70 of 320 [21.9%]), sensitization only (13 of 77 [16.9%]), and suspected AD trigger (6 of 45 [13.3%]) did not significantly differ ($P = .63$). Wheat was more likely to be avoided than the other 4 foods for AD concerns ($P < .001$).

Conclusion: The frequency of OFC failure among those who removed foods suspected as AD triggers was 13.3%, indicating a loss of tolerance. Restriction of foods to manage AD must be done with caution and close monitoring.

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Introduction

Common reasons for food avoidance include a history of IgE-mediated allergic reactions to a food; positive skin prick test (SPT) results and/or specific IgE (sIgE) test results to a food, without any exposure to the food (sensitization without introduction); and removal of a food from the diet because positive SPT and/or sIgE test results found during an evaluation for atopic dermatitis (AD).^{1–4} AD affects 10% to 30% of children in industrialized countries.⁴ Up to 40% of children with moderate to severe AD have been reported to have an IgE-mediated food allergy.¹ Food-triggered AD is defined as having a positive SPT and/or sIgE test result to a food, in addition to a clinical history of worsened AD on introduction of the food, and improved AD on removal of the food.^{5,6} Patients with AD have rates of sensitization to foods that range from

30% to 80%.^{7–9} Accordingly, both SPT and sIgE tests can have low positive predictive values in determining culprit foods as AD triggers.^{7,10}

Evaluating the role of food sensitization in contributing to AD often relies on parental report. Pruritus, excoriations, and/or increased eczematous patches hours to days after consumption of a particular food have been reported as signs of food-triggered AD.^{11,12} The Expert Panel, from the 2010 National Institute of Allergy and Infectious Diseases guidelines regarding food allergy, discussed the lack of high-quality evidence to support elimination diets in the management of AD. Aggressive skin care should be pursued before elimination diets.¹ Determining whether a food actually triggers AD requires monitoring and reassessment of the skin 4 to 6 weeks after diet changes have been implemented.¹³

Negative consequences of prolonged elimination diets include impaired quality of life, nutritional deficiencies, increased financial costs, and loss of tolerance to the avoided food.^{2,13–15} Oral tolerance has been defined as a state of active nonresponsiveness to ingested antigens, resulting from multiple factors, including frequency and forms of exposure.^{16,17} Loss of tolerance has not been extensively studied among children who undergo diet restriction for AD.

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In one case series, 11 children developed acute allergic reactions to cow's milk after eliminating it from their diet to help control AD. The AD did not improve, and the children developed reactions, ranging from hives to anaphylaxis.¹⁸ A fatal reaction to milk after an elimination diet to treat AD has been reported.¹⁹ In another study, nearly 19% of children with no history of immediate reactions who pursued an elimination diet to treat AD based on positive SPT and/or sIgE test results developed new, immediate food allergic reactions. Parental reports of reactions that occurred outside a medical setting and documentation of OFCs were both used to analyze reactions. Many different food reactions were reported but 18.3% were to foods than had been consumed before elimination without immediate allergic reactions.²

The purpose of this study was to examine the frequency of office-based OFC failures to foods that had been consumed without immediate reaction, before diet elimination to treat AD, based on positive SPT and/or sIgE test results. Prior studies on this type of loss of tolerance have used self-report and OFCs from multiple settings. This study involved OFCs performed at one pediatric allergy program. This study focused on egg, milk, peanut, soy, and wheat because they are the most common food allergens in the United States.¹ As comparisons for the rate of failure in the AD group, we also assessed the OFC failure rate among children who had OFCs with a history of food allergy and sensitization only without any exposure.

Methods

OFCs performed at the allergy clinics of Riley Hospital for Children at Indiana University Health, in Indianapolis and Carmel, Indiana, from 2008 to 2014 were analyzed through retrospective medical record review. Plain and extensively heated milk OFCs were grouped together, as were plain and extensively heated egg OFCs. The institutional review board considered this study to be exempt from review.

Three board-certified allergists (K.K., F.L., G.V.) conducted all the histories, examinations, laboratory studies, and OFCs. Coexisting conditions of allergic rhinitis, asthma, and other food allergy were based on physician diagnosis, most often by clinical history. Regarding asthma, pulmonary function tests were conducted depending on the child's age. Other food allergies were diagnosed using criteria of history, skin testing, and sIgE studies as indicated. SPTs were performed using Greer (Lenoir, North Carolina) extracts, using the Greer pick. The tests were placed on the child's back, and the results read after 15 minutes. A positive skin test result was defined as having a skin prick test response more than 3 mm bigger than the negative control. Wheal diameter was not measured for most patients during the time frame of this review. OFCs were conducted with the same

standardized protocols for each food.⁹ OFCs were offered if the child had not had an overt clinical reaction to the food in the previous 12 months and had sIgE levels that suggested a reasonable probability of passing the OFC based on 95% positive predictive values.²⁰ OFCs to extensively heated foods were offered regardless of sIgE levels. Ten OFCs were offered at higher sIgE levels because of suspected, tolerated exposures. Total IgE levels were not measured on most patients and are not reported.

