epinephrine being delivered intramuscularly, the concern is that it might. Needle lengths of EAIs have already been cited as potentially inadequate to reliably deliver epinephrine to the muscle bed.[5,6] Any amount of unexpected recoil that occurs while using a real EAI during an emergency might further reduce the likelihood of successful intramuscular administration.[7] On the basis of this pilot study, it might be prudent for practitioners to inform patients that there are indeed differences with regard to how much force is required to activate different brands of EAIs, as well as differences in recoil generated. This might be of particular importance for those patients or providers who have been using one brand of EAI exclusively and then switch to a different brand of EAI. Encouraging patients to practice with real expired EAIs on tissue simulants, such as an orange, might also be beneficial. Regardless of the brand of EAI used, providers should instruct patients to firmly grasp the device and to continually depress the EAI into the thigh after activation occurs. This compression might also help displace subcutaneous fat and reduce the distance to muscle in some patients, potentially increasing the likelihood of intramuscular administration of epinephrine.[5,6,8]

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Predetermined challenge eligibility and cessation criteria for oral food challenges in the HealthNuts population-based study of infants

To the Editor:

Oral food challenges (OFCs) remain the gold standard for diagnosing food allergy.[1] However, to date, most studies describing the use of OFCs for the purposes of diagnosing food allergy have been retrospective clinical audits that have not clearly described crucial methodological characteristics, such as eligibility for challenge and exclusion and inclusion criteria.[2,3] Study outcomes from these retrospective audits are difficult to generalize to other clinic or population cohorts because undeclared physician and parent selection bias is likely to significantly affect the inclusion or exclusion of, for instance, a child with a history of anaphylaxis. Furthermore, the validity of challenge cessation criteria cannot be formally assessed if they have not been prospectively developed and applied using objective and reproducible allergic signs.

To date, there are no standard cessation criteria for the definition of a positive OFC result. Differences in food challenge cessation criteria across different studies and different centers will hinder the ability to (1) compare food allergy prevalence estimates between studies, (2) identify risk factors for the development of food allergy (because phenotypes might vary across different study cohorts), and (3) assess the success of various treatment strategies (including oral immunotherapy).

Using a clear definition of eligibility criteria (with prospective decisions regarding inclusion/exclusion of those with a history of previous reactions, including anaphylaxis) and predetermined cessation criteria, we describe outcomes from more than 1000 OFCs in 12-month-old population-recruited infants that will help to inform future standardization of food challenges.

The study methods have been described in detail elsewhere.[4,5] Briefly, all participating infants recruited from a population-based sample (n = 4457; response rate, 73%; mean age, 12.7 months; SD, 0.8 months) underwent skin prick tests (SPTs) to peanut, egg, and sesame. Those with a detectable wheal (≥1 mm) on SPTs (21%) underwent a hospital-based OFC to peanut butter, raw egg, or tahini paste. A subset of those with positive results to raw egg underwent a challenge to baked egg in the form of a muffin (dose equivalent to one sixth of an egg).

We prospectively developed minimum objective criteria for defining a positive food challenge result and hence stopping a challenge in infants based on data from published studies[6] and expert peer consultation.

Infants were considered to have food allergy (and thus not offered a food challenge) if a parent reported a recent history of an objective allergic reaction (see below for the criteria used to define an objective reaction within the HealthNuts study) occurring within 2 hours of ingestion of the food and the infant had a

