

# Food-Induced Anaphylaxis in Infants: Can New Evidence Assist with Implementation of Food Allergy Prevention and Treatment?



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**Overall Purpose/Goal:** To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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**List of Design Committee Members:** Angela Tsuang, MD, MSc, Edmond S. Chan, MD, and Julie Wang, MD (authors); Scott H. Sicherer, MD (editor)

### Learning objectives:

1. To list the most common food triggers of anaphylaxis in infants compared with older children.
2. To describe the unique clinical presentation of food-induced anaphylaxis in infants.
3. To counsel caregivers regarding the risk and severity of food-induced anaphylaxis in infants.
4. To identify challenges in the diagnosis of food allergies and the status of potential food allergy treatment therapies in infants.

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**Previous guidance on infant anaphylaxis largely relied on data from older children and adults. Infants are a unique subgroup, which presents specific challenges because infants are unable to verbalize symptoms, although the magnitude of underrecognition is not well studied. Data show that strict avoidance of allergens is difficult to achieve in the infant age**

**group and a source of stress and anxiety for their caregivers. Recent studies suggest that infant anaphylaxis is less severe than in older children, which could greatly assist with implementation of food allergy prevention and treatment. New evidence from clinical trials and observational and real-world studies show that infant anaphylaxis is rare on first ingestion of a**

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*Abbreviations used*

EAI- Epinephrine autoinjector  
 ED- Emergency department  
 EPITOPE- Safety and Efficacy Study of Viaskin Peanut in  
 Peanut-allergic Young Children 1-3 Years of Age  
 IMPACT- Oral Immunotherapy for Induction of Tolerance and  
 Desensitization in Peanut-Allergic Children  
 LEAP- Learning Early About Peanut  
 MILES- Efficacy and Safety of Viaskin Milk in Children With  
 IgE-Mediated Cow's Milk Allergy  
 NIAID- National Institute of Allergy and Infectious Diseases  
 OFC- Oral food challenge  
 OIT- Oral immunotherapy  
 POSEIDON- Peanut Oral Immunotherapy Study of Early  
 Intervention for Desensitization  
 SPT- Skin prick test

**new food and typically not severe when it occurs, which parents may not be aware of when preparing to introduce peanut or other common food allergens to infants for the purpose of prevention. The better safety and efficacy of oral immunotherapy in infants and preschoolers could help prevent undesired psychosocial consequences of longstanding food allergy such as anxiety, bullying, and poor quality of life. Evidence from recent years on the lower risk of infant anaphylaxis and its severity could move allergy practice toward the confidence that regular, long-term ingestion provides.** © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:57-69)

**Key words:** Anaphylaxis; Foods allergy; Allergic reaction; Epinephrine; Children; Infant

## INTRODUCTION

Anaphylaxis is a severe, life-threatening allergic reaction, which should be treated immediately with epinephrine. Improved clinical outcomes have been reported when anaphylaxis is recognized and treated promptly.<sup>1-3</sup> The estimated prevalence of food allergies in children is approximately 8%, which continues to increase.<sup>4,5</sup> The most common cause of anaphylaxis in children presenting to the emergency department (ED) is food.<sup>6-9</sup>

The results from the landmark Learning Early About Peanut (LEAP) study were published in 2015 and reported that early introduction of peanut between age 4 and 11 months in high-risk infants was associated with decreased risk in the development of peanut allergy.<sup>10</sup> Based on these findings, the Addendum Guidelines to the Development of Peanut Allergy in the United States were published by the National Institute of Allergy and Infectious Diseases (NIAID) in January 2017.<sup>11</sup> All infants at high risk of peanut allergy are advised to be evaluated, and depending on allergy testing, potentially introduced to peanut between age 4 and 6 months. High risk is defined as infants with severe eczema or egg allergy. In addition, infants with mild to moderate eczema are advised to be introduced to peanut as early as around age 6 months. Several studies have also evaluated the effect of early introduction of egg in infants with mixed results,<sup>12-17</sup> with cooked egg having much better safety and efficacy than raw egg. According to an American Academy of

Pediatrics clinical report, it still remains unclear whether early introduction of heated or cooked forms of egg leads to tolerance of all forms of egg,<sup>18</sup> although other international guidelines have fully endorsed early introduction of cooked (not raw) egg.<sup>19,20</sup>

With these major changes in food introduction guidance focusing on earlier introduction, more information is needed on the risk of infant anaphylaxis.<sup>21-23</sup> There exists variability among studies in how infants are defined, which may be up to age 12 months or 24 months. For the purpose of this review, studies defining infants up to age 24 months are included. The recommendations from a consensus panel of experts published in 2019 have provided some guidance on the recognition, diagnosis, and treatment of anaphylaxis in infants.<sup>22</sup> Many recommendations have been extrapolated from evidence on older children, and this expert panel agreed that more research is needed to support specific anaphylaxis guidance for infants.

