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Oral food challenge outcomes children under 3 years of age

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To promote efforts at preventing peanut allergy, the National Institute of Allergy and Infectious Diseases (NIAID) published early peanut introduction guidelines in the United States in 2017.¹ Recent findings that 10% of infants in HealthNuts may have IgE-mediated food allergy by age 12 months² have further stressed the need for infant oral food challenges (OFCs), but barriers to implementing NIAID guidelines may include clinician discomfort with infant OFCs.³ An expert panel recently agreed that when considering anaphylaxis in very young children, infants and toddlers should be grouped separately from older children, because younger children have less advanced verbal skills.⁴ Although this may be intuitive, there are limited data in the United States on allergic reactions and safety of OFCs in children younger than 3 years. To determine the safety of OFCs within our clinical practice, we sought to systematically evaluate OFCs in this younger population and compare outcomes between infants (age 5–11 months) and toddlers (age 12–35 months). We also sought to determine whether OFC outcomes differ by food.

This was a convenience sample from internal referrals from clinicians in the Massachusetts General Hospital for Children Food Allergy Center using (1) NIAID guidelines for early peanut introduction when applicable and (2) the allergist's clinical judgment. All participants had either a documented positive skin prick test (SPT) result or food-specific IgE (sIgE) and/or history of IgE-mediated reaction to the food antigen to be included. The foods selected as the main challenge foods to the cohort for OFCs were peanut, baked egg, and baked milk. All OFCs were open challenges and were conducted in the Massachusetts General Hospital Translational Clinical Research Center. OFC data from October 2017 to August 2018 were gathered prospectively and analyzed. Patient SPT and sIgE results closest in date preceding the OFC, as well as previous reaction history, were recorded retrospectively from chart review. Positive SPT results were defined as a mean wheal diameter 3 mm or greater than that achieved with the negative control, and positive sIgEs were defined as levels 0.35 kU/L or greater. A trained dietitian prepared the challenge foods with prescribed dosing in 5 to 6 steps (available as Table E1 in this article's Online

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Conflicts of interest: M. Pistiner is recipient of grants from Kaleo, DBV, and National Peanut Board; has served on advisory panels for Kaleo, DBV, and Allergenix; and is also cofounder of AllergyHome and Allergy Certified Training. W. G. Shreffler is recipient of grants from SAB and Aimmune Therapeutics; was medical advisor for FARE; served on advisory panels for DBV, Sanofi, Novartis, and GlaxoSmithKline; and received clinical trial funding from DBV, Aimmune, and Vedanta. The rest of the authors declare that they have no relevant conflicts of interest.

Repository at www.jaci-inpractice.org). Challenge outcomes were categorized as pass, fail, or indeterminate on the basis of clinician's judgment. Indeterminate OFCs were defined as either (1) the child developing very mild symptoms that were difficult to confirm as IgE-mediated, or (2) being unable to consume past the initial steps with no evidence of IgE-mediated symptoms. Statistical analyses were performed using t tests, χ^2 test, or Fisher exact test, and 1-way ANOVA where appropriate, with an $\alpha = 0.05$. All analyses were conducted using R version 3.5.1.⁵ The MGH Institutional Review Board approved this study.

One hundred eighteen OFCs were performed to peanut, baked egg, or baked milk on 107 children younger than 3 years (for consort diagram, see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Of the 118 OFCs, 66% OFCs passed, 26% OFCs failed, and 8% OFCs were indeterminate. Demographic and allergic clinical characteristics of participants by OFC outcome are described in Table I. Peanut skin testing and egg white sIgE levels were significantly larger in failed OFCs. The remainder of allergy tests were not significantly different across OFC outcome. Only ovomucoid sIgE changed and was significantly larger in failed OFCs, when indeterminate OFCs were removed. Allergic clinical characteristics by age at challenge are described in Table E2 in this article's Online Repository at www.jaci-inpractice.org. Toddler OFCs had a trend for smaller milk and peanut SPT wheal diameter and a significantly higher previous reaction history to the challenge antigen as reported by the child's allergist ($\chi^2 = 25.10$, $P < .001$) compared with infant OFCs. There were no observed differences in OFC outcome by age group (see Table E2). Repeating these analyses without indeterminate OFCs yielded the same results. Table E3 in this article's Online Repository at www.jaci-inpractice.org subcategorizes previous reaction history versus sensitization alone by food antigen and age. There were no observed differences in proportion of failed challenges in those with a previous reaction history versus sensitization alone for all OFCs ($\chi^2 = 0.46$; $P = .5$).

