Pediatric oral food challenges in the outpatient setting: A single-center experience

Nicole Koutlas, MD,[a] Amy Stallings, MD,[a] Geoffrey Hall, DO,[a] Cynthia Zhou, MD,[b] Julie Kim-Chang, MD,[a] and Talal Mousallem, MD[a] *Durham, NC*

Background: Oral food challenge (OFC) is the criterion standard for diagnosing food allergy (FA). It is important to have parameters to aid in selecting ideal OFC candidates.
Objective: We sought to characterize outcomes and predictors of OFCs for common food allergens.
Methods: We completed a retrospective chart review of all OFCs for IgE-mediated FA performed at Duke University pediatric allergy clinics from June 2017 through May 2022. Patients were deemed eligible for milk, egg, and nut OFC if testing revealed a specific IgE level not exceeding 2 kU/L and a skin prick test (SPT) resulting in a wheal size not exceeding 5 mm. Different parameters were followed for selecting candidates for baked challenge.
Results: A total of 663 OFCs were conducted on 510 patients (59% male). The most common foods challenged were peanut (26%), plain egg (23%), baked egg (8%), and milk (8%), with pass rates of 84%, 88%, 62%, and 84%, respectively. Of the patients who failed OFC, 84% had objective symptoms, 23% had multisystemic reactions, and 15% required epinephrine. Although the presence of a personal or family history of atopy or prior failed OFC was not associated with outcomes, a history of anaphylaxis (regardless of the trigger) was associated with increased risk of failure.
Conclusion: Although there are no established consensus guidelines, our study provides a benchmark illustrating that cutoffs of a specific IgE level not exceeding 2 kU/L and SPT finding not exceeding 5 mm result in a failure rate of approximately 13% for nonbaked milk, nonbaked egg, and nuts. The high rate of failed baked egg OFCs is likely related to selection bias, but our results illustrate the low negative predictive value of ovomucoid. (J Allergy Clin Immunol Global 2024;3:100187.)

Key words: *Food allergy, oral food challenge, milk allergy, egg allergy, peanut allergy, anaphylaxis, ovomucoid, skin prick testing, specific IgE, component testing*

Abbreviations used
Ara h: *Arapis hypogaea*
EHR: Electronic health record
FA: Food allergy
FPIES: Food protein–induced enterocolitis
OFC: Oral food challenge
QOL: Quality of life
sIgE: Specific IgE
SPT: Skin prick testing

Food allergy (FA) prevalence in the United States is between 2% and 10%.[1] There is a much higher prevalence of self-reported FA, with 1 study showing a caregiver-reported FA prevalence of 11.4% compared with an estimated true FA prevalence of 7.6% based on convincing reaction history.[2] The US Food and Drug Administration's National Electronic Injury Surveillance System estimates that FA results in 125,000 emergency department visits and more than 3,000 hospital admissions annually.[3] Although FA-related morbidity is significant, the fatality rate is low, with a recent systematic review suggesting an incidence of 1.8 per million person years of food-induced fatal anaphylaxis.[4]

FA poses a significant economic burden.[5] The overall estimated cost of FA in the United States is around $24 billion annually, with most of this financial burden being costs incurred by patients and families.[6]

FA can have a dramatic impact on the quality of life (QOL) of patients and their families. Multiple food allergies and prior reactions requiring parents to administer epinephrine autoinjectors have been associated with lower QOL scores.[7,8] Additionally, QOL is lower for those with more difficult-to-avoid food allergens such as milk and egg.[8]

The natural history of FA varies, but many of the common allergens (ie, milk, egg, wheat, and soy) are frequently outgrown, with more than 50% of children becoming tolerant before their teen years.[1] Identifying patients who are, or have become, tolerant aids in reducing the burden of FA on patients, families, health care, and society. Although double-blind placebo-controlled food challenge remains the criterion standard for diagnosis of FA, it is rarely used in clinical practice because of the increased time and cost associated with blinding procedures.[9] Instead, unblinded oral food challenges (OFCs) have become common practice. During this procedure, a suspected allergenic food is consumed in gradually increasing amounts under medical supervision to accurately diagnose or rule out a FA. It can confirm an allergy when the testing results and/or history are indeterminate, or demonstrate tolerance to food when patients have outgrown their allergy. However, OFCs are costly and time-intensive, and they carry the risk of systemic reactions. Therefore, it is important to use various parameters to help determine the ideal candidates for OFC.

