Use of emergency backup resources during open food challenges at a pediatric tertiary care center

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ABSTRACT

Background: *Oral food challenge (OFC) remains the criterion standard diagnostic procedure for food allergy. Although the need for OFCs has increased, some allergists may not perform them due to the risk for adverse events and lack of backup resources.*

Objective: *The study aimed to elucidate the frequency of reactions in which emergency backup resources were used and reported on various challenge outcomes at a tertiary pediatric hospital.*

Methods: *We retrospectively reviewed children and young adults (ages, 0–21 years) who completed OFCs in 2013–2018 at Cleveland Clinic Children's Hospital. Demographics, atopic history, culprit food, reaction history, and diagnostic testing as well as challenge details and outcomes were collected and analyzed.*

Results: *A total of 1269 challenges of 812 unique patients ages 5 months to 21 years were reviewed. More than half of challenges were performed in patients with a history of a reaction and positive testing result before challenge. The foods with the highest proportion of allergic outcomes were egg, sesame, and baked egg. More than one-third of challenge reactions were grade 3 or 4 anaphylaxis when using a food-induced anaphylaxis grading scale. Epinephrine was used for reactions in 7.2% of all challenges. Reactions in five challenges (0.4%) prompted utilization of backup emergency resources.*

Conclusion: *On review of nearly 1300 OFCs, emergency backup resources were rarely used, despite a large proportion of moderate-to-severe reactions. The need for backup resources during food challenges is rare, which suggests that most typical allergy offices are able to treat OFC reactions.*

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Food allergy (FA) affects 2–10% of people, and the prevalence is increasing.[1] Oral food challenge (OFC) remains the criterion standard diagnostic procedure for an FA diagnosis. Advances in FA research and management, including early peanut introduction guidelines, routine introduction of baked egg and milk products into the diets of patients with egg and milk allergy, realization of the limitations of skin-prick testing (SPT) and specific immunoglobulin E (sIgE) as well as increasing use of oral immunotherapy, have contributed to the increased need for OFCs. A survey showed that two-thirds of allergists perform five or fewer OFCs per month.[2,3] Although results of studies demonstrated the safety of in-office OFCs,[4–11] the risk of adverse events and the lack of a nearby hospital have been cited by allergists as some of the barriers to performing OFC in the office.[2,3]

Two recent deaths during OFC[12,13] have highlighted the importance of anaphylaxis management skills and resources. Important aspects of OFC safety include awareness of augmentation factors and understanding the frequency of severe reactions that may require additional assistance.[14,15] Cofactors that contribute to more severe reactions during OFC have previously been described and include age, concomitant illness, uncontrolled asthma, and the time to administration of epinephrine, among several other cofactors.[16] However, there remains no method for predicting the severity of reactions during a challenge. The rate at which patients require emergency treatment for an OFC reaction that uses resources beyond what is routinely available and administered in the outpatient allergy setting is exceedingly low and rarely reported.[5] Rates of emergency assistance, emergency department (ED) transfer, and hospitalizations have not been published in detail. To address this, we sought to elucidate the frequency of reactions when emergency backup resources were used. We also reported on various

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outcomes of OFC, including the severity of reactions and epinephrine use during OFCs.

METHODS

After approval was obtained by Cleveland Clinic Institutional Review Board (18–716), we conducted a retrospective electronic medical record (EMR) review of all OFCs performed at Cleveland Clinic Children's Hospital allergy outpatient offices between January 1, 2013, and December 31, 2018, in patients ≤ 21 years old. Three clinics staffed by seven pediatric allergists were included. There were several patients who underwent challenges to multiple foods, and some patients who underwent multiple challenges to the same food. The food challenge protocols were open, varied among physicians, and ranged from two to six doses given every 15–20 minutes, with the goal ingestion of an age-appropriate amount of the food protein. Challenges undertaken for suspected food protein–induced enterocolitis syndrome were excluded. The need for emergency backup resources, type of treatment, and challenge outcome were determined by the physician conducting challenges.

Emergency backup resources were defined as any personnel not immediately available in the allergy clinic, such as a rapid response team, or emergency medical services (EMS), such as paramedics. Cleveland Clinic Children's main campus clinic has a pediatric medical emergency team that consists of an ED nurse and emergency medical technician who respond to an alert in the outpatient clinic. One of the two regional sites included in the study has a similar emergency medical team from the attached ED, which is used by the outpatient clinics. The second regional site is located across the street from a pediatric ED and requires activation of EMS *via* 911 to transport a patient *via* ambulance to the ED.

In addition to patient demographics, we collected information with regard to a history of reaction to the challenge food, documentation of comorbid conditions, including physician-determined diagnosis of asthma, eczema, and/or allergic rhinitis at the time of challenge; and prechallenge SPT and sIgE test results to the food challenged, as available. Prechallenge sIgE testing was used if obtained within 6 months of the challenge date. By obtaining reaction history details for food challenge, the patients were placed into one of four classifications, including the following: (1) positive skin prick and/or *in vitro* testing results with a history of reaction, (2) positive skin prick and/or *in vitro* testing results without a history of reaction (*i.e.,* possible sensitization), (3) negative skin prick and/or *in vitro* testing results with a history of reaction, and (4) negative skin prick and/or *in vitro* testing results without a history of reaction. Documentation of each challenge encounter was reviewed for signs or symptoms that suggested a reaction to the food in question.

A patient was defined as having a "reaction" to the food if he or she had objective or subjective signs or symptoms documented in the chart. Reaction signs and/or symptoms were graded and assigned a score, regardless of the physician-determined challenge outcome. Reaction severity grading was based on the food-induced anaphylaxis grading system developed by Sampson *et al.*[17] Reaction symptom scoring was based on the scoring system modified in the 2009 food challenge work group report.[18] Both the severity grading and symptom score were determined by one of us (S.K.) based on the details found in the EMR. We recorded the treatment administered, including none, antihistamines, epinephrine, corticosteroids, inhaled β-agonists, oxygen, and intravenous (IV) fluids. The challenge outcome consisted of two classifications: (1) allergic/continue to avoid and (2) nonallergic/continue to eat.

Continuous and ordinal variables, summarized as medians and ranges, were compared by using the Wilcoxon rank sum test or Kruskal-Wallis test, as appropriate; categorical variables, summarized as counts and percentages, were compared by the Pearson χ^2 test or the Fisher exact test. Bonferroni adjustment was used for multiple comparisons. All tests were two-tailed and performed at an overall significance level of 0.05. SAS 9.4 software (SAS Institute, Cary, NC) was used for analyses, and R software (version 3.5; Vienna, Austria) was used for visualizations.

RESULTS

Demographics are listed in Table 1. A total of 1269 open OFCs were included among 812 unique patients. The median age was 59 months (range, 5–257 months), and 67.8% were male patients. Only nine of the challenges were in patients > 18 years old. Thirty percent of challenges were conducted in patients with diagnoses of asthma, eczema, and allergic rhinitis. An additional 56% of patients had eczema and allergic rhinitis, with no diagnosis of asthma. Most challenges were conducted in patients with a history of reaction and positive skin or *in vitro* testing result (53.7%) or in patients who were sensitized and without a history of reaction to the specific food (38.7%). A minority of the patients had neither a convincing history nor a positive testing result and OFC was done for family reassurance.

Foods challenged and the percentage of allergic outcomes within each food group are shown in Fig. 1 The most commonly challenged foods included peanut (24%), tree nuts (20.9%), egg (13.9%), and baked egg (11.8%). The group of foods listed as "other" included foods infrequently challenged, such as pizza cheese, sunflower seeds, oats, fruits, and gelatin.

