Letter to the Editor

Outcomes of office-based, open food challenges in the management of food allergy

To the Editor:

Given the increasing use of diagnostic testing and an apparent increase in food allergy prevalence,[1] it is vital that allergists correctly identify patients with clinical reactivity to foods as opposed to sensitization only. With the use of a detailed medical history, skin testing, and food-specific serum IgE levels, physicians can often predict the likelihood of an allergic reaction if a particular food is ingested, although in many instances the oral food challenge (OFC) is required to definitively prove tolerance.[2] The double-blind, placebo-controlled OFC is the accepted gold standard for this, but such challenges can be expensive and time-consuming, and, for most practicing allergists, are often not feasible in the everyday office setting. While the open OFC is an accepted alternative, few studies have examined the test's feasibility, efficacy, and safety.[3-5]

We report results from a retrospective chart review of all open OFCs performed at the Jaffe Food Allergy Institute, a university-based, outpatient practice, between August 2008 and May 2010. All patients were referred for open OFC based on allergists' clinical impression in conjunction with family interests (ie, likelihood of reaction was discussed with families and an OFC was offered unless it was felt by the allergist to be too high risk). Patients were referred by 9 different allergists. No specific cutoff serum IgE (sIgE) value or skin test size precluded challenge; however, patients were typically not referred if the likelihood of a positive reaction was thought to be greater than 50%.[2] sIgE levels (ImmunoCAP; Phadia, Uppsala, Sweden) were measured and/or skin prick test (SPT) was performed by using standardized extracts (Greer Laboratories, NC) within 6 months of the OFC on all patients. The OFCs were performed in the outpatient setting by a trained nurse or physician (while the supervising physician was on site at all times) per guidelines established by the current Working Group on Food Challenges report, with most challenges using doubling doses every 15 minutes until an age-appropriate serving size was administered.[6] For subjective symptoms, challenges were temporarily paused and then continued following resolution of symptoms if the supervising physician deemed it safe to proceed. All treatment decisions were based on the supervising clinician's judgment. All patients were monitored for at least 2 hours postchallenge and instructed to contact the clinic for any delayed reactions.

We performed a total of 701 open OFCs in 521 different patients. The majority of the patients were male (62.6%) and ages ranged from 8 months to 21.8 years (median, 5.67 years). Overall, 132 (18.8%) of the challenges elicited a reaction. There were no differences in age or gender between the group that passed the OFCs and the group that failed. Breakdown of challenge results by food is shown in Table I.

Patients who passed the OFC without adverse symptoms had significantly smaller SPT wheal size (median, 3.00 mm [0-9 mm] vs 4.00 mm [0-12 mm], $P = .0001$) and significantly lower sIgE levels to the challenged foods (median, 0.63 kU_A/L [0.0 to >100] vs 1.06 kU_A/L [0.0-68.2], $P = .027$) as compared with the group that had a reaction during the OFC (Table II). Patients who had an identifiable history of anaphylaxis to the challenged food were more likely to have a reaction during the OFC (5/13, 38.5%) than those who did not have a history of anaphylaxis (127/684, 18.6%), but this difference did not reach statistical significance ($P = .08$). In addition, patients who had never actually ingested the challenged food but were avoiding it because of evidence of sensitization were less likely to have a reaction during the OFC (46/328, 14.0%) as compared with those patients who had previously ingested the challenged food and had a reaction (86/361, 23.8%), $P = .0013$.

The majority of reactions, 56.8%, were cutaneous. All but 16 reactions (87.9%) were treated with antihistamine alone. Twelve reactions were treated with epinephrine (including one that required 2 doses of epinephrine), 7 with prednisolone, and 2 with albuterol (Table III). All but one reaction was managed in the office setting; 1 patient was transferred to the emergency department for monitoring and intravenous fluids due to persistent vomiting following a challenge to peanut.