From [a]the Department of Pediatrics, Division of Allergy and Immunology, and [b]the Department of Pediatrics, Duke University Medical Center, Durham.
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Corresponding author: Talal Mousallem, MD, Duke University Medical Center, Box 2644, Durham, NC 27710. E-mail: talal.mousallem@duke.edu.

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Currently available diagnostic tests, including skin prick testing (SPT), measurement of levels of specific IgE (sIgE) to food and component sIgE levels, help guide clinical decision making. Positive and negative predictive values have been published for levels of sIgE to common food allergens and SPT results, which have helped guide clinicians.[10-15] However, there are no clear guidelines to determine who should undergo an OFC. Individual allergists or academic institutions may use different cutoff values for sIgE level and SPT result, in part because of different resource availability. Certain foods such as peanut and cashew, multiple FAs, and a history of atopic dermatitis have all been associated with higher rates of OFC failure.[16,17] There may also be additional underrecognized factors that help predict which patients will pass an OFC. We sought to evaluate the outcomes and predictors of recent OFCs performed in our tertiary care, single-center population.

METHODS

A retrospective chart review was performed on all standard-of-care OFCs conducted at Duke University Medical Center Pediatric Allergy and Immunology Clinics between June 1, 2017, and May 30, 2022. This study was evaluated by the Duke Institutional Review Board (Pro00111020) and determined to be exempt. OFCs were identified on the basis of Current Procedural Terminology billing code for ingestion challenge. OFCs for food protein–induced enterocolitis (FPIES) were excluded. OFCs were offered to patients by their allergy provider on the basis of clinical history and results of SPT and/or measurement of sIgE level (ImmunoCAP [Thermo Fisher Scientific, Waltham, Mass]). SPT was performed using commercial extracts (Greer Laboratories [Lenoir, NC]) and the Greer prick, with wheal diameter measured at 15 minutes. All patients had appropriate positive (histamine) and negative (saline) controls, with a positive test result defined as a mean wheal diameter 3 mm larger than that of the negative control. For egg-specific testing, either egg or egg white SPT or sIgE were utilized. Strict institutional and divisional cutoff values were not established to qualify for OFC. In general, patients were offered OFC if the food-specific SPT wheal diameter was no larger than 5 mm and the sIgE level was no greater than 2 kU/L for milk, egg, peanut, and tree nuts. All challenges were voluntary on the part of the parent and/or patient. Informed consent was obtained before every challenge, and all OFCs were unblinded.

The food was administered in incremental doubling doses every 15 to 30 minutes at the discretion of the clinic provider until a full, age-appropriate serving had been ingested. OFCs were terminated and considered failed if the patient developed objective symptoms consistent with an IgE-mediated reaction (eg, urticaria, wheezing, or emesis) or worrisome subjective symptoms, such as excessive oropharyngeal pruritus or abdominal pain. In cases where the patient and/or parent refused to continue the challenge in the absence of symptoms, results were considered indeterminate. All patients were observed for at least 1 hour following ingestion of the final portion of food. If there was evidence of an adverse reaction, patients were observed for a minimum of 1 hour from onset of the reaction and until symptoms resolved.

Data were collected and managed by using REDCap electronic data capture tools hosted at Duke University.[18,19] Statistical analysis was performed using JMP Pro 17. The Pearson chi-square or Fisher exact test were used for categoric variables. The Kruskal-Wallis test was used to compare continuous distributions between groups. Statistical significance was set to a P value less than .05.

RESULTS

Between June 2017 and May 2022, a total of 663 food challenges were performed on 510 patients with a possible IgE-mediated FA. There was a slight male predominance (59.4%). Race and ethnicity were self-reported within the electronic health record (EHR) as independent variables, with the majority of participants being White (64%) and non-Hispanic (88%) (Table I). The median age was 4 years (range 7 months-21 years).

Table II lists the challenged foods and their failure rates. Peanut was the most commonly challenged food (26%), followed by plain egg (23%), baked egg (8%), and milk (8%). The top 9 allergens (peanut, tree nuts, milk, egg, shellfish, fish, wheat, soy, and sesame) accounted for 90% of all OFCs.

The overall failure rate for all OFCs was 12.5%. A significant difference in the food-specific failure rate was observed. Baked egg had a significantly higher failure rate (27%) than plain egg (9.2%), peanut (14%), or milk (13%) ($P = .004$). The majority of patients undergoing a peanut (90%), plain egg (95%), or plain milk (88%) challenge met the criteria of sIgE level not exceeding 2 kU/L and SPT result not exceeding 5 mm. Although higher failure rates existed for those with an SPT result greater than 5 mm, excluding outliers resulted in minimal difference in group failure rates (Table III). Age had no significant association with the OFC outcome; however, some allergen-specific trends were appreciated. Peanut had a lower failure rate in those younger than 2 years (8% vs 16.5% [$P = .12$]), whereas plain and baked egg OFCs had a higher failure rate in those younger than 2 years (24% vs 12% [$P = .051$]). Around 4% of OFCs were classified as inconclusive because patients were unable to consume an age-appropriate serving. The majority of inconclusive OFCs were in children aged 2 years or younger (56%) and plain or baked egg challenges (50%).