Reasons for food avoidance were classified into 3 groups: (1) food allergy, (2) sensitization without introduction, and (3) removal from the diet because of positive SPT and/or sIgE test results found during AD evaluations. Food allergy was defined as the development of typical signs and symptoms of an allergic reaction—hives, vomiting, and respiratory changes—within 2 hours of ingestion, with supporting SPT or sIgE data.^{1,9} The sensitization group consisted of those who had never been introduced to a food item because of positive SPT and/or sIgE results found during evaluations for AD or other food allergies. Children in the food allergy and sensitization categories had seen both Riley Hospital and outside practitioners for their initial assessments.

Children in the AD group were all known to have consumed the food without any reactions within 2 hours but then removed the food from the diet because of SPT and/or sIgE test results found during AD evaluations. All the families who had removed foods for AD purposes had done so based on evaluations by outside practitioners before visits to the Riley Hospital allergy clinics. Reasons for avoidance were documented in the medical record during the initial clinic visit and at the time of the OFC.

Data were analyzed by SAS statistical software, version 9.4 (SAS Institute Inc, Cary, North Carolina). Analyses were performed and *P* values determined with Wilcoxon nonparametric tests for continuous variables and the Fisher exact test for categorical variables.

Results

A total of 452 OFCs to egg, milk, peanut, soy, and wheat were completed from 2008 to 2014 in the Riley Hospital allergy clinics. Ten of the OFCs were excluded from this study because they were missing the reason for food avoidance, leaving 442 OFCs for the final analysis. Table 1 gives the clinical and laboratory background of patients in relation to the reason for food avoidance. OFCs were most commonly performed because of a history of food allergy (320 of 442 [72.4%]), followed by sensitization (77 of 442 [17.4%]) and then AD (45 of 442 [10.2%]). There were no significant differences among these 3 groups regarding age at time of OFC, sex, race, history of asthma and allergic rhinitis, and SPT status. SPTs were performed within a year of the OFC

Table 1
Clinical and Laboratory Characteristics of Patients in Relation to Reason for Food Avoidance^a

Characteristic	Overall (N = 442)	Food allergy (n = 320 [72.4%])	Sensitization only (n = 77 [17.4%])	Atopic dermatitis (n = 45 [10.2%])	<i>P</i> value ^b
Age at OFC, median (range), y	5 (0.9–16)	5 (0.9–16)	5 (1–15)	4 (1–14)	.39
Female	144 (32.6)	106 (33.1)	28 (36.4)	10 (22.2)	.25
Race					
White	257 (81.7)	257 (81.6)	67 (87.0)	33 (73.3)	.36
Black	40 (9.2)	29 (9.2)	4 (5.2)	7 (15.6)	
Other (Asian, biracial)	40 (9.2)	29 (9.2)	6 (7.8)	5 (11.1)	
Medicaid	73 (16.5)	57 (17.8)	4 (5.2)	12 (26.7)	.004
Asthma	164 (37.1)	119 (37.2)	27 (35.1)	18 (40.0)	.86
Atopic dermatitis	230 (52.0)	141 (44.1)	48 (62.3)	45 (100.0)	<.001
Allergic rhinitis	113 (25.6)	80 (25.1)	20 (26.0)	13 (28.9)	.86
Other food allergy	204 (46.2)	126 (39.4)	53 (68.8)	25 (55.6)	<.001
Positive SPT result	197 (44.6)	135 (42.2)	40 (52.0)	22 (48.9)	.25

Abbreviations: OFC, oral food challenge; SPT, skin prick test.

^aData are presented as number (percentage) of participants unless otherwise indicated.

^b*P* values are from Wilcoxon rank-sum tests and χ^2 tests.

Table 2
Demographic Characteristics of Patients Undergoing OFCs^a

Characteristic	Overall (N = 442)	Failed OFCs (n = 89 [20.1%])	Passed OFCs (n = 353 [79.9%])	P value ^b
Age, median (range), y	5 (0.9–16)	5 (1–14)	5 (0.9–16)	.14
Female	144 (32.6)	29 (32.6)	115 (32.6)	.99
Race				
White	257 (81.7)	75 (87.2)	282 (80.3)	.12
Black	40 (9.2)	8 (9.3)	32 (9.1)	
Other	40 (9.2)	3 (3.5)	37 (10.5)	
Medicaid	73 (16.5)	9 (10.1)	64 (18.1)	.07
Asthma	164 (37.1)	36 (40.5)	128 (36.3)	.46
Atopic dermatitis	230 (52.0)	40 (44.9)	190 (53.8)	.13
Allergic rhinitis	113 (25.6)	22 (24.7)	91 (25.9)	.83
Other food allergy	204 (46.2)	35 (39.3)	169 (47.9)	.15

Abbreviation: OFC, oral food challenge.

^aData are presented as number (percentage) of participants unless otherwise indicated.^bP values are from Wilcoxon rank-sum tests and χ^2 tests. There were no significant differences between those who passed and those who failed OFCs.**Table 3**
Reasons for Food Avoidance in Relation to Specific IgE Levels Among Individual Foods

Food	Specific IgE, median (range), Ku/L			P value ^a
	Food allergy (n = 320)	Sensitization only (n = 77)	Atopic dermatitis (n = 45)	
Egg ^b	0.38 (0–57.5)	0.41 (0–90.8)	0.64 (0–49.9)	.03
Milk	0.38 (0–93.1)	0.58 (0.58–0.58)	0 (0–10.6)	.54
Peanut	0 (0–7.9)	0 (0–16.3)	0 (0–0)	.26
Soy	1.01 (0–13.6)	2.6 (1.9–3.4)	13.3 (2.1–21.4)	.14
Wheat	2.18 (0–39.9)	1.9 (1.9–1.9)	1.11 (0–67)	.93

^aP values are from Wilcoxon rank-sum tests and χ^2 tests.^bMedian egg IgE was significantly higher in those who had oral food challenges for egg with a history of atopic dermatitis.

in 95.7% of egg OFCs, 94.5% of milk OFCs, 97.8% of peanut OFCs, 78.6% of soy OFCs, and 85.7% of wheat OFCs. The percentage of positive SPT results to the food did not significantly differ among the reasons for food avoidance. Specific IgE studies were performed within a year of the OFC on nearly all study participants. The AD group was significantly more likely to have AD ($P < .001$) and to have Medicaid insurance ($P = .004$) vs the food allergy and sensitization groups.

Overall, the OFC failure rate was 20.1% (Table 2). There were no significant differences among overall demographics and clinical history between OFC successes and failures. Table 3 gives the reasons for food avoidance in relation to sIgE test and SPT results among individual foods. Median egg IgE was significantly higher in those who had OFCs for egg, with a history of AD. Skin test results were significantly less likely to be positive in those who had OFCs to peanut and milk, with a history of AD. There were no other differences among food allergy, sensitization only, and AD with regard to median IgE or SPT result. As noted in Table 1, frequency of positive SPT results did not differ among these 3 groups.

The OFC failure rate for those avoiding a food because of AD was 13.3% ($n = 6/45$) and did not significantly differ from those avoiding foods because of other reasons (Table 4). Of the 6 OFC failures in the AD group, the reactions involved hives or hives with 1 episode of emesis. The failed OFCs involved egg and wheat (Table 5). All reactions resolved with antihistamines. There was no significant difference in the length of time of food avoidance in the AD group between those who passed OFCs (median, 26.5 months; range, 3–120 months) and those who failed (median, 27.0 months; range, 3–100 months) ($P = .97$). There were also no significant differences among the 5 foods in OFC outcome, when AD was the initial reason for avoidance ($P = .87$).

Figure 1 displays the reasons for food avoidance in relation to the individual food. Wheat was significantly more likely to be avoided

Table 4
Reason for Food Avoidance in Relation to OFC Outcome^a

Reason	OFC pass (n = 353 [79.9%])	OFC fail (n = 89 [20.1%])
Food allergic reaction (n = 320 [72.4%])	250 (78.1)	70 (21.9)
Sensitization only (never ingested) (n = 77 [17.4%])	64 (83.1)	13 (16.9)
AD (n = 45 [10.2%])	39 (86.7)	6 (13.3)

Abbreviations: AD, atopic dermatitis; OFC, oral food challenge.

^aReaction history was not associated with OFC outcome ($P = .30$).**Table 5**
OFC Outcome for Foods Avoided as Suspected AD Triggers^a

Foods (n = 45)	Fail (n = 6 [13.3%])	Pass (n = 39 [86.7%])
Egg (n = 24) (plain and extensively heated)	4 (16.7)	20 (83.3)
Milk (n = 9) (plain and extensively heated)	0 (0)	9 (100)
Wheat (n = 6)	2 (33.3)	4 (66.7)
Soy (n = 3)	0 (0)	3 (100)
Peanut (n = 3)	0 (0)	3 (100)

Abbreviations: AD, atopic dermatitis; OFC, oral food challenge.