The objective of this review was to provide an overview of the prevalence and characteristics of food-induced anaphylaxis as well as specific challenges related to anaphylaxis in infants. Increased awareness and knowledge about anaphylaxis in this infant age group may lead to improved diagnosis and management and prevention of allergic reaction recurrence. As caregivers are being asked to introduce potential food allergens earlier on in infants, clinicians will need to be able to address caregiver concerns and provide appropriate counseling.

## PREVALENCE AND SEVERITY

### Prevalence of anaphylaxis

The exact prevalence of anaphylaxis in infants remains unknown.<sup>22,23</sup> Several studies estimate that between 3% and 22% of anaphylaxis cases presenting to the ED are infants.<sup>6,24-26</sup> Cases of food-related anaphylaxis have been reported in infants as young as age 1 or 2 months.<sup>26,27</sup> It is apparent that food is the most common cause of anaphylaxis in infants, with reports of up to 83% of anaphylaxis cases attributed to food in 1 study.<sup>28</sup> Food was found to be significantly more likely to be a trigger for anaphylaxis in infants compared with older children ( $P < .001$ ).<sup>25</sup> Consistent with older children, the frequency of food-induced anaphylaxis seems to be increasing over time in infants. Jeon et al<sup>29</sup> reported that the number of infant anaphylaxis cases in Korea quadrupled from 2009 to 2013.

Although more evidence is needed on whether infant anaphylaxis is truly increasing around the world, studies suggest that anaphylaxis may occur less frequently in infants in comparison to older children. In a registry of food-induced anaphylaxis reactions ( $n = 1951$ ) reported voluntarily by French-speaking allergists (Allergy Vigilance Network), there were 386 episodes of food-induced anaphylaxis among 375 children younger than 7 years.<sup>27</sup> Pouessel et al<sup>27</sup> noted that 3% of anaphylactic reactions ( $n = 61$ ) occurred in infants 12 months or younger, whereas 20% ( $n = 325$ ) were reported in preschool children aged 1 to 6 years and 45% ( $n = 884$ ) in older children aged 7 to 15 years. Ko et al<sup>30</sup> similarly demonstrated that there was a trend for decreased anaphylaxis frequency in children younger than 2 years (infants and toddlers) compared with preschoolers younger than 5 years (31% vs 42%;  $P = .06$ ). Samady et al<sup>26</sup> reported that 13% of food-induced anaphylaxis cases presenting to the ED between 2015 and 2017 occurred in infants younger than 12 months, 12% in toddlers (12-23

