



Letters

Outcomes of 88 infant food challenges conducted in the allergy office

The National Institute for Allergy and Infectious Disease 2017 guidelines' recommendation for early testing and introduction of peanut for at-risk infants has led to an increased demand for practitioners to offer skin prick testing (SPT) and oral food challenges (OFCs) to infants as young as 4 months of age.¹ Data from clinical trials^{2–4} and population-based studies^{5,6} suggest that severe reactions and epinephrine use during infant OFCs are uncommon. The safety data for infant OFCs performed in clinical practices is limited to 1 previous report of 18 infants, among whom only 1 reaction (hives) occurred.⁷ To augment the body of safety data on infant OFCs performed in outpatient clinical practices, we reviewed outcomes and epinephrine use for infant OFCs conducted in an outpatient academic allergy practice over a 13-month period.

Approval from the institutional review board of Weill Cornell Medicine with a waiver of informed consent was obtained. All OFCs in infants younger than 1.5 years conducted between September 2017 and October 2018 were reviewed. An age cutoff of 18 months reflects real-world limitations in conducting infant OFCs, with 3 to 6 months as the typical time from patient referral to OFC.

The reasons for initial evaluation included atopic dermatitis, history of food reactions, and family history of food allergy (FA). The diagnostic evaluation included SPT using Quintip (Hollister-Stier Laboratories, Spokane, Washington) to food extracts (Stallergenes Greer Boston, Massachusetts), and serum-specific immunoglobulin E (sIgE) with ImmunoCAP (Thermo Fisher Scientific, Waltham, Massachusetts). The OFCs were offered on the basis of the clinician's assessment of testing, family preferences, and reaction history. In cases with previous reaction to challenged food, OFCs were offered if the reaction was mild (limited cutaneous) or if the history of causation was unclear. Trained staff conducted open OFCs using established protocols, with 4 doses doubled every 15 minutes until a full serving was achieved, followed by a 2-hour observation.⁸ Because of individualized infant eating patterns, the dose interval was lengthened or the dose was repeated as required to achieve a full serving. Servings varied by age and parent assessment of typically consumed food quantities (Table 1). If reactions occurred, challenges were stopped and reactions were treated per physician's discretion. Vital signs were obtained at the start and end of challenges and during systemic reactions until complete resolution of symptoms was achieved. Analyses (conducted with RStudio, Boston, Massachusetts) included general descriptive frequencies and comparisons using odds ratios with Fisher exact test for continuous variables and Wilcoxon rank-sum test for categorical variables.

During this 13-month interval, 62 patients underwent 89 OFCs for suspected IgE-mediated FA. One OFC was excluded owing to reaction consistent with food protein–induced enterocolitis syndrome. Of the 88 included OFCs, 64 (73%) passed, 24 (27%) failed, and 5 (6%) met the criteria for anaphylaxis⁹ (as defined in Table 1). One severe reaction was reported, in which emesis, cough, and stridor occurred in a 12-month-old boy who underwent cow's milk OFC despite a high likelihood of reaction, due to danger of home introduction against medical advice should in-office OFC be withheld (Table 1).

Among the 24 OFC failures, the most common symptoms were cutaneous (14 [58%] limited, 10 [42%] widespread), and 7 (29%) were gastrointestinal. Four (17%) had mild respiratory symptoms (sneeze, nasal congestion, cough) without wheeze or distress. One had respiratory distress (as detailed previously). Three developed biphasic reactions with widespread cutaneous symptoms, 2 of which occurred after the in-office observation period. There were no instances of cardiovascular compromise or death.

Of the 24 failed OFCs, 6 (25%) improved with no treatment, whereas 8 (33%) were managed with antihistamines only. Ten (42%) were treated with intramuscular epinephrine—5 for widespread urticaria not improving with antihistamines, 4 for nonsevere anaphylaxis with emesis and urticaria, and 1 for severe anaphylaxis (as detailed previously). Eight administrations occurred in-office and 2 after the in-office observation period owing to biphasic reactions. Of the 5 cases with widespread urticaria with initial symptom resolution from antihistamines, 3 went on to receive epinephrine for biphasic reactions. There were no biphasic reactions for cutaneous reactions treated with timely epinephrine. In the 3 cases of mild and rapidly improved 2-system involvement, no epinephrine was used.

A comparison of passes and fails (Table 1) indicated a trend toward increased odds of passing for those with a history of a previous reaction to an OFC food compared with those without (odds ratio 2.73, $P = .06$). The age range was similar for passes and fails, but lower for reactions treated with epinephrine ($P = .02$). The SPT wheal size was larger for fails compared with passes ($P < .001$) and similar for reactions treated with and without epinephrine. The sIgE was higher for those failing and those treated with epinephrine (both $P < .001$). The trend toward younger age and increased wheal size and higher sIgE in those treated with epinephrine may reflect provider willingness to challenge infants with no previous ingestion/reaction history, despite higher test values. Other baseline characteristics (Table 1) were similar between the compared groups.