^aThere was no significant difference among the 5 foods with regard to OFC pass-fail rates, when the initial reason was suspected AD trigger ($P = .33$ [nonsignificant]).

because of AD than the other 4 foods ($P < .001$). Milk was significantly more likely to have been avoided because of an allergic reaction ($P = .002$).

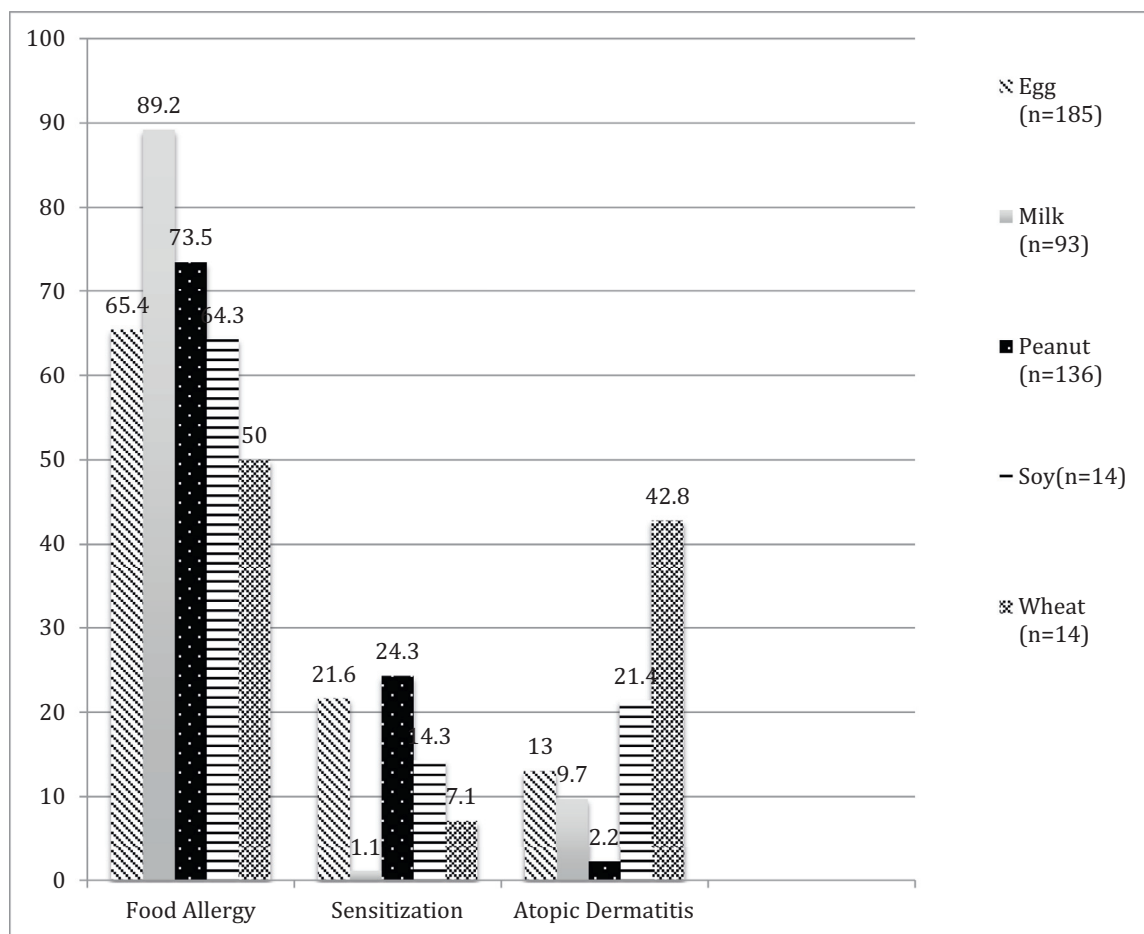


Figure 1. Frequencies of reasons (as percentages) for food avoidance in relation to individual foods. Wheat was significantly more likely to be avoided because of atopic dermatitis ($P < .0001$). Milk was significantly more likely to be avoided because of food allergy ($P < .001$).

Discussion

In this study, 13.3% of children who had a food removed from their diet because of positive SPT and/or sIgE test results, during an AD evaluation, failed OFCs to that specific food. Tolerance to these foods was lost after the food had been withdrawn from the diet and then not reintroduced until the OFC. Tolerance was lost as early as 3 months after withdrawal of a food item for this reason.

The rate of OFC failure did not differ significantly in relation to the reason for food avoidance—food allergy, sensitization only, or AD. Data on the role of foods in contributing to AD have been conflicting. Recent evidence suggests a decreasing role for diet in flares of AD.²¹ The earliest studies on this topic recommended that close monitoring was necessary to assess the effect of food restriction and that diet changes alone could not address AD.²² One recent study that suggested a favorable role for food restriction in AD also emphasized the need for reassessment within 3 weeks of implementing diet changes to address the skin changes and decide whether restriction should continue and in what manner.²³

For the general public, food-triggered AD remains a poorly defined entity. Increased itching and changes in rashes, with varying timelines, are often attributed to foods. Many of these changes rely on parent report. Families often have difficulty differentiating causality and coincidence. Changes in skin care are often implemented at the same time as diet changes, creating uncertainties in assessing the effect of food restriction alone.^{11,12} AD is a multifactorial disease, involving skin inflammation, barrier dysfunction, infection, and other atopic

conditions. Adjunctive therapies will need to be used, regardless of any diet changes implemented.²⁴

The concept of sensitization to a food vs actual allergy continues to create challenges in the implementation of food allergy guidelines.³ This study adds to the evidence that SPT and sIgE test results detected in patients with AD are often clinically irrelevant.^{7,8} Wheat was restricted for AD significantly more than other foods. Wheat avoidance negatively affects the quality of life of children and families.²⁵ Many of the OFCs that were performed may have been avoided if patients had timely visits to monitor the significance of their diet changes.

Strengths of this study include the large number of overall OFCs performed. This study is the first, to our knowledge, to use in-office OFCs to assess loss of tolerance because of dietary avoidance for AD based on positive SPT and/or sIgE test results. All OFCs were performed at 1 institution by 3 practitioners using the same protocol, improving the reliability of the findings. All OFC results are based on clinical observation and documentation, and none rely on parental report. We also focused on the 5 most common food allergens in the United States. Another study on this issue used parental report and OFCs to assess loss of tolerance.²

Limitations include the small numbers of patients who had diet restriction because of AD vs other causes for food avoidance. We also rely on parental recall as to the initial reasons for avoidance. We lack objective data on the actual value of diet changes on skin issues, with AD scoring systems, such as Scoring AD (SCORAD) or Eczema Area and Severity Index (EASI). Having such data may help

identify subsets of children who would benefit from diet changes with their skin condition.

In addition, children with AD often have high serum IgE levels.^{26,27} We did not measure total serum IgE on most of our patients. Knowing these values may have helped place some of the sIgE values in better context. We also used stringent sIgE criteria in offering OFCs. On one hand, children may have been excluded who could have passed the OFC, altering the overall results. However, even with sIgE levels that suggested a reasonable probability of OFC success, 13.3% of children in the AD avoidance group failed their OFCs. Wheal diameters were also not analyzed in this study and could have potentially provided further information in assessing OFC outcomes among the 3 groups. However, reviews and studies have suggested that, although there is modest evidence that SPT size may predict which children have a high probability of persistent food allergy, wheal sizes may not predict pass rates for OFCs or severity of reactions.^{20,28,29}

Both AD and food allergies are conditions that adversely affect the quality of life and finances of a family.^{14,15} Children with both AD and food allergy also have lower growth compared with their peers who do not have these issues.³⁰ The consequences of further diet restrictions on growth will need further study. Loss of tolerance to a food once consumed without immediate reactivity must now be considered another risk of removing foods based on testing results in the context of AD, particularly without appropriate follow-up. If such diet changes are implemented, families may also need education on anaphylaxis and use of epinephrine. There was a wide range in length of food avoidance before OFCs, but 1 case of tolerance was lost after only 3 months of restriction.

In conclusion, 13.3% of children who had foods consumed without any immediate reaction but then removed from the diet to address AD based on SPT and sIgE test results failed OFCs, losing tolerance to that food. The OFC failure rate for AD did not differ from the OFC failure rates for food allergy and sensitization. Eliminating these commonly consumed foods significantly affects the quality of life for the child and the family. Primary care practitioners need to counsel families on the limits of allergy testing and diet changes in addressing AD. Families should be advised to consistently use measures of skin hydration, emollients, and topical medications to address AD. Any diet changes that are pursued to manage AD must be made with extreme caution. The risks of IgE-mediated allergic reactions on food reintroduction may outweigh the value of food elimination on AD management. Families and practitioners need to be aware of the risks of excessive testing and diet manipulation in trying to manage AD, including loss of tolerance.

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