The symptoms reported during failed OFCs and treatments are outlined in Table IV. Cutaneous manifestations were most common, occurring in 60% to 83.3% of cases depending on the food. There was no statistical difference in the rates of cutaneous (eg, urticaria, angioedema), respiratory (eg, cough, wheezing), or oculonasal reactions (eg, rhinorrhea, sneezing, conjunctivitis, ocular pruritus) among challenges for different foods. However, there were more gastrointestinal reactions (eg, emesis, diarrhea) in baked egg challenges than in the challenges to other allergens ($P < .001$). Two of those included delayed repetitive emesis that was concerning for FPIES. Multisystemic reactions, including anaphylaxis, were rare overall, occurring on average in 23% of failed challenges and less than 5% of all challenges (Tables IV and V). However, the rates of serious reactions in the failed challenges varied, with baked egg having a significantly higher rate (33%) than plain egg (21%), peanut (24%), or milk (0%) ($P = .03$). A smaller proportion of challenges required epinephrine, similarly with the highest rates occurring with baked egg challenges (5%), compared with in the plain egg (1%), peanut (2%), or milk (0%) challenges, although not statistically significant ($P = .18$). Following a failed peanut challenge, 1 patient developed anaphylaxis requiring treatment with epinephrine and was admitted to the hospital for observation. The majority of adverse reactions occurring during OFCs were managed with antihistamines only.

Associations between OFC outcome and patient's history were assessed for peanut, egg, and milk (Table VI). A history of

TABLE I. Study population demographics

Characteristic	Value
Overall sample size, N	510
Male, no. (%)	303 (59%)
Race, no. (%)	
Asian	29 (6%)
Black	82 (16%)
White	325 (64%)
≥2 races	13 (2%)
Other	46 (9%)
Unknown	15 (3%)
Ethnicity, no. (%)	
Hispanic	40 (8%)
Non-Hispanic	452 (89%)
Unknown	17 (3%)

Other includes American Indian, Pacific Islander, and those who self-identified as "other."

anaphylaxis, regardless of the trigger, was correlated with a higher failure rate than in those without a history of anaphylaxis (22% vs 11.6% [$P = .01$]; odds ratio = 2.14 [95% CI = 1.21-3.80]). Furthermore, 40% of the patients who failed OFC had a history of any anaphylaxis compared with 23.7% of those who passed ($P = .01$).

Peanut challenges

A total of 173 peanut challenges were completed in 169 patients. The median patient age at the time of challenge was 3 years (range 8 months–19 years). The OFC failure rates were 14% for all subjects and 12.9% among subjects with an SPT not exceeding 5 mm and sIgE level not exceeding 2 kU/L. The majority of challenges (62%) were performed in patients who had a history of a reaction, whereas the remaining patients were challenged because of a positive testing result in the context of atopic disease. Of the 24 patients who failed a peanut challenge, 23 required treatment (4 of whom were treated with epinephrine). Most of the failed challenges were due to objective symptoms, with 95% having cutaneous involvement (Table IV). Multisystemic reactions were seen in 6 patients (3% of challenges), with 67% of those reactions being rash and rhinorrhea (Tables IV and V). Interestingly, none of the patients who experienced anaphylaxis during the challenge had prior component testing done, as most of them were evaluated before 2020, when component testing was performed less frequently in our clinic.

Peanut SPT was performed before all but 1 challenge (Table VII). SPT size ranged from negative to 12.5 mm. The patient who had an SPT result of 12.5 mm also had birch tree pollen allergy with serum peanut component testing that was positive only for *Arapis hypogaea* (Ara h) 8. The patient failed the challenge because of extensive oral itching that required treatment with antihistamines. All but 7 patients had an sIgE measurement taken before challenge (Table VII), with the result ranging from less than 0.1 kU/L to 32.9 kU/L. Two patients had high levels of peanut sIgE and sensitization predominantly to Ara h 8 or Ara h 9. Both of those patients had an Ara h 2 level less than 0.35 kU/L and passed the challenge. The median peanut SPT results and sIgE levels were not associated with OFC outcome. The median component levels were not significantly associated with the OFC outcome in the 74 patients who had peanut component testing. The highest Ara h 2 value among the patients challenged was 1.33 kU/L.