TABLE I. Selection of clinical studies on infant anaphylaxis

| Author,<br>Year of<br>publication,<br>Location                                                | Study type (years<br>of data collection)                                                                                           | Population                                                                                                        | Infant age (n),<br>Comparison age<br>groups                                                                                            | Clinical symptoms in<br>infants                                                                                                                                                                                                                                                | Triggers in infants                                                                                                                                                                                                    | Anaphylaxis<br>definition<br>(severity)                                                                                   | Fatalities in<br>infants | % Anaphylaxis,<br>Severity                                                                                                                                                                   | % Treated with<br>epinephrine                                                                                                                                                   |
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| Ko et al, 2020, <sup>30</sup><br>USA (California)                                             | Retrospective case<br>series from<br>review of ED<br>records (from<br>Jan 2016 to Dec<br>2018)                                     | 1518 children<br>younger than 5 y<br>presenting to the<br>ED with <i>food-<br/>induced allergic<br/>reactions</i> | Infants <12 mo<br>(n = 448)<br>Compared with<br>toddlers 12 mo<br>to <2 y (n =<br>494) and<br>preschoolers 2 y<br>to <5 y (n =<br>576) | Mucocutaneous 99%<br>GI 32%<br>Respiratory 7%*<br>CV 0.9%<br>Hypotension 0.2%<br>Mucocutaneous<br>symptoms more<br>common in infants and<br>toddlers compared with<br>preschoolers ( $P < .001$ )                                                                              | Hen's egg 34%<br>Peanut 22%<br>Cow's milk 16%<br>Tree nuts 8%<br>Seeds 4%<br>Finned fish 3%<br>Hen's egg ( $P < .001$ ) and<br>cow's milk ( $P = .02$ )<br>more likely in infants<br>compared with other<br>age groups | Not reported                                                                                                              | None                     | Anaphylaxis: 32%<br>of infants<br>Infants and<br>toddlers 0-2 y<br>trended toward<br>decreased<br>anaphylaxis<br>compared with<br>preschoolers<br>( $P = .06$ )<br>Severity:<br>Not reported | <i>In the ED:</i><br>Infants 10%<br>Toddlers 12%<br>Preschoolers 16%<br>( $P = .36$ )<br><i>Prehospital:</i><br>Infants 4%<br>Toddlers 12%<br>Preschoolers 13%<br>( $P = .12$ ) |
| Pouessel et al, <sup>27</sup><br>2020<br>France and other<br>French-<br>speaking<br>countries | Retrospective case<br>series,<br>voluntary<br>reports to the<br>Allergy<br>Vigilance<br>Network<br>registry (from<br>2002 to 2018) | 375 children aged 0-<br>6 y with <i>food-<br/>induced<br/>anaphylaxis</i>                                         | Infants $\leq$ 12 mo<br>(n = 59)<br>Compared with<br>preschool<br>children 1-6 y<br>(n = 316)                                          | Mucocutaneous 79%<br>GI 49%<br>Respiratory 48% (dyspnea<br>31%, wheezing 11%,<br>laryngeal edema 11%,<br>cough 10%)<br>Neuro 26%<br>CV 21%†<br>Hives ( $P = .02$ ),<br>hypotension ( $P =$<br>.004), and neurological<br>symptoms ( $P = .002$ )<br>more common in<br>infants† | Cow's milk 59%<br>Hen's egg 20%<br>Wheat 7%<br>Peanut 3%<br>Cow's milk ( $P < .001$ )<br>and hen's egg ( $P <$<br>.001) more likely in<br>infants compared with<br>other age group                                     | Sampson et al, <sup>31</sup><br>NIAID/FAAN<br>2006<br>(Severity defined<br>by Ring and<br>Messmer, <sup>32</sup><br>1977) | None                     | Anaphylaxis: Not<br>reported<br>Severity: severity<br>ring <sup>32</sup> grade 2,<br>58%; grade 3,<br>42%; grade 4,<br>0%                                                                    | Infants 25%<br>Preschoolers 22%<br>( $P = .61$ )                                                                                                                                |
| Jeon et al, <sup>29</sup> 2019<br>Korea                                                       | Retrospective case<br>series from<br>review of<br>medical records<br>from 23<br>hospitals (from<br>2009 to 2013)                   | 363 infants aged 0-2<br>y presenting with<br><i>anaphylaxis due<br/>to any trigger</i>                            | Infants <2 y (n =<br>363)<br>No comparison<br>group                                                                                    | Cutaneous 99%<br>Respiratory 83%*<br>GI 30%<br>Neuro 12%<br>CV 8%                                                                                                                                                                                                              | Food 93%<br>Cow's milk 44%<br>Hen's egg 22%<br>Wheat 8%<br>Walnut 8%<br>Peanut 5%<br>Other nuts 3%<br>Finned fish 2%<br>Soybean 2%                                                                                     | Sampson et al, <sup>31</sup><br>NIAID/FAAN<br>2006                                                                        | Not<br>reported          | Anaphylaxis: Not<br>reported<br>Severity:<br>Not reported                                                                                                                                    | Infants 47%                                                                                                                                                                     |

(continued)

TABLE I. (Continued)