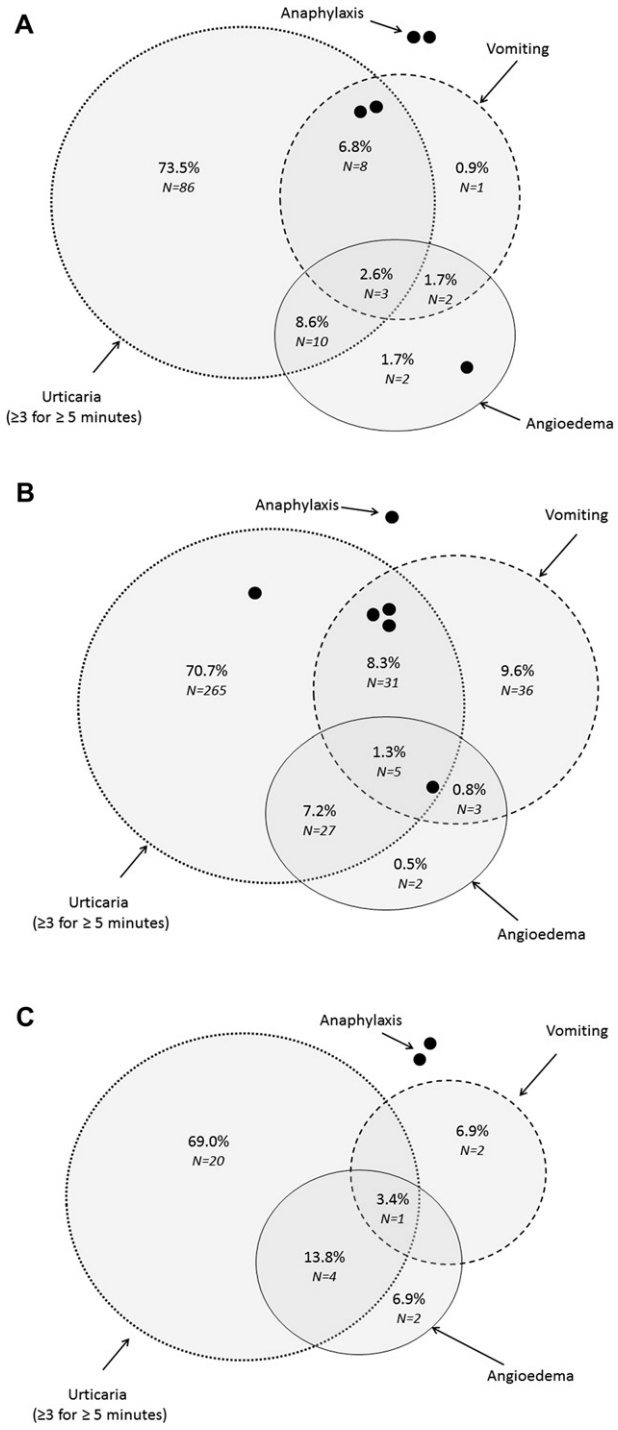

FIG 1. Reactions as defined by HealthNuts food challenge criteria observed during positive peanut **(A)**, raw egg **(B)**, and sesame **(C)** challenges. Baked egg challenges are not shown because only 1 infant had more than 1 type of reaction (that infant had both hives and vomiting). *Solid circles,* Individual episodes of anaphylaxis. Of the 5 infants with respiratory symptoms and no other symptoms meeting the HealthNuts challenge criteria, 2 also had erythema and transient hives, 1 had transient hives only, and 1 had rhinorrhea. The remaining infant had only respiratory symptoms.

positive SPT response (≥1 mm) in the immunization clinic and was currently avoiding the food in question. A recent history was defined as less than 1 month before the clinic food challenge for egg (because egg allergy can resolve rapidly in infancy) or 2 months for peanut and sesame. Only 11 infants were excluded from egg challenge and 5 from peanut challenge based on these criteria (<2% of sensitized infants were excluded). No infants were excluded from sesame challenge. Food challenge involved gradually increasing doses on day 1 in the hospital and continued ingestion of the maximum day 1 dose (1 teaspoon of peanut butter or tahini paste or 1 whole raw egg white) on days 2 through 7.

HealthNuts standardized cessation criteria for a positive OFC result were any of the following signs occurring within 2 hours of ingestion:

- 3 or more concurrent noncontact urticaria persisting for at least 5 minutes;
- perioral or periorbital angioedema;
- vomiting (excluding gag reflex); and
- evidence of circulatory or respiratory compromise (anaphylaxis[7]; eg, persistent cough, wheeze, change in voice, stridor, difficulty breathing, and collapse).

The food challenge result was also considered positive if any of the above reactions occurred within 2 hours of ingestion of the food on days 2 to 7 of the challenge at home.

Allergic reactions meeting the HealthNuts food challenge criteria occurred in 121 (33%) of 370 peanut challenges, 385 (65%) of 594 raw egg challenges, and 29 (30%) of 97 sesame challenges. Of the 130 subjects with raw egg allergy who completed a challenge to baked egg, 84% tolerated an egg-containing muffin.