With growing numbers of patients presenting to allergists with laboratory findings of food sensitization and low likelihood of reaction, it is imperative that the allergist be able to give patients and parents a definitive answer regarding their allergic status. Clinical history, SPT, and sIgE levels can only provide

TABLE I. Results of all challenges, broken down by specific food and organ system of reaction

Food	No. (% of all challenges)	No. positive (%)	Reaction organ involvement				
			Skin	Oral/nasal symptoms	Lower respiratory	Gastrointestinal	>1 System
Peanut	124 (17.7)	26 (21.0)	16	1	1	6	2
Tree nuts	121 (17.0)	22 (18.2)	7	13	0	1	1
Egg	112 (16.0)	15 (13.4)	8	2	1	1	3
Milk	55 (7.8)	22 (40.0)	14	6	0	2	0
Soy	54 (7.7)	10 (18.5)	7	2	1	0	0
Fish*	49 (6.9)	6 (12.2)	4	2	0	0	0
Sesame	44 (6.3)	7 (15.9)	4	1	0	1	1
Shellfish†	29 (4.1)	3 (10.3)	1	2	0	0	0
Wheat	28 (4.0)	6 (21.4)	4	0	0	0	2
Other	85 (12.1)	15 (17.6)	10	2	0	2	1
All foods	701	132 (18.8)	75	31	3	13	10

*Fish causing reactions include codfish, halibut, tilapia, and tuna.

†All shellfish reactions to shrimp.

TABLE II. Skin test results and sIgE levels for the most commonly challenged foods (ie, foods with 50 challenges or more)

	Skin test (mm)*			sIgE (kU_A/L)*		
Food	**Positive challenge**	**Negative challenge**	***P* value**	**Positive challenge**	**Negative challenge**	***P* value**
Peanut	4.00 (0-12)	2.00 (0-8)	.0009	0.36 (0.0-6.0)	0.18 (0.0-6.7)	.734
Tree nuts	4.00 (0-7)	1.00 (0-7)	.0012	0.44 (0.0-9.5)	0.00 (0.0-13.6)	.387
Egg	4.00 (0-10)	3.00 (0-8)	.0419	1.30 (0.0-2.7)	0.59 (0.0-4.9)	.229
Milk	5.00 (0-8)	3.00 (0-8)	.0048	0.97 (0.0-7.1)	0.58 (0.0-25.7)	.308
Soy	5.00 (0-8)	3.00 (0-9)	.0899	4.26 (0.74-25.2)	3.41 (0.0-29.3)	.659
All foods	4.00 (0-12)	3.00 (0-9)	<.0001	1.06 (0.0 to >100)	0.63 (0.0-68.2)	.027

*Skin test results and sIgE levels displayed as medians (ranges).

TABLE III. Patients requiring epinephrine

Age (y)	Food	Clinical history	SPT mean wheal diameter (mm)	Food-specific sIgE (kU_A/L)	Reaction	Dose causing reaction
9.2	Beef	Urticaria	7	3.60	A, U, V	3 oz Hamburger (~20 g protein)
12.6	Egg	Never ingested	4	2.28	C, W, U	1 g Protein
4.2	Egg	Eczema flare	10	1.91	V, U	1/10 Egg (~0.75 g protein)
5.5	Peanut*	Never ingested	2	<0.35	V	2 Tablespoons peanut butter (~8 g protein)
5.75	Peanut	Never ingested	0	3.71	C, W, D	1 Teaspoon peanut butter (~1.3 g protein)
4.8	Peanut	Never ingested	5	<0.35	S, C, U	5 g Protein
5.1	Peanut	No known reactions	4	1.65	S, C, U, V	5/8 Tablespoon peanut butter (~2.5 g protein)
14.9	Sesame	No known reactions	6	16.2	U, V, W	2 Teaspoons tahini (~2 g protein)
1.2	Soy	Never ingested	5	1.49	U, A	120 mL Soymilk (~4 g protein)
4.0	Walnut	Never ingested	4	4.05	S, OP, U	5 g (~1.3 g protein)
6.4	Wheat	Perioral rash	ND†	>100	OP, V, U	~1 g Protein
5.5	Wheat	Urticaria (but mother reported recent tolerance to accidental ingestion)	0	10.3	U, C, W	1 Slice bread (~4 g protein)