Table 1 **Demographics (total 812 patients)***

Demographic	Total Challenges (N = 1269)*
Age, median (min, max), mo (*N* = 1269)	59.0 (5.0, 257.0)
Gender, *n* (%) (*N* = 1269)	
Females	409 (32.2)
Males	860 (67.8)
Food challenged, *n* (%) (*N* = 1269)	
Baked egg	150 (11.8)
Baked milk	75 (5.9)
Egg	177 (13.9)
Finned fish	18 (1.4)
Milk	120 (9.5)
Peanut	304 (24.0)
Sesame	21 (1.7)
Shellfish	24 (1.9)
Soy	29 (2.3)
Tree nuts	265 (20.9)
Wheat	14 (1.1)
Other	72 (5.7)
History of asthma, *n* (%) (*N* = 1268)	
No	868 (68.5)
Yes	400 (31.5)
History of asthma, eczema, and allergic rhinitis, *n* (%) (*N* = 1268)	
Asthma and eczema, and allergic rhinitis	375 (29.6)
Asthma but no eczema, and allergic rhinitis	25 (2.0)
No asthma but eczema, and allergic rhinitis	706 (55.7)
No other atopy	162 (12.8)
Prechallenge sIgE level to food challenged, median (min, max) (*N* = 1204) (kU/L)	1.1 (0.00, 101.0)
Year of challenge, *n* (%) (*N* = 1269)	
2013	148 (11.7)
2014	159 (12.5)
2015	207 (16.3)
2016	227 (17.9)
2017	232 (18.3)
2018	296 (23.3)
Reaction history, *n* (%) (*N* = 1269)	
No history of reaction, negative test result	52 (4.1)
No history of reaction, positive test result	491 (38.7)
History of reaction, positive test result	682 (53.7)
History of reaction, negative test result	44 (3.5)
Reaction, *n* (%) (*N* = 1269)	
No	816 (64.3)
Yes	453 (35.7)
Challenge outcome, *n* (%) (*N* = 1269)	
Allergic	309 (24.3)
Nonallergic	960 (75.7)

Min = Minimum; max = maximum; sIgE = specific immunoglobulin E.
**Note difference in number is attributed to a total of 1,269 challenges among 812 unique patients, some of whom underwent multiple challenges.*

There was evidence of any reaction in 36% and "allergic" outcome in 24% of all challenges. Examples of patients who had a reaction but ultimately were deemed nonallergic included those with mouth itching, which resolved, or contact urticaria, and who were able to continue the ingestion challenge with no

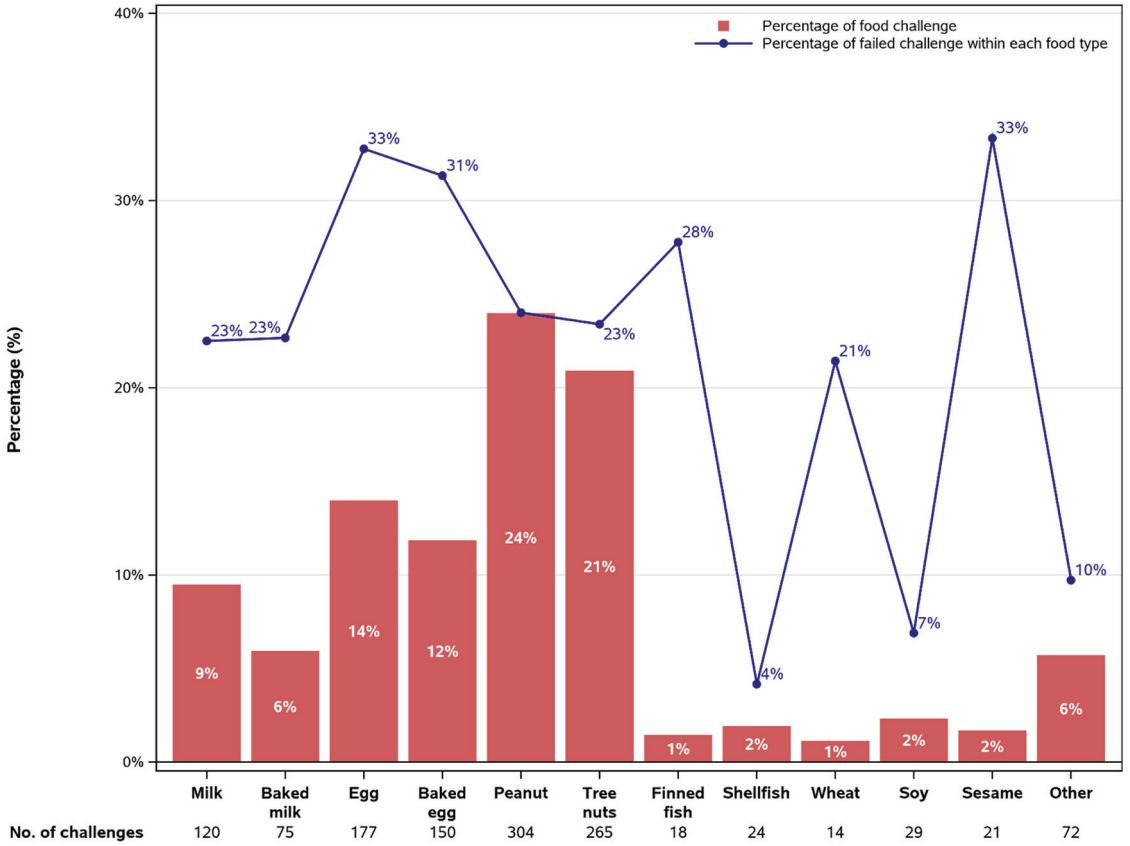

Figure 1. *Foods challenged (red bar indicates percentage) and allergic (failed) outcomes within each food group (line indicates percentage).*