Fig 1 shows the occurrence and overlap of each of the different signs included in the HealthNuts cessation criteria for each food allergen for those infants who reacted on day 1 during the in-hospital challenge. Anaphylaxis occurred less often in subjects with positive egg challenge results (1.6%) compared with both peanut (4.3%, $P = .09$) and sesame (6.3%, $P = .07$) challenges. Of the 13 episodes of anaphylaxis, all were treated with intramuscular adrenaline, and 9 of these subjects also received albuterol (Ventolin; GlaxoSmithKline, London, United Kingdom). No biphasic reactions were observed.

Overall, 1.6% of the infants who underwent OFCs did not react on day 1 of the challenge but subsequently had symptoms meeting the criteria for a positive OFC result on days 2 or 3 of the challenge at home: 3.6% for raw egg challenges, 1.3% for peanut challenges, and 0% for sesame and baked egg challenges. None of the reactions occurring at home required treatment with adrenaline.

Transient urticaria and cases with only 1-2 urticarial wheals were common during challenges in infants who did not have any other signs of a positive reaction, occurring as the only sign of a reaction in 16% of peanut challenges, 20% of sesame challenges, and 29% of egg challenges. Less than 1% of infants with no urticaria during food challenges had a reaction meeting the HealthNuts criteria on continuing the challenge at home. In comparison, 10.6% and 5.0% of infants with some urticaria on day 1 (not meeting the HealthNuts criteria for a positive challenge result) had a reaction at home to egg and peanut, respectively (Table I).

We have reported the largest series of OFCs ever undertaken in a single age group (1-year-old infants). We found that our predefined challenge criteria could be applied safely in 12-month-old infants with a low prevalence of anaphylaxis during challenge and no episodes of anaphylaxis occurring in those continuing the challenge at home, despite challenges being performed in all children with a detectable SPT wheal response irrespective of wheal size or a previous history of less than recent reaction. Furthermore, few of those (<2%) who completed day

TABLE I. Proportion of infants with only transient urticaria or only 1-2 urticarial wheals during OFCs who had later objective symptoms meeting HealthNuts diagnostic criteria for food allergy on continuing the food challenge at home

Food being challenged	Total number classified as tolerant on day 1†	Transient urticaria during OFC (yes/no)	Proportion with a reaction on days 2-7 at home meeting HealthNuts criteria, % (95% CI)*	*P* value‡
Peanut	226	No (n = 187)	0.5 (0.01-2.9)	.002
		Yes (n = 39)	5 (0.6-17.3)	
Egg	166	No (n = 119)	0.8 (0.02-4.6)	.023
		Yes (n = 47)	10.6 (3.5-23.1)	
Baked egg	109	No (n = 89)	0	ND§
		Yes (n = 20)	0	
Sesame	59	No (n = 50)	0	ND
		Yes (n = 9)	0	

*Objective reaction meeting HealthNuts diagnostic criteria for food allergy developed on a subsequent dose of the OFC at home.
†Infants did not have a reaction meeting HealthNuts criteria for a positive challenge result on day 1.
‡*P* value for Pearson χ^2 comparisons of infants with and without transient urticaria during OFCs.
§Not determined because no infants had reactions on days 2 to 7 to baked egg or sesame meeting the HealthNuts criteria for a positive challenge result.

1 of the challenge without a reaction subsequently had immediate reactions on days 2 to 7 of the challenge at home.

Although we found that infants with transient urticaria (insufficient to meet our cessation criteria on day 1) were more likely to have positive challenge criteria on subsequent days of the challenge than those with no transient urticaria, decreasing the threshold criteria to include transient urticaria would increase the false-positive rate of food challenges significantly.

Although our criteria appear appropriate for 1-year-old patients, alternate criteria might be required for older children, and further studies are required to address this.

Development of a standardized set of criteria to define a positive challenge result has the potential not just to inform clinical practice but also to allow direct comparison across studies of prevalence and risk factors for the development of food allergy, including genotype/phenotype correlations. Such criteria will also enable direct comparison of the effectiveness of novel therapeutics, such as oral immunotherapy and peptide vaccines, that are currently in development. We have shown that our clearly defined inclusion/exclusion and predetermined cessation criteria can be safely applied to OFCs in infants. Development of challenge cessation criteria that can be applied across different age groups is urgently required to improve food challenge standardization.

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