A, Angioedema; *C*, cough; *D*, dyspnea; *OP*, oropharyngeal itching/pain; *S*, sneeze; *U*, urticaria; *V*, vomiting; *W*, wheeze.
*Reaction initially thought to be IgE mediated but after challenge, history most consistent with food protein– induced enterocolitis syndrome given negative SPT and sIgE and nature of symptoms.
†Patient unable to come off antihistamines for skin testing or for challenge.

data to suggest the likelihood of reaction. While a double-blind challenge is the optimal method for defining clinical reactivity, it may not be feasible in a busy, outpatient practice. An open challenge requires less time and resources and provides the parent/patient with objective evidence of tolerance or reactivity. In this largest study of open OFCs to date, we show that the procedure can be done in a high-volume practice, with approximately 35 challenges being performed per month. While no specific inclusion or exclusion cutoff criteria were utilized for OFC referrals, we believe that this cohort is highly reflective of a population encountered in a typical allergy practice, especially given that the reported cohort represents patients referred by 9 different physicians. Given the median specific IgE levels and the skin test results, the majority of these patients were at relatively "low risk" for reaction; however, it is this exact population for which the risk-to-benefit ratio is optimal for performing an OFC. A previous report of open OFC by Perry et al in a higher-risk population (ie, individuals with higher median specific IgE levels) demonstrated an OFC reaction rate of 43%, a rate that is higher than may be desirable for a busy office practice.[3] In fact, by ruling out clinical reactivity in more than 80% of our patients, we were able to add foods back into the diets of the majority of patients. Utilizing such challenges avoids the need to have these "low-risk" patients ingest and potentially experience allergic reactions to the food at home. For example, while SPTs overall showed strong negative predictive values, there were 23 patients with negative skin test results who reacted to the food, 3 of whom had significant systemic reactions. In addition, 34 patients with undetectable food-specific IgE had reactions during OFC and 10 patients who had a reaction had both negative SPT and sIgE results. Some of these reactions likely represent false-positive OFCs (eg, persistent subjective symptoms in anxious patients) or non-IgE–mediated reactions, but had they occurred after introduction of the food at

home, they may have put the patient at risk and the family under unnecessary stress. For highly anxious patients or for those experiencing equivocal symptoms, it may be advisable to perform blinded OFCs in order to reduce the likelihood of a false-positive OFC. Finally, we have shown that in this population, the open OFC is safe, provided it is carried out in an allergist's office. Only 1.7% of the challenges required treatment with epinephrine, a rate that is equivalent to or lower than those in most published studies on systemic reactions to subcutaneous immunotherapy.[7]

In conclusion, open OFCs are safe and effective for establishing tolerance in patients with suspected food allergy.

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REFERENCES

1. Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics 2009;124:1549-55.
2. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol 2010;125: s116-25.
3. Perry TT, Matsui EC, Conover-Walker MK, Wood RA. Risk of oral food challenges. J Allergy Clin Immunol 2004;114:1164-8.
4. Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Gant C, et al. Comparison of open and double-blind placebo-controlled food challenges in diagnosis of food hypersensitivity amongst children. J Hum Nutr Diet 2007;20:565-79.
5. Mankad VS, Williams LW, Lee LA, LaBelle GS, Anstrom KJ, Burks AW. Safety of open food challenges in the office setting. Ann Allergy Asthma Immunol 2008;100: 469-74.
6. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS, et al. Work group report: oral food challenge testing. J Allergy Clin Immunol 2009;123:S365-83.
7. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. Ann Allergy Asthma Immunol 2001;87:47-55.

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