TABLE II. Outcomes of all OFCs by allergen

Allergen challenged	Total no. of OFCs	No. of failed OFCs (%)
Peanut	173	24 (14%)
Egg		
Plain egg	153	14 (9.2%)
Baked egg	55	15 (27%)
Milk		
Plain milk	48	6 (13%)
Baked milk	8	1 (13%)
Tree nuts		
Cashew*	14	2 (14%)
Pistachio*	8	1 (13%)
Almond	30	0
Walnut	12	2 (17%)
Pecan	9	1 (11%)
Hazelnut	9	1 (11%)
Brazil nut	3	0
Sesame	11	2 (18%)
Shellfish		
Shrimp†	20	1 (5%)
Crab	2	0
Lobster	2	0
Scallop†	1	0
Fish		
Salmon‡	9	0
Tilapia‡	3	0
Flounder	1	0
Trout	1	0
Tuna	1	0
Wheat	11	2 (18%)
Soy	15	3 (20%)
Beef	6	2 (33%)
Fruit (excluding coconut)	21	2 (9.5%)
Legume (excluding peanut)	6	0
Corn	4	1 (25%)
Oat	4	0
Coconut	7	1 (14%)
Other	19	2 (11%)

Other challenges include pork, pine nut, chicken, sunflower, spices, and specific meals that had previously been associated with a reaction. All combined challenges were passed.
*Combined cashew and pistachio challenge.
†Combined shrimp and scallop challenge.
‡Combined salmon and tilapia challenge.

One patient, who had negative SPT and undetectable peanut sIgE level, failed owing to development of urticaria. The patient subsequently showed evidence of sensitization with an SPT result of 3 mm, peanut sIgE level of 0.4 kU/L, and Ara h 2 level of 0.46 kU/L. The patient was rechallenged 2 years later and passed.

Plain egg challenges

Among the 153 plain egg challenges conducted in 149 patients, an overall failure rate of 9.2% was observed compared with 8.3% in those with an SPT not exceeding 5 mm and sIgE level not exceeding 2 kU/L. Their median age was 3 years (range 7 months–18 years). Most of these patients (81%) had a prior reaction to plain egg, with 25% of those having anaphylaxis. The details of adverse reactions (3 multisystemic) and treatments for the 14 patients who failed plain egg OFCs are outlined in Tables IV and V.

TABLE III. Prevalence and outcomes of OFCs using strict cutoffs

Allergen OFC		sIgE level ≤ 2 kU/L and SPT result ≤ 5 mm	sIgE level > 2 kU/L	SPT level > 5 mm	sIgE level > 2 kU/L and SPT result > 5 mm
Peanut	Total, no.	155	4	14	1
	Failed, no. (%)	20 (12.9%)	0	4 (28.6%)	0
Plain egg	Total, no.	145	2	5	0
	Failed, no. (%)	12 (8.3%)	0	2 (40%)	—
Plain milk	Total, no.	42	1	4	0
	Failed, no. (%)	5 (11.9%)	0	1 (25%)	—

TABLE IV. Symptoms experienced during failed peanut, egg, and milk OFCs and treatment administered