In this retrospective analysis of 88 consecutive, open infant OFCs conducted in an academic allergy office over a 13-month period, we found that most cases resulted in the removal of restrictions from

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Table 1
Outcomes of 88 OFCs for 62 Infants Under 1.5 Years of Age Conducted in the Allergy Office Over a 13-Month Interval

	Outcomes of 88 OFCs					Epinephrine use for 24 OFC failures ^a		
	All	Pass ^b	Fail ^c	Anaphylaxis ^d	Severe ^e	Not given	Given	Given after discharge
All								
N (%)	88 (100)	64 (73)	24 (27)	5 (6)	1 (1)	14 (58)	10 (42)	2 (8)
Baseline								
Age, mo, median (IQR)	10 (9-12)	11 (9-12)	10 (9-12.3)	9 (8-9)	12	11.5 (10-14)	9 (8.3-10)	8 (7.5-8.5)
Characteristics								
Eczema, n (%)	76 (86)	54 (84)	22 (92)	5 (100)	1 (100)	13 (93)	9 (90)	2 (100)
Allergic rhinitis, n (%)	5 (6)	4 (6)	1 (4)	0	0	1 (7)	0	
Wheeze, n (%)	3 (3)	3 (5)	0	0	0	0	0	
Previous reaction, n (%)	41 (47)	34 (53)	7 (29)	2 (40)	0	3 (21)	4 (40)	1 (50)
Testing								
SPT, mm, median (IQR)	4 (3-7)	4 (2-6)	7 (4-8)	7 (7-7)	7	7 (4-8)	7 (3-7)	8 (8-9)
SPT available, n (%)	86 (98)	63 (98)	23 (96)	5 (100)	1 (100)	13 (93)	10 (100)	2 (100)
slgE kIU/L, median, (IQR)	1.6 (0.9-4.8)	1.4 (0.7-2.9)	4.9 (2.2-11.7)	7.1 (4.1-15)	9.21	3.8 (2.6-8.6)	8.5 (3.2-11.3)	18.72 (11.8-25.6)
slgE available, n (%)	47 (53)	33 (52)	14 (58)	4 (80)	1 (100)	7 (50)	7 (70)	2 (100)
By food goal dose ^f	N (% of all)	N (% of specific food OFC)				N (% of specified food OFC failures)		
Peanut								
1-4 tsp butter	32 (36)	21 (66)	11 (34)	2 (6)	0	8 (73)	3 (9)	1 (3)
Baked hen's egg ^g								
¼-1 muffin	23 (26)	19 (83)	4 (17)			1 (25)	3 (13)	0
Unbaked hen's egg								
½-1 egg	8 (9)	7 (88)	1 (12)			1 (100)	0	
Baked cow's milk ^g								
¼-1 muffin	2 (2)	2 (100)	0					
Cow's milk								
3-6 oz butter	5 (6)	3 (60)	2 (40)	1 (20)	1 (20)	1 (50)	1 (20)	0
Almond								
1-4 tsp butter	3 (3)	3 (100)	0					
Other tree nut ^h								
1-4 tsp butter	7 (8)	5 (71)	2 (29)			2 (100)	0	
Wheat								
¼-1/2 cup pasta	4 (4)	0	4 (100)	2 (50)	0	1 (25)	3 (75)	1 (25)
Sesame								
1-2 tsp paste	2 (2)	2 (100)	0					
Soy								
3-6 oz	2 (2)	2 (100)	0					

Abbreviations: IQR, interquartile range; OFC, oral food challenge; oz, ounce; slgE, specific immunoglobulin E; SPT, skin prick test wheal diameter, tsp, teaspoon.

NOTE. Values in bold indicate a statistically significant difference ($P < .05$) or a trend toward a significant difference ($P < .06$) as detailed in the manuscript text.^aAdministered as per provider preference and not according to strict criteria. "Given" includes all administrations. "Given after discharge" is a subset of total administrations.^bPass was defined as consuming a full age-appropriate quantity without dose-limiting symptoms or need for treatment.^cFail was defined as having symptoms during OFC requiring either cessation of feeding or need for treatment.^dAs defined in Sampson et al.⁹^eSevere was defined as having either respiratory distress (stridor, wheeze, or labored breathing) or cardiovascular compromise (hypotension or signs of hypotension).^fGoal dose offered depending on age and parent assessment of typically consumed food quantities.^gDesignated food was cooked into a muffin (recipe as per Bird et al⁸), ¼ to 1 muffin.^hOther tree nuts included almond cashew (N = 2), hazelnut (N = 4), walnut (N = 1), and walnut with cashew (N = 1).

the infant's diet (73%), even in 41 cases with a history of a possible or previous reaction to challenge food (53%). This was particularly relevant for 32 peanut OFCs, with 66% ($n = 21$ passes) allowing incorporation of peanut to the diet. The National Institute of Allergy and Infectious Diseases guidelines recommend the home introduction of peanut for infants with SPT of 0 to 2 mm.¹ In our study, 100% of patients with wheals smaller than 2 mm passed, 65% with wheals larger than or equal to 2 mm but smaller than 8 mm passed, and 75% with wheals of 8 mm or larger failed.

Reactions during infant OFCs were not severe (with 1 exception, as previously noted) and safely managed in the office. The frequency of epinephrine use (42%) for 24 failed OFCs in this study was high compared with most previous reports. A population-based cohort study reported epinephrine use in just 2.4% of 535 failed OFCs.^{5,6} Clinical trials of early introduction of peanut² and egg^{3,4} similarly report rare or no cases of epinephrine use, with the exception of 1 trial, which reported anaphylaxis in 11 of 16 infants who reacted during an egg OFC.¹⁰ This stark contrast may be

partially attributed to an academic allergy office having a greater concentration of high-risk patients and a low threshold for epinephrine use, including for cutaneous reactions that do not meet criteria for anaphylaxis. The timely use of epinephrine for substantial cutaneous symptoms during infant OFC seemed to reduce the frequency of biphasic reactions. Biphasic reaction occurred in 3 of 5 widespread cutaneous reactions treated with antihistamines only; there were none in those treated with timely epinephrine.

This report is limited by its retrospective nature, the use of nonstandardized criteria for offering OFCs, and its small sample size.

In summary, this retrospective review of 88 infant OFCs suggests that infant OFCs can be safely conducted in the allergy office under physician supervision to expand the infant diet, even in cases with a history of a possible or previous reaction. With epinephrine use in 42% of OFC failures, our study also emphasizes the benefit of in-office OFC over home feeding in cases of suspected FA in infancy.

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