

Clinical Communications

Oral food challenge outcomes in children under 3 years of age

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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.

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) or food-specific IgE (sIgE) result and/or history of IgE-mediated reaction to the food antigen to be included. The foods selected as the main challenge foods to 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 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 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

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	118	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
		Minimum: <0.1				
		Maximum: 3				
Egg white	42	4.5 $\pm$ 5.2	2.9 $\pm$ 3.6	7.0 $\pm$ 5.6	8.9 $\pm$ 9.3	.017
		Minimum: 0.3				
		Maximum: 22.7				
Ovomucoid	36	0.9 $\pm$ 1.0	0.7 $\pm$ 0.8	1.5 $\pm$ 1.3	0.35 $\pm$ 0.0	.060†
		Minimum: <0.1				
		Maximum: 4.5				
Milk	18	4.0 $\pm$ 5.4	3.4 $\pm$ 5.0	7.2 $\pm$ 8.4	—	.303*
		Minimum: 0.4				
		Maximum: 17.9				
Casein	17	1.5 $\pm$ 2.4	1.5 $\pm$ 2.6	1.5 $\pm$ 1.1	—	.976*
		Minimum: <0.1				
		Maximum: 9.2				
Cumulative OFC dose (g of protein), mean $\pm$ SD	118	1.4 $\pm$ 1.0	1.9 $\pm$ 0.9	0.6 $\pm$ 0.8	0.3 $\pm$ 0.4	<.001
OFC Outcome by food, n (%)						
	118					.686
Peanut		53 (44.9)	32 (60.4)	17 (32.1)	4 (7.5)	
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, $P = .105$.

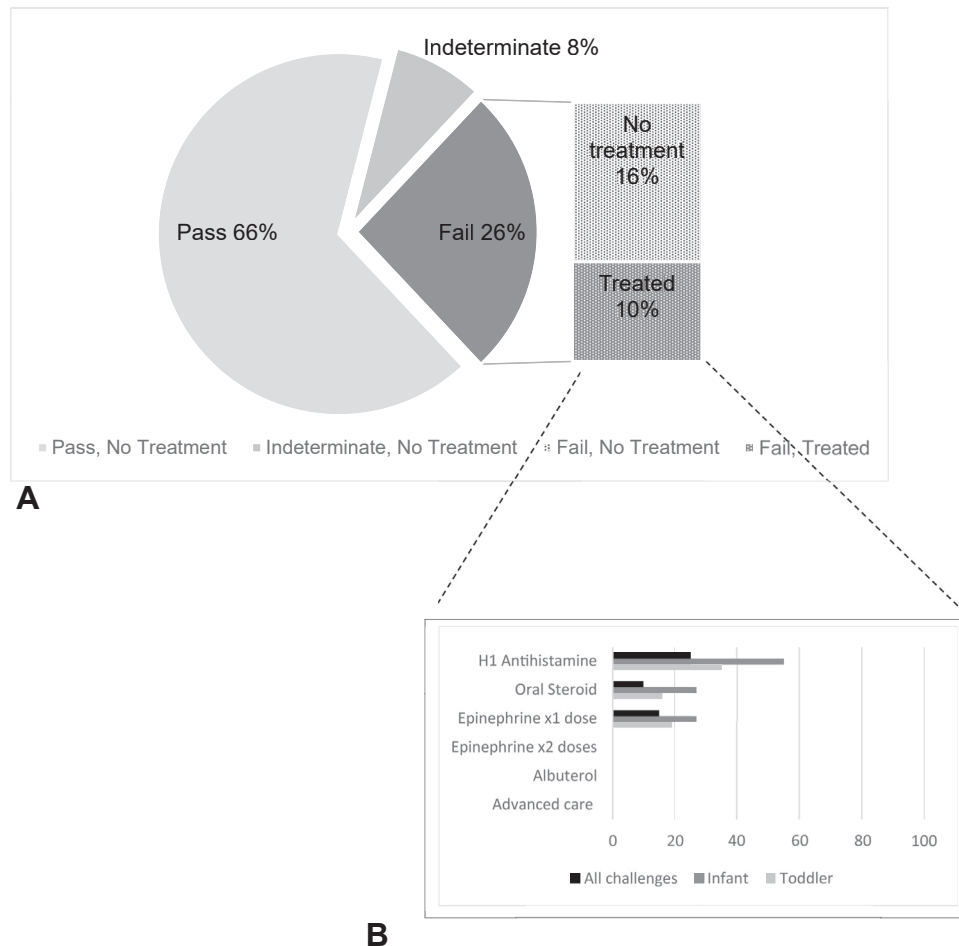


FIGURE 1. (A) Treatment used at all OFCs. Failed OFCs were 26%, and 10% required treatment. **(B)** Treatment used at failed OFCs by age group. Of the failed OFCs requiring treatment, no differences were observed in H1 antihistamine, epinephrine, or oral steroid use by age.

(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, 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 Health-Nuts 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.

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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 Allergen; and is also cofounder of AllergyHome and Allergy Certified Training. W. G. Shreffler is on the Scientific Board Advisory of Aimmune Therapeutics and is 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.