Reaction and treatment administered	Peanut (n = 24)	Plain egg (n = 14)	Baked egg (n = 15)	All milk (n = 7)	*P* value
Objective, no. (% failed)	21 (87.5%)	13 (92.9%)	13 (86.7%)	5 (71.4%)	
Cutaneous, no. (% failed)	20 (83.3%)	10 (71.4%)	9 (60%)	5 (71.4%)	.26
Rash	20 (83.3%)	10 (71.4%)	8 (53.3%)	5 (71.4%)	
Angioedema	2 (8.3%)	2 (14.3%)	1 (6.7%)	0	
Gastroenterology, no. (% failed)	2 (8.3%)	1 (7.1%)	7 (46.7%)	0	<.001
Emesis	1 (4.2%)	1 (7.1%)	5 (33.3%)	0	
Respiratory, no. (% failed)	2 (8.3%)	1 (7.1%)	0	0	1.00
Wheezing	1 (4.2%)	0	0	0	
Cough	1 (4.2%)	1 (7.1%)	0	0	
Oculonasal, no. (% failed)	6 (24%)	2 (14.3%)	3 (20%)	0	.16
Rhinorrhea/sneezing	4 (16.7%)	1 (7.1%)	3 (20%)	0	
Ocular	2 (8.3%)	1 (7.1%)	0	0	
Irritable/fussy, no. (% failed)	1 (4.2%)	2 (14.3%)	0	0	
FPIES, no. (% failed)	1 (4.2%)	0	2 (13.3%)	0	
Multisystemic, no. (% failed)	6 (24%)	3 (21.4%)	5 (33.3%)	0	.03
Subjective, no. (% failed)	7 (3 with subjective symptoms only) (12.5%)	6 (1 with subjective symptoms only) (7.1%)	7 (2 with subjective symptoms only) (13.3%)	6 (2 with subjective symptoms only) (28.6%)	.25
Mouth itching	5 (20.8%)	4 (28.6%)	1 (6.7%)	3 (42.9%)	
Skin itching	0	3 (21.4%)	0	1 (14.3%)	
Abdominal pain	2 (8.3%)	1 (7.1%)	4 (26.7%)	1 (14.3%)	
Nausea	0	0	0	1 (14.3%)	
Sensation of swelling	0	1 (7.1%)	0	0	
Other, no. (% failed)	0	0	2 (eye itching, parental anxiety) (13.3%)	1 (eye itching) (14.3%)	
Treatment needed, no. (% failed)	23 (95.8%)	12 (85.7%)	12 (80%)	5 (71.4%)	
Diphenhydramine	22 (91.7%)	12 (85.7%)	12 (80%)	4 (57.1%)	
Epinephrine	4 (16.7%)	2 (14.3%)	3 (20%)	0	.18
IV fluids	3 (12.5%)	0	1 (6.7%)	0	
Albuterol	1 (4.2%)	1 (7.1%)	0	0	
Methylprednisolone	2 (8.3%)	0	0	0	
Ondansetron	1 (4.2%)	0	1 (6.7%)	0	

Oculonasal symptoms include rhinorrhea, sneezing, ocular pruritus, and conjunctivitis.
IV, Intravenous.

Egg SPT and measurement of egg sIgE level were performed before all OFCs, with the exception of 1 patient who did not have serum sIgE testing. The median SPT result and sIgE level were not associated with OFC outcome (Table VII). One patient with a negative egg SPT result and undetectable sIgE level developed urticaria and failed their plain egg challenge.

Baked egg challenges

There was a 62% pass rate in the 55 baked egg challenges performed in 51 patients. Baked egg challenge had the highest failure rate (27%) among all foods challenged. The median patient age at the time of challenge was 2 years (range 9 months-17 years). Although the majority (69%) reported a prior reaction to plain egg, only 15% had previously reacted to baked egg. The majority had never consumed baked egg before OFC; 20% had a history of anaphylaxis to plain egg, but none had a history of anaphylaxis to baked egg. In the 15 patients who failed baked egg challenge, cutaneous symptoms were less common and gastrointestinal symptoms were more common than in those who failed challenges to other foods (Table IV). Two patients failed because of delayed repetitive