Table E4 in this article's Online Repository at www.jaci-inpractice.org lists the range of body systems and symptoms exhibited during failed OFCs by children younger than 3 years. The most frequent system affected was cutaneous (87%), followed by upper respiratory (29%), gastrointestinal (16%), lower respiratory (13%), and cardiovascular (7%). The most commonly seen symptom in each system category was hives, sneezing, tongue-out, cough, and tachycardia, respectively. Of note, ear-rub was also seen (see Table E4). Symptoms listed in Table E4 were seen in isolation 42% of the time. One body system was involved 58% of the time. There were no differences in symptoms between failed infant and toddler OFCs. Although we found cutaneous symptoms to be similar in range to the 83% to 93% frequency found in the HealthNuts study comparing OFCs in 1- and 4-year-olds in Australia,⁶ angioedema was not common in our toddler age group. This may be because the toddlers in our study had a mean age of 21 months and were younger than the 4-year-olds studied in HealthNuts.⁶

Of the 118 OFCs, 10% required treatment (see Figure 1, A). Treatments used during failed OFCs were H1 antihistamines (35%), epinephrine (1 dose; 19%), and oral corticosteroids (16%; see Figure 1, B). Oral corticosteroids were given in addition to other treatments when needed, not as sole treatment during allergic reactions. There were no significant differences by age (infant or toddler at challenge) for use of H1 antihistamines ($P = .21$), epinephrine (P

= .64), or oral corticosteroids ($P = .32$). No child received a second dose of epinephrine, intravenous fluids, bronchodilators, or oxygen, or required hospitalization during the period of study (see Figure 1, B). For the subsample of infants challenged to peanut based on NIAID guidelines ($n = 15$), 4 failed their OFC (27%), with 1 (7%) receiving epinephrine. The overall epinephrine rate for all OFCs was 5%.

This study was a clinical application of OFCs in children younger than 3 years referred using clinician judgment and NIAID guidelines for skin testing, where applicable, for infants. This is in contrast to the Australian population—based HealthNuts longitudinal cohort study of 1-year-old children who had OFCs, repeated at age 4 years with persistent or new food allergy, irrespective of skin test wheal size at both time points.⁶ In our study, we found OFCs for children younger than 3 years to be safe with minimal need for epinephrine. Our findings suggest that peanut skin testing and egg white sIgE may be useful predictors in this younger population. More study is needed for other allergy testing. Our lack of observed differences in OFC outcome by age group or previous reaction history needs further study with more participants. Referral clinicians in our outpatient setting may have waited for the SPT wheal size/sIgE level of toddlers (who were older with higher previous reaction history) to decrease over time before referring for challenge. For infants, more data are needed regarding early peanut introduction in US settings, beyond the Learning Early About Peanut Allergy (LEAP) study⁷ in the United Kingdom. Failed OFCs in our infant early peanut introduction subsample were 27% (43% in another US study,⁸ vs 13% in the LEAP study using LEAP skin test criteria for randomization to consumption⁷). Epinephrine use for our early peanut introduction subgroup was 7% (14% in another small US study,⁸ vs 0% in the LEAP study⁷). Limitations of our study include a small sample size, potential referral bias, referral clinician discretion for past testing, and lack of investigator blinding to allergy test results during challenge.

Few data are available to characterize the diversity of presenting symptoms in children younger than 3 years.^{4,9} Similar to the literature,^{6,7} our study found cutaneous symptoms to be most frequent. However, we describe symptoms in this age group, such as sneezing, ear-rub, tongue-pull (roll or lip-licking), and tachycardia, which are potentially underrecognized in the literature.⁹ These symptoms may be useful in younger children who are nonverbal or for whom it may be difficult to obtain a blood pressure.⁴ More data are needed in the United States to describe symptoms and treatment in very young children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Implications

- Oral food challenges are important for infants/toddlers. Oral food challenges to peanut, baked egg, and baked milk were safe in a small sample of infants/toddlers referred from a clinic population. Sneezing, ear/tongue itching, and tachycardia may be present in this nonverbal age group.

(A) Treatment used at all OFCs. Failed OFCs were 26%, and 10% required treatment. (B) Treatment used at failed OFCs by age group. Of the failed OFCs requiring treatment, no differences were observed in H1 antihistamine, epinephrine, or oral steroid use by age.