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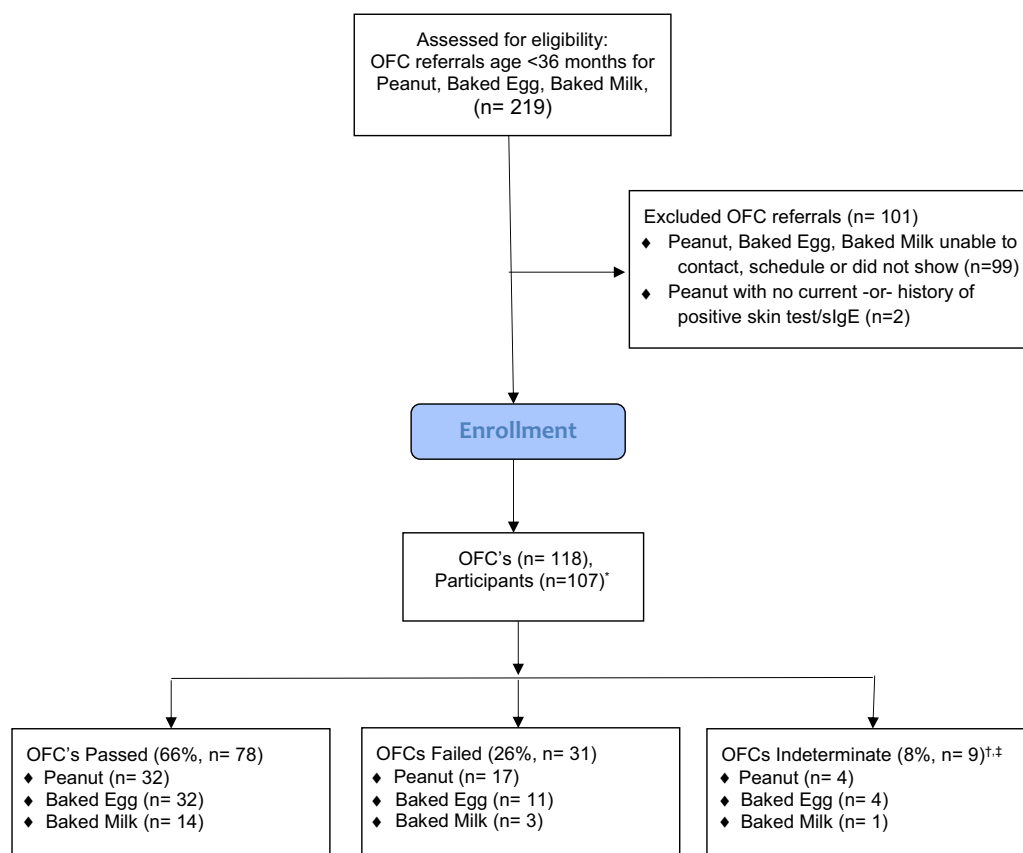


FIGURE E1. CONSORT flow diagram of OFCs. *Eleven individuals had OFCs to 2 foods. Of these 11 individuals, 2 individuals had peanut OFC when they were an infant and baked egg OFC when they were a toddler. OFC outcomes were retained in analyses because the challenge food was different. †One individual was indeterminate (to baked egg) as an infant, then passed as a toddler. Infant challenge was a duplicate and excluded. Toddler challenge was retained. ‡Two individuals passed a repeat challenge performed (1 for peanut and 1 for baked egg). In both cases, the latest challenge was selected for analysis and the previous indeterminate challenge was excluded.

TABLE E1. Dietitian-prepared challenge foods with prescribed dosing

Dose no.	Peanut		Baked egg		Baked milk	
	Teaspoon	Cumulative grams of protein	Muffin	Cumulative grams of protein	Muffin	Cumulative grams of protein
1	1/16	0.07	1/32	0.06	1/32	0.05
2	1/8	0.22	1/16	0.19	1/16	0.15
3	1/4	0.52	1/8	0.44	1/8	0.35
4	1/2	1.11	1/4	0.94	1/4	0.75
5	1	2.3	Remaining 1/2	2	Remaining 1/2	1.6
6 (optional)	1.5	4.07	NA	NA	NA	NA

NA, Not available/applicable.

Lower predoses were allowed at the discretion of the challenge investigator.