TABLE V. Details of patients who experienced multisystemic reactions during OFC

Age (y)	Food	Hx	Reaction	Treatment	SPT (mm [avg])	Time since SPT (mo)	sIgE level (kU/L)	Time since sIgE (m)	Component sIgE level (kU/L)	Cumulative dose consumed before reaction	Hx of any anaphylaxis	Hx of asthma and/or eczema	Family Hx atopy
4	Pecan	No prior reaction, avoided because of other FA	Rash, rhinorrhea/ sneezing	Diphenhydramine	0	3	<0.35	3	NA	1/2 serving	–	+	+
1	Baked egg	No Hx of reaction, positive testing result because of other FA	Angioedema, emesis	Diphenhydramine	8.5	4	3.0	4	Ovomucoid <0.1	Complete serving	+	+	+
4	Egg	Rash	Rash, diarrhea, mouth itching	Diphenhydramine, epinephrine	5	4	0.52	5	Ovomucoid 0.67	1/4 serving	+	+	+
3	Peanut	Anaphylaxis, rash, emesis	Rash, angioedema, rhinorrhea/sneezing, ocular symptoms, irritable	Diphenhydramine, epinephrine	5	4	0.36	5	NA	Complete serving	+	+	+
11	Peanut	No Hx of reaction, positive testing due to other FA	Rash, rhinorrhea/ sneezing	Diphenhydramine	3	2	0.26	2	NA	Complete serving	–	–	+
3	Baked egg	Rash (plain egg)	Rash, rhinorrhea/ sneezing (mild)	None	12	3	4.19	3	Ovomucoid 0.37	1/16 serving	+	+	+
4	Baked egg	Anaphylaxis, rash, emesis (plain egg)	Rash, emesis, abdominal pain	Diphenhydramine, epinephrine	3	1	9.79	1	Ovomucoid 1, ovalbumin 6.01	Complete serving	+	+	+
7	Baked egg	Anaphylaxis, rash, emesis (plain egg) abdominal pain (baked egg)	Emesis, rhinorrhea/ sneezing, abdominal pain	Diphenhydramine	5.5	Same day	1.86	4	Ovomucoid 0.13	Complete serving	+	+	+
14	Egg	Anaphylaxis, rash, angioedema, shortness of breath, emesis, cyanosis, syncope	Rash, difficulty swallowing, sensation of swelling, mouth itching	Diphenhydramine, epinephrine	0	6	0.6	9	Ovomucoid 0.5, ovalbumin 0.39	1/2 serving	+	+	+
1	Baked egg	Emesis (plain egg)	Rash, emesis	Diphenhydramine	4	4	2.28	4	Ovomucoid <0.1, ovalbumin 3.56	Complete serving	–	+	+
3	Peanut	Rash	Rash, rhinorrhea/ sneezing, ocular symptoms	Diphenhydramine	2.5	3	0.29	3	NA	1/2 serving	–	+	+
15	Peanut	Mouth itching	Rash, abdominal pain	Diphenhydramine, epinephrine, IV fluids, methylprednisolone	6	5	1.47	5	NA	1/6 serving	–	+	-
3	Peanut	No Hx of reaction, positive testing due to other FA	Rash, cough, rhinorrhea/ sneezing	Diphenhydramine	4	2	0.24	2	NA	1/12 serving	–	+	+
7	Peanut	Rash	Rash, wheezing, voice change, mouth itching	Diphenhydramine, epinephrine, albuterol, IV fluids, methylprednisolone, admission for observation	0	Same day	0.47	12-24	NA	Complete serving	–	+	+
1	Egg	Anaphylaxis, rash, emesis	Angioedema, cough, ocular symptoms, irritable, pruritus	Diphenhydramine, albuterol	3	Same day	0.27	1	NA	1/4 serving	+	+	+

Plus sign indicates positive history and minus sign indicates negative history.
Hx, History; *NA*, not available.

emesis that was concerning for FPIES. Multisystemic involvement was observed in 5 patients (accounting for 33% of failed challenges and 9% of challenges), and 3 required epinephrine (Tables IV and V).

Egg SPT and egg sIgE measurement were performed before all OFCs, and the results were not predictive of the outcome (Table VII). Ovomucoid level was measured before all challenges except in 3 cases. Ovomucoid sIgE was undetectable in 50% of the failed challenges, including in 2 patients who had anaphylaxis during the challenge. There was no difference in median ovomucoid sIgE level between those who passed OFC and those who failed it. In our cohort, ovomucoid sIgE level with a cutoff of less than 0.1 kU/L had a sensitivity of 53% and negative predictive value of 72%.

Cow's milk (plain and baked) challenges

A total of 56 milk (48 plain and 8 baked) challenges were conducted. The failure rate was 13% in both the plain and baked challenges. Among the plain milk OFCs with an SPT result not exceeding 5 mm and sIgE level not exceeding 2 kU/L, 11.9% were failed. Most patients (75%), had a history of prior reaction to

TABLE VI. Prevalence of possible predictors of peanut, egg, and milk OFC outcomes

Predictor, no. (%)	Prevalence among passed OFCs (n = 359)	Prevalence among failed OFCs (n = 60)	Prevalence among all OFCs (n = 419)	*P* value
History asthma or eczema	287 (79.9%)	52 (86.7%)	339 (80.9%)	.22
Asthma	82 (22.8%)	14 (23.3%)	96 (22.9%)	.92
Eczema	278 (77.4%)	47 (78.3%)	325 (77.6%)	.88
Allergic rhinitis	123 (34.3%)	21 (35.0%)	144 (34.4%)	.91
Family history atopy	249 (69.4%)	44 (73.3%)	293 (69.9%)	.77
History of failed OFC to challenged food	23 (6.4%)	5 (8.3%)	28 (6.7%)	.58
History of any failed OFC	29 (8.1%)	7 (11.7%)	36 (8.6%)	.36
Other food allergies	269 (74.9%)	49 (81.7%)	318 (75.9%)	.26
History of reaction to challenged food	251 (69.9%)	48 (80.0%)	299 (71.4%)	.09
History of anaphylaxis to challenged food	51 (14.2%)	13 (21.7%)	64 (15.3%)	.15
History of any anaphylaxis	85 (23.7%)	24 (40.0%)	109 (26.0%)	.01

Percentage of patients with each predictor, stratified by outcome. Most patients met the criteria for more than 1 possible predictor.

TABLE VII. Food-specific SPT result (wheal size) and sIgE level based on outcome of challenge

	SPT result (mm)					Serum-specific IgE (kU/L)				
	Failed OFC, no.		Passed OFC, no.			Failed OFC, no.		Passed OFC, no.		
Food	Median,	IQR	Median	IQR	*P* value	Median	IQR	Median	IQR	*P* value
Peanut	3.0	1-4.25	2.5	0-4	.08	0.34	<0.1-0.82	0.34	<0.1-0.63	.22
Plain milk	1.25	0-3	2.5	0-3.5	.66	0.44	0.12-1.02	0.34	<0.1-0.99	1.00
Plain egg	3.0	0-4	0.5	0-3	.19	0.395	0.28-0.6	0.34	0.17-0.73	.72
Baked egg (egg)	5.5	4.37-6.37	5.75	2.5-9	.84	2.54	1.9-6.4	2.25	0.59-4.16	.36
Baked egg (ovomucoid)						0.13	<0.1-0.83	<0.1	<0.1-0.58	.74

IQR, Interquartile range.

plain milk, and 7% had a prior reaction to baked milk as well. A history of anaphylaxis to milk was present in 21% of those challenged. There were 7 failed milk challenges in total (6 plain and 1 baked). Urticaria was present in 71% of patients who failed challenges, and with the remaining 29% reporting only subjective oral pruritus. There were no multisystemic reactions, and no reactions required epinephrine (Table IV). Milk SPT result and sIgE level were checked before all plain milk challenges, except one. The results of SPT and sIgE level measurement were not associated with outcome (Table VII).

Tree nut challenges

A total of 85 tree nut challenges were conducted, with almond being the most frequent (35%), followed by cashew (16%) and walnut (14%) (Table II). The cashew and walnut OFCs had pass rates of 86% and 83%, respectively, in contrast to the 100% pass rate for almond and Brazil nut. Among the patients who underwent almond challenge, a minority (17%) had a prior reaction to almond, but most avoided almond because of other coexisting nut allergies. The almond SPT result ranged from 0 to 7 mm, and the sIgE level ranged from less than 0.1 to 1.43 kU/L.

OFCs to other foods

The other food allergens challenged were not as common and were excluded from further analysis given lack of statistical power (Table II). The OFCs to shellfish (mostly shrimp) and finned fish (mostly salmon) were frequently passed. The only failed seafood challenge occurred with shrimp. In contrast, the OFCs to sesame, wheat, and soy had higher failure rates (18%, 18% and 20%, respectively).

DISCUSSION

FA remains prevalent in the pediatric population.[1] It contributes to patient morbidity, affects QOL, and imposes a heavy economic burden in the United States.[5-8] The primary tool available to allergists to alleviate these effects is successful completion of OFCs and reduction of unnecessary food avoidance. Ongoing analysis of observational data is necessary to identify optimal testing and clinical criteria that can be used to risk stratify candidates for OFCs.

Identifying patients with FA who would be ideal candidates for OFCs is complicated by an absence of established consensus guidelines and significant provider and institutional practice variation. Our real-world retrospective study showed an overall failure rate of 13% among patients undergoing milk, egg, and peanut OFCs (12% when baked challenges are excluded). Interestingly, when strict cutoffs of SPT result not exceeding 5 mm and sIgE level not exceeding 2 kU/L are applied, there is a similar failure rate of 11%. We speculate the similarity in failure rates is, in part, related to the expanded use of component testing and previous reaction history. These factors influence risk stratification and occasionally permit OFC results above the cutoff criteria. Our OFC failure rate is comparable to those previously reported in the literature, but it falls within the lower end of the range from 12% to 43%.[12,16,20-23] The acceptable failure rate depends on a variety of factors, with the clinical setting being of considerable importance. Clinics with increased access to higher-level care are more likely to tolerate higher failure rates. As such, some centers may be more liberal in selection of OFC candidates. In contrast, those who perform challenges in independent allergy clinics without immediate-access higher-level care may use lower testing cutoffs. We found that applying

a threshold of sIgE level not exceeding 2 kU/L and SPT result not exceeding 5 mm is a reasonable approach to limit OFC failure. Within these parameters, our study suggests that the sIgE value and SPT size were not predictive of the OFC outcome. Our low failure rate suggests that more liberal cutoffs could be used to capture more patients who may tolerate their food allergen(s), thereby reducing the burden of FA.

Component testing has improved our ability to predict clinical reactivity and become an important tool when choosing appropriate candidates for OFC.[24-27] During the course of our retrospective review, peanut component testing became more commonly used in clinical practice. We observed that the increased use of peanut component testing was correlated with a decrease in anaphylaxis in patients undergoing peanut OFCs. In all, 83% of the peanut OFCs that resulted in anaphylaxis were performed before 2020. There were no cases of anaphylaxis among patients who had peanut component testing. Peanut component testing also offers an additional benefit in identifying those with elevated peanut sIgE levels, who traditionally would have been excluded from an OFC, but are now able to undergo and pass a peanut challenge owing to primary sensitization to Ara h 8, which is low-risk for a multisystemic reaction.

When the relative benefits of egg component testing are considered, our study illustrates a low negative predictive value of ovomucoid sIgE level for baked egg challenges, as has been reported previously.[28,29] Half of the failed baked egg challenges had an undetectable ovomucoid level, including the challenges of 2 patients who experienced multisystemic reactions. This suggests that additional heat-stable egg allergenic epitope(s) exist. In addition, baked egg challenges can prove difficult, as they are frequently performed in young children who may not be able to tolerate a full serving of baked egg. Selection bias may account for the high failure and multisystemic reaction rates with baked egg challenges. Parents of babies with egg allergy are often instructed to introduce baked egg at home. This eliminates a group of patients who would have likely passed OFC to baked egg and selects for higher-risk patients.

Despite the complexity of performing OFCs in young children (eg, difficulties related to food textures, lack of cooperation), there is clear benefit to early allergen introduction. The LEAP trial and other studies have demonstrated decreased rates of sensitization and associated food aversion, so using these challenges remains necessary.[15,30-36] It is important to accommodate patients' and families' lifestyles when possible, including by coordinating challenges around nap and meal times.

Compared with other tree nuts, almond is considered a low-risk nut, which is supported by our findings.[23,37,38] There was a 100% pass rate among patients completing almond challenges. Most of the patients had no prior reaction to almond and avoided it owing to a peanut or other tree nut allergy. On the basis of our findings, we recommend considering home almond introduction for low-risk patients.

In total, less than 5% of challenges elicited a multisystemic reaction, and fewer required treatment with epinephrine, supporting the existing evidence that OFCs are safe to perform in the outpatient clinical setting. One patient required admission for observation because of the reaction symptoms persisting late in the day. This illustrates the importance of scheduling OFCs early, thereby allowing sufficient time for prolonged observation when required.

There are limitations to our study owing to its retrospective nature, such as reliance on preexisting data, uncontrolled study design, and selection bias. The reliance on preexisting EHR data hindered exploration of certain sociodemographic variables. Importantly, social constructs, including race and ethnicity, were deemed inappropriate identifiers, given their poor biologic correlation and inaccuracies within EHR "self-reporting."[39,40] One cause of selection bias is differences between those who are clinically eligible for an OFC and those who undergo an OFC, as some patients and families prefer continued avoidance. The primary limitation of single-center data is small population size. Another limitation is that all challenges were unblinded, creating a potential for false-positive (failed) OFCs, especially among those with exclusively subjective symptoms.

In conclusion, our study suggests an sIgE level not exceeding 2 kU/L and an SPT result not exceeding 5 mm for peanut, milk, and egg as benchmark parameters when considering patient eligibility for OFCs in the outpatient setting. In our experience, use of these parameters resulted in an 11% failure rate on average. However, more liberal parameters may be considered in clinical environments with access to higher-level care. This study illustrates the barriers to OFCs in young children as well as the low negative predictive value of ovomucoid sIgE, both of which contribute to a low pass rate of baked egg challenges (62%). Additionally, it supports the growing body of evidence demonstrating that OFCs are a safe and effective tool in the outpatient setting. Furthermore, some foods rarely induce IgE-mediated reactions, so home introduction may be a reasonable consideration for low-risk patients. Lastly, the addition of component testing has significantly improved our ability to predict systemic reactions. Recently developed cellular tests, including basophil activation tests and measurement of epitope-specific IgE level, have improved accuracy and may become more accessible in the future.[41] These may allow allergists to better identify ideal candidates for OFCs, predict which patients are likely to react, and minimize the occurrence of severe adverse multisystemic reactions.

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Clinical implications: The OFC outcomes for nuts, milk, and egg at our institution provide a benchmark for food sIgE level and SPT result cutoffs, which can be optimized according to clinical setting and available resources.

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