TABLE I.
Demographic characteristics, allergic clinical characteristics, and challenge food by OFC outcome

Characteristic	N	Overall (n = 118)	Pass (n = 78)	Fail (n = 31)	Indeterminate (n = 9)	P
Demographic						
Sex: female, n (%)	118	41 (34.7)	26 (33.3)	10 (32.3)	5 (55.6)	.392
Age at challenge (mo), mean $\pm$ SD	118	17.0 $\pm$ 7.7	17.3 $\pm$ 7.7	15.3 $\pm$ 7.4	19.7 $\pm$ 9.0	.264
Race, n (%)	118					.067
White		65 (55.1)	44 (56.4)	19 (61.3)	2 (22.2)	
Asian		10 (8.5)	5 (6.4)	2 (6.5)	3 (33.3)	
Black or African American		4 (3.4)	3 (3.8)	0 (0.0)	1 (11.1)	
Other		39 (33.1)	26 (33.3)	10 (32.3)	3 (33.3)	
Hispanic/Latino		3 (2.5)	3 (3.8)	0 (0.0)	0 (0.0)	.738
Allergic clinical						
SPT wheal size (mm), mean $\pm$ SD for food being challenged						
Peanut	53	4.06 $\pm$ 3.3	2.9 $\pm$ 2.4	6.2 $\pm$ 3.8	4.25 $\pm$ 3.1	.002 [*]
		Minimum: 0				
		Maximum: 14				
Egg white	46	8.2 $\pm$ 2.9	7.7 $\pm$ 2.7	9.6 $\pm$ 3.5	8.8 $\pm$ 1.3	.158
		Minimum: 3				
		Maximum: 16				
Milk	18	7.6 $\pm$ 4.6	7.2 $\pm$ 4.7	8.0 $\pm$ 5.3	—	.801 [†]
		Minimum: 0				
		Maximum: 16				
Casein	16	4.4 $\pm$ 3.4	3.6 $\pm$ 3.5	6.7 $\pm$ 0.6	—	.166 [‡]
		Minimum: 0				
		Maximum: 11				
sIgE in kU/L, mean $\pm$ SD for food being challenged						
Peanut	33	3.02 $\pm$ 4.7	1.7 $\pm$ 2.9	3.9 $\pm$ 4.4	8.4 $\pm$ 11.1	.051 [‡]
		Minimum: <0.1				
		Maximum: 21				
Ara h 2	22	0.4 $\pm$ 0.7	0.2 $\pm$ 0.2	0.7 $\pm$ 1.0	0.1 $\pm$ 0.0	.276

Characteristic	N	Overall (n = 118)	Pass (n = 78)	Fail (n = 31)	Indeterminate (n = 9)	P
Egg white	42	Minimum: <0.1				
		Maximum: 3				
		4.5 ± 5.2	2.9 ± 3.6	7.0 ± 5.6	8.9 ± 9.3	.017 [*]
Ovomucoid	36	Minimum: 0.3				
		Maximum: 22.7				
		0.9 ± 1.0	0.7 ± 0.8	1.5 ± 1.3	0.35 ± 0.0	.060 [‡]
Milk	18	Minimum: <0.1				
		Maximum: 4.5				
		4.0 ± 5.4	3.4 ± 5.0	7.2 ± 8.4	—	.303 [‡]
Casein	17	Minimum: 0.4				
		Maximum: 17.9				
		1.5 ± 2.4	1.5 ± 2.6	1.5 ± 1.1	—	.976 [‡]
Cumulative OFC dose (g of protein), mean ± SD	118	Minimum: <0.1				
		Maximum: 9.2				
		1.4 ± 1.0	1.9 ± 0.9	0.6 ± 0.8	0.3 ± 0.4	<.001 [*]
OFC Outcome by food, n (%)	118					
Peanut		53 (44.9)	32 (60.4)	17 (32.1)	4 (7.5)	.686
Baked egg		47 (39.8)	32 (68.1)	11 (23.4)	4 (8.5)	
Baked milk		18 (15.3)	14 (77.8)	3 (16.7)	1 (5.6)	

* ■■■■.

[‡]One milk OFC was Indeterminate. It was removed from analysis to enable comparison of milk allergy testing by OFC pass/fail outcomes.

[‡]Repeating analysis without indeterminate OFCs yielded ovomucoid sIgE, $P = .03$, and peanut sIgE, $P = .105$.