TABLE E2. Allergic clinical characteristics and OFC outcome by age at challenge

Characteristic and outcome	n	Infant OFC (n = 37)	Toddler OFC (n = 81)	P
Age (mo), mean $\pm$ SD	118	9.2 $\pm$ 1.8	20.5 $\pm$ 6.7	<.001
Allergic clinical characteristic				
SPT wheal size (mm), mean $\pm$ SD before challenge				
Peanut	53	5.1 $\pm$ 3.2	3.4 $\pm$ 3.2	.071
Egg white	46	8.5 $\pm$ 2.3	8.1 $\pm$ 3.1	.641
Milk	18	12.0 $\pm$ 4.0	6.7 $\pm$ 4.3	.066
Casein	16	4.5 $\pm$ 0.7	4.4 $\pm$ 3.7	.979
sIgE (kU/L), mean $\pm$ SD before challenge				
Peanut	33	5.34 $\pm$ 7.1	2.3 $\pm$ 3.6	.111
Ara h 2	22	0.3 $\pm$ 0.3	0.4 $\pm$ 0.8	.549
Egg white	42	6.3 $\pm$ 6.6	3.7 $\pm$ 4.4	.150
Ovomucoid	36	0.8 $\pm$ 0.9	0.9 $\pm$ 1.0	.813
Milk	18	6.8 $\pm$ 9.6	3.4 $\pm$ 4.5	.339
Casein	17	0.4 $\pm$ 0.04	1.7 $\pm$ 2.5	.375
Previous reaction history to challenge antigen as reported by allergist, n (%)	118	8 (21.6)	59 (72.8)	<.001
OFC Outcome, n (%)	118			.738
Pass		24 (64.9)	54 (66.7)	
Fail		11 (29.7)	20 (24.7)	
Indeterminate		2 (5.4)	7 (8.6)	

TABLE E3. Sensitization alone vs previous reaction history by food antigen and age with corresponding allergy test*

	N	Sensitization alone, no previous reaction history	Previous reaction history	
		Positive SPT result or sIgE	Positive SPT result or sIgE	Negative SPT result or sIgE (<0.35 kU/L) at OFC†
Peanut, n (%)	53	26 (49)	18 (34)	9 (17)
Infant		17 (32)‡	3 (6)	—
Toddler		9 (17)§	15 (28)	9 (17)
Egg, n (%)	47	21 (45)	26 (55)	
Infant		11 (24)	3 (6)	
Toddler		10 (21)	23 (49)	
Milk, n (%)	18	4 (22)	14 (78)	
Infant		1 (5)	2 (11)	
Toddler		3 (17)	12 (67)	

*All OFCs had a documented positive allergy test result.

†Nine toddler OFCs with a history of previous reaction had a negative allergy test result to peanut closer to OFC but had history of positive skin test result within the past year primarily from a different allergist. We defined negative sIgE in this study as <0.35 kU/L because not all sIgE laboratories systematically measured down to 0.1 kU/L. Of the 9 toddler OFCs, 4 had documented peanut sIgE between 0.1 and 0.34 kU/L at OFC.

‡Fifteen infant OFCs met NIAID criteria for peanut challenge referral (at-risk infant with skin test wheal 3-7 mm to peanut, without reaction history). Two additional infant OFCs did not meet NIAID criteria (one had SPT wheal 10 mm but low sIgE and was challenged per referral clinician judgment; and another one was referred with SPT wheal at 6 mm, which had just increased to 10 mm shortly before challenge, and decided to go ahead with challenge). The 2 infant OFCs with SPT wheals greater than 7 mm were failed OFCs.

§One toddler OFC, without reaction history, with peanut sensitization at time of OFC referral but negative test result just before OFC went ahead with challenge per clinician judgment and is categorized here as sensitization alone.

||All previous reactions to egg and milk were to unbaked egg and unbaked milk. All baked egg and baked milk OFCs had a positive allergy test result at challenge.

TABLE E4. Body system and symptom involvement identified during failed OFCs for children younger than 3 y (n = 31)

Reported by system*	n (%)
Cutaneous	27 (87)
Upper respiratory	9 (29)
Gastrointestinal	5 (16)
Lower respiratory	4 (13)
Cardiovascular	2 (7)
Reported by symptom	n (%)
Hives	23 (74)
Confluent erythema	7 (23)
Angioedema, perioral/periorbital	2 (7)
Persistent scratching, no hives	1 (3)
Other macules	1 (3)
Sneezing	9 (29)
Ear rubbing/pulling	4 (13)
Rhinorrhea	1 (3)
Tongue-out (pulling/thrusting/rolling/lip-licking)†	3 (10)
Vomiting	2 (7)
Coughing	4 (13)
Wheezing	1 (3)
Stridor	1 (3)
Tachycardia‡	2 (7)

*Some reactions were multisystemic. Symptoms that belonged to one body system were grouped together (eg, a participant having hives and angioedema counted as 1 cutaneous).

†Tongue-out behavior was classified as gastrointestinal (oral).

‡Tachycardia was defined as 25% increase from baseline, and was associated with cutaneous, upper respiratory, and gastrointestinal systems. Blood pressure was not routinely measured because it tended to increase crying unnecessarily. Keeping the child calm and easily approachable during a reaction for accurate assessment was important. Acute inconsolable crying/irritability occurred in 3 failed challenges (10%) and was associated with systemic symptoms, 2 of which involved tachycardia. In 1 participant, inconsolable crying/irritability was associated with profound pruritis, diffuse urticaria, periorbital angioedema, and tachycardia; in another participant, inconsolable crying/irritability was associated with hives, vomiting, and tachycardia; and in a third participant, inconsolable crying/irritability was associated with 50% confluent erythema, diffuse urticaria, and sneezing, but no tachycardia.