other symptoms. Of the challenges in which patients were deemed allergic, 65.7% were male patients, and 65% of the patients had a history of reaction to the challenged food ($p = 0.17$). Egg (33%), sesame (33%), and baked egg (31%) had the highest proportion of allergic outcomes (Fig. 1). Grade 3 or 4 reactions occurred in 35% of challenges ($p < 0.001$). There were no grade 5 reactions. The patients who experienced reactions classified as grade 3 or 4 were older than those with grade 1 or 2 reactions (median age, 76 months versus 54 months, respectively; $p < 0.001$), had significantly higher prechallenge sIgE levels (2.8 versus 1.8 kU/L, respectively; $p < 0.010$) and were more likely to have concomitant allergic rhinitis (54.8 versus 41.1%; $p = 0.011$). No significant difference in asthma or eczema history was found between these groups. Tree nuts, predominantly cashew, had the largest proportion of grade 3 to 4 reactions (48.4%, $p = 0.024$) (Fig. 2), despite having fewer overall challenges (n = 59) than walnut (n = 64) and almond (n = 61).

Details of reactions treated with epinephrine are shown in Table 2. Epinephrine was used for reactions in 7.2% of all challenges and 29.7% of those who were ultimately allergic ($p < 0.001$). When epinephrine was administered, 39% of those challenges were grade 2, 32% were grade 3, and 29% were grade 4. Patients who required epinephrine had higher prechallenge sIgE levels (3.3 versus 1.8 kU/L, respectively; $p < 0.001$), multiple organ systems were involved when compared with gastrointestinal and/or cutaneous alone (59.8 versus 29.9%, respectively; $p = 0.002$) and had higher reaction symptom scores (5 versus 2, respectively; $p < 0.001$). Of these challenges, 18.5% were given two doses of epinephrine and two patients were given three doses of epinephrine during OFC; one patient received a fourth dose in the ED. Tree nuts (35%), peanuts (19.6%), and baked egg (21.3%) had significantly higher proportions of epinephrine use during OFC ($p = 0.002$). Five OFC reactions in five separate patients (0.4% of all challenges and 1.6% of all challenges in which patients were deemed allergic) prompted utilization of backup emergency resources with details of each patient's challenge outlined in Table 3.

DISCUSSION

Of 1269 challenges, five patients had reactions severe enough to warrant activation of emergency backup services. In each case, the treatment provided by the backup resources included more epinephrine, oxygen, antihistamines, and steroids as well as IV fluids. The value added to the allergy clinic was the ability to

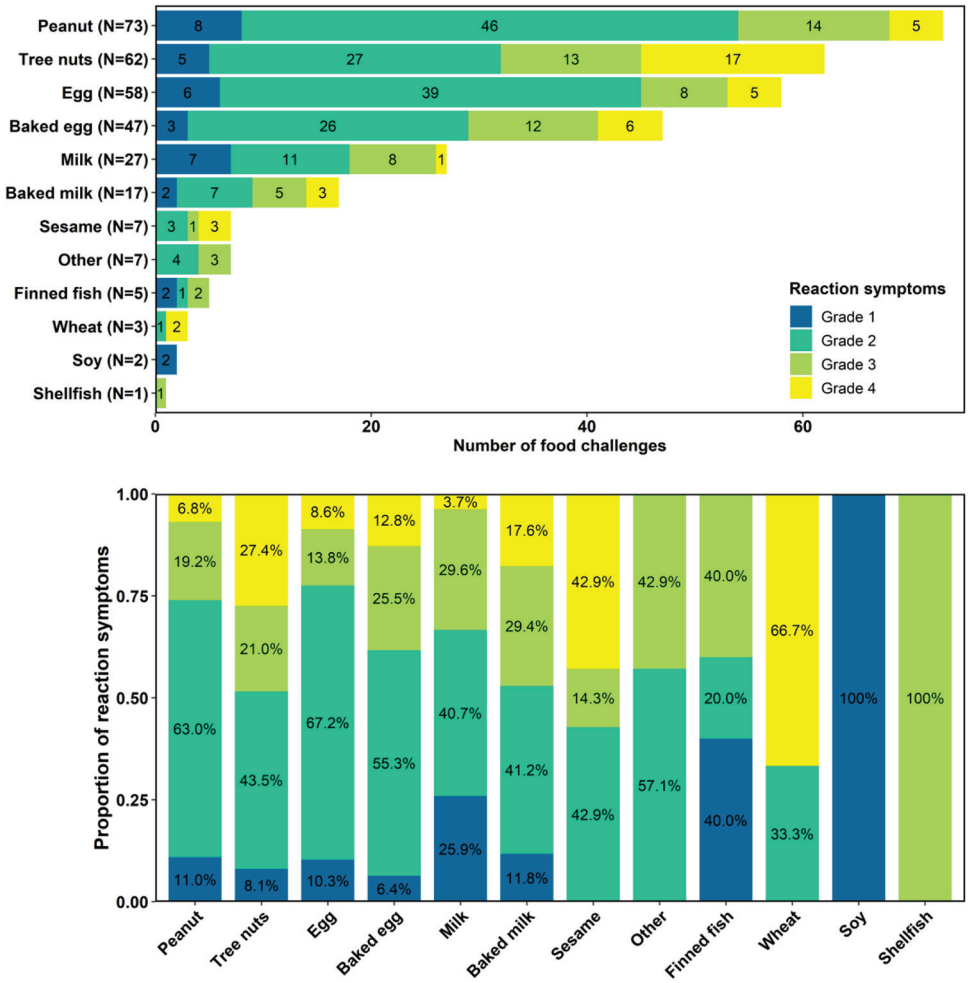

Figure 2. *Allergic outcomes per food, classified by reaction grade.*

monitor patients and allow allergy personnel to continue to see other patients. The safety of the OFC has been studied for at least the past 2 decades, with the general consensus that the procedure is safe. In 2004, Perry *et al.*[10] showed that, although 28% of challenges were severe and 11% of failed challenges required epinephrine, the majority of reactions were either treated with antihistamines or did not require treatment. No hospitalizations were reported in that study.[10]

Multiple single-center studies have mirrored such results over the ensuing 15 years.[4,6–11] Our study was also consistent with these studies, which revealed the use of epinephrine in 7% of challenges. In 2017, a multicenter survey study of five U.S. FA centers showed a pooled anaphylaxis rate of 2% during OFCs, with 1% overall who required epinephrine.[5] The study did address that 19 OFCs (0.3%) over 6 years among five institutions resulted in hospital admission for observation, although further details were not described.[5] This is of particular importance for those who decline performing OFCs due to the lack of a nearby hospital.

A nearby hospital may provide reassurance for those performing OFCs in the office. The 2009 work group report on food challenges recommended the outpatient office setting for low-risk challenges but advised that caution should be undertaken for any higher-risk challenges, which takes into account the availability of additional staff, the distance from a hospital, and EMS response time.[18] This recommendation was not included in the updated 2020 work group report.[19] Emergency backup resources were rarely used despite their immediate availability at our institution. Treatment administered in the cases that used backup services are able to be administered in the office, with the exception of IV fluids, which may or may not be available. This suggests that personnel, time, and space for monitoring, and not the ability to intervene, were the main advantages to ED transfer in these patients in five cases. Our experience with food challenge reactions provided additional evidence that a nearby hospital should not be a prerequisite for offering food challenges.

Table 2 **Characteristics of reactions during which epinephrine was administered**

Factor	Overall (N = 453)	No Epinephrine (*n* = 361)	Epinephrine (*n* = 92)	*p*
Age				0.52*
No. patients	453	361	92	
Median (min, max), mo	61.0 (6.0, 253.0)	59.0 (6.0, 227.0)	63.0 (9.0, 253.0)	
Gender				0.053#
No. patients	453	361	92	
Males, *n* (%)	295 (65.1)	243 (67.3)	52 (56.5)	
Females, *n* (%)	158 (34.9)	118 (32.7)	40 (43.5)	
Prechallenge sIgE				<0.001*
No. patients	440	349	91	
sIgE level, median (min, max) (kU/L)	2 (0, >100)	1.8 (0, >100)	3.3 (0, >100)	
History of asthma				0.71#
No. patients	452	360	92	
No, *n* (%)	307 (67.9)	246 (68.3)	61 (66.3)	
Yes, *n* (%)	145 (32.1)	114 (31.7)	31 (33.7)	
History of allergic rhinitis				0.48#
No. patients	453	361	92	
No, *n* (%)	251 (55.4)	203 (56.2)	48 (52.2)	
Yes, *n* (%)	202 (44.6)	158 (43.8)	44 (47.8)	
History of eczema				0.44#
No. patients	453	361	92	
No, *n* (%)	133 (29.4)	109 (30.2)	24 (26.1)	
Yes, *n* (%)	320 (70.6)	252 (69.8)	68 (73.9)	
History of asthma, eczema, AR				0.34#
No. patients	452	360	92	
Asthma, eczema, and AR, *n* (%)	133 (29.4)	105 (29.2)	28 (30.4)	
Eczema and AR only, *n* (%)	253 (56)	198 (55)	55 (59.8)	
Asthma only, *n* (%)	12 (2.7)	9 (2.5)	3 (3.3)	
No asthma, eczema, or AR, *n* (%)	54 (11.9)	48 (13.3)	6 (6.5)	
Time from the first dose to symptom onset				0.83*
No. patients	447	355	92	
Median (min, max), min	30 (1, 300)	30 (1, 300)	25 (1, 205)	
Reaction symptom score				<0.001*
No. patients	453	361	92	
Median score (min, max)	3 (1, 12)	2 (1, 8)	5 (2, 12)	
Reaction grade				<0.001*
No. patients	453	361	92	
Grade, *n* (%)				
1	146 (32.2)	146 (40.4)	0 (0)	
2	192 (42.4)	156 (43.2)	36 (39.1)	
3	72 (15.9)	43 (11.9)	29 (31.5)	
4	43 (9.5)	16 (4.4)	27 (29.3)	
Reaction symptom				<0.001#
No. patients	453	361	92	
Skin only, *n* (%)	110 (24.3)	104 (28.8)	6 (6.5)	
GI only, *n* (%)	104 (23)	87 (24.1)	17 (18.5)	
Skin and GI only, *n* (%)	58 (12.8)	44 (12.2)	14 (15.2)	
Respiratory only, *n* (%)	21 (4.6)	18 (5)	3 (3.3)	
Combination, *n* (%)	160 (35.3)	108 (29.9)	52 (56.5)	

min = Minimum; max = maximum; sIgE = specific immunoglobulin E; AR = allergic rhinitis; GI = gastrointestinal.
**Wilcoxon rank sum test.*
#Pearson χ^2 test.

Table 3 **Summary of the patients who required backup emergency resources during OFC**

	Patient No.				
	1	**2**	**3**	**4**	**5**
Age/gender	19 mo/male	11 years/male	13 years/male	16 mo/female	12 mo/female
Food challenged	Egg	Cashew	Sesame	Egg	Peanut
Reaction history	Eczema, never eaten, tolerated baked egg products	Peanut allergy, walnut allergy, never eaten cashew	Hives at age 2–3 years	Positive SPT/sIgE testing at prior institution; hives during previous challenge, delayed onset emesis	Delayed onset large volume emesis after peanut puff snack
Prechallenge sIgE level, kU/L	6.77	4.22	13.7	0 (SPT 0 × 0 mm)*	0 (SPT 3 × 7 mm)*
Time to symptoms	1.5 hr	Immediate	15 min	20 min	2.5 hr
Reaction symptoms	Flushing, itching, crying initially; then generalized hives, angioedema, hypotension, tachycardia, grunting	Throat and abdominal pain, wheezing, generalized hives, hypoxia	Throat and abdominal pain, then sneezing, emesis, pharyngeal edema with dysphagia and wheezing	Two hives on the abdomen after the first dose, 2 hr later repetitive forceful emesis, tachycardia	Repetitive emesis and tachycardia
Reaction symptom score	9	8	10	5	7
Reaction grade	4	4	4	3	3
No. epinephrine doses given in the office	3	2	2	2	2
Activation of emergency backup	PMET called, attached ED transfer	EMS called, local ED transfer	Code blue/PMET called, attached ED transfer	EMS called, local ED transfer (across street)	PMET called, ED transfer
ED Management	One epinephrine dose given, IV corticosteroids and diphenhydramine	Observation for 4 hr	Observation for 4 hr	IV fluids, ondansetron and corticosteroids, observation for 4 hr	IV fluids, corticosteroids, observation for 4 hr
Disposition	PICU admission, observation < 24 hr, no additional intervention required	Home	Home	Home	Home

OFC = Oral food challenge; SPT = skin-prick test; PMET = pediatric medical emergency team; ED = emergency department; EMS = emergency medical service; IV = intravenous; PICU = pediatric intensive care unit.
**Wheal x flare (mm)*

Review of our five patient cases provided reflection on anaphylaxis management, including assessment of prechallenge risk factors, recognition of symptom escalation, efficient use of epinephrine, and understanding what backup resources are available. None of these patients had obvious evidence of cofactors, which suggests an increased risk for a severe reaction, although one patient had well-controlled moderate-persistent asthma. Three of the cases included classic IgE-mediated symptoms consistent with anaphylaxis, whereas two cases had delayed vomiting ~2 hours after ingestion, a feature that overlaps both IgE and/or non-IgE reactions. The patients in the latter two cases did not respond rapidly to epinephrine, which raised concern for a non–IgE-mediated process. If the history reveals delayed vomiting in a time frame that overlaps both IgE-mediated and typical food protein–induced enterocolitis syndrome reactions, then allergists who perform the OFC should be prepared to provide standard treatment of both reaction types.[20]

The 2020 food challenge work group report further highlights the importance of safety considerations, particularly ensuring that the involved staff and facility are properly equipped for treating anaphylaxis.[19] The vast majority of practicing allergists offer aeroallergen immunotherapy (AIT) in their offices, which infers preparedness and comfort with anaphylaxis management. In comparison, anaphylaxis during individual OFC seems to occur at much higher rates than does AIT, given epidemiologic immunotherapy studies, which indicate systemic reaction rates of 0.7% and life-threatening reactions in 0.005% of patients treated.[21] Although the potential symptoms of anaphylaxis are consistent among different allergens (*i.e.*, aeroallergen, food, venom), the most common presenting symptoms of anaphylaxis and the treatments used may be different during AIT than during OFC,[21] which thus highlights the importance of previous experience with food challenges.

Our study was limited by its retrospective design. Although retrospective studies can only be representative of that specific population, our institution is representative of a typical allergy practice that consists of several providers with various backgrounds and methods of conducting OFCs. As with previous studies of this nature, the patients with the highest likelihood of reactions were excluded from being offered OFC. However, the majority of patients who were challenged had a history of reaction and positive prechallenge testing. In addition, grading and symptom scores were assigned retrospectively and limited by details documented in the EMR as well as being one author's interpretation (SK).

The grading system used is one of many established anaphylaxis grading systems. Thus, our grading of a certain reaction may be different from other institutions or individuals, depending on the system they use or their experience. When compared with the Consortium for Food Allergy Research (CoFAR) grading system for allergic reactions,[22] many of the grade 3 and 4 reactions in our study would likely fall into the CoFAR mild-to-moderate categories (grade 1 and 2). This may reassure some providers who are more familiar with the CoFAR grading scale. Regardless of the grading scale, anaphylaxis can and will occur during food challenges, and the vast majority of reactions are of moderate severity or less and can be adequately treated in the office.

In an exciting era in which food oral immunotherapy is becoming available and early introduction of foods, *e.g.*, peanut, are being used to prevent clinical allergy,[15,23] the OFC is still an important tool for practicing allergists. Many of these patients may have a higher chance of reacting. This study of patients who had a moderate-to-high likelihood of reacting during challenges can provide reassurance for allergists who may have reservations about offering OFCs. Of nearly 1300 OFCs, there were few food-induced anaphylactic reactions severe enough to warrant emergency backup resources. Importantly, anaphylaxis preparedness and physician experience are key for incorporating more food challenges into the outpatient allergy practice. Although a medical emergency response team and attached EDs are luxuries at many academic centers, the majority of allergy offices should have the tools and experience to treat the reactions reported here.

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