| Author,<br>Year of<br>publication,<br>Location                                                                                      | Study type (years<br>of data collection)                                                            | Population                                                                                                                                        | Infant age (n),<br>Comparison age<br>groups                                                                                                                   | Clinical symptoms in<br>infants                                                                                                                                                                                                                                                                                                                           | Triggers in infants                                                                                                                                                                                                                                 | Anaphylaxis<br>definition<br>(severity)                                                                            | Fatalities in<br>infants | % Anaphylaxis,<br>Severity                                                                                                                               | % Treated with<br>epinephrine                |
|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Samady et al, <sup>26</sup><br>2018<br>USA (Illinois)                                                                               | Retrospective case<br>series from<br>review of ED<br>records (from<br>June 2015 to<br>June 2017)    | 357 children aged 0-<br>18 y presenting to<br>the ED with <i>food-<br/>induced<br/>anaphylaxis</i>                                                | Infants <12 mo<br>(n = 47)<br>Compared with<br>toddlers 12-23<br>mo (n = 43),<br>preschoolers 2-<br>6 y (n = 96),<br>and school<br>children >6 y<br>(n = 171) | Cutaneous 94%<br>GI 89%<br>Respiratory 17%<br>(breathing difficulty<br>11%, cough 9%,<br>wheezing 2%,<br>shortness of breath 0%)<br>Oropharyngeal 9%<br>CV 2%<br>Skin symptoms more<br>common in infants<br>compared with school<br>children ( $P < .001$ ). GI<br>symptoms more<br>common in infants<br>compared with other<br>age groups ( $P < .01$ ). | Hen's egg 38%<br>Cow's milk 17%<br>Peanut 13%<br>Tree nut 6%<br>Hen's egg more likely<br>compared with any age<br>group ( $P \leq .001$ ).<br>Cow's milk more likely<br>compared with school<br>children ( $P = .04$ )                              | Sampson et al, <sup>31</sup><br>NIAID/FAAN<br>2006                                                                 | None                     | Anaphylaxis: Not<br>reported<br>Severity:<br>Not reported                                                                                                | Not reported                                 |
| Topal et al, <sup>25</sup> 2013<br>Turkey                                                                                           | Retrospective case<br>series from<br>review of<br>medical records<br>(from Jan 2007 to<br>Dec 2011) | 104 children aged 0-<br>17 y, presenting<br>with <i>anaphylaxis<br/>due to any trigger</i>                                                        | Infants $\leq 12$ mo<br>(n = 23)<br>Compared with<br>children aged<br>>12 mo to 17 y<br>(n = 81)                                                              | Cutaneous 100%<br>Respiratory 78% (stridor<br>48%, cough 30%,<br>wheezing 17%,<br>hoarseness 4%,<br>dyspnea NA)<br>GI 26%<br>CV 0%<br>Persistent vomiting was<br>more commonly<br>reported in infants ( $P = .023$ )                                                                                                                                      | Food 91%<br>Cow's milk 61%,<br>Hen's egg 22%<br>Walnut 9%<br>Food is more likely the<br>trigger in infants<br>compared with children<br>( $P < .001$ )                                                                                              | Sampson et al, <sup>31</sup><br>NIAID/FAAN<br>2006<br>(Severity defined<br>by Muraro<br>et al, <sup>33</sup> 2007) | None                     | Anaphylaxis: Not<br>reported<br>Severity:<br>Mild 48%<br>Moderate 44%<br>Severe 9%<br>Severe<br>anaphylaxis less<br>frequent in<br>infants ( $P = .04$ ) | Infants 30%<br>Children 40%<br>( $P > .05$ ) |
| Fleischer et al, <sup>34</sup><br>2012<br>5 sites in USA<br>(New York,<br>Maryland,<br>Arkansas,<br>Connecticut,<br>North Carolina) | Multicenter,<br>prospective,<br>observational<br>study (median<br>follow-up 36<br>mo)               | 512 infants with<br>documented or<br>likely milk and/or<br>egg allergy, 367<br>of which<br>experienced 1171<br>food-induced<br>allergic reactions | Infants 3-15 mo<br>(n = 512)<br>No comparison<br>age group                                                                                                    | Not reported                                                                                                                                                                                                                                                                                                                                              | Cow's milk 42%<br>Hen's egg 21%<br>Peanut 8%<br>Wheat 4%<br>Finned fish 3%<br>Tree nuts 3%<br>Annualized rate of<br>reactions:<br>Milk 0.34/y, (95% CI,<br>0.31-0.37)<br>Egg 0.17/y (95% CI, 0.15-<br>0.19)<br>Peanut 0.06/y (95% CI,<br>0.05-0.08) | (Severity defined<br>by Perry et al, <sup>35</sup><br>2004)                                                        | Not<br>reported          | Anaphylaxis: Not<br>reported<br>Severity:<br>Mild 70%<br>Moderate 18%<br>Severe 11%                                                                      | Infants 30% of<br>severe reactions           |

|                                                               |                                                                                 |                                                                             |                                                                                                                                           |                                                                                                                                    |                                                                                                                                                                           |                                                    |              |                                                     |              |
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| Rudders et al, <sup>7</sup><br>2011<br>USA<br>(Massachusetts) | Retrospective case series from review of ED records (from Jan 2001 to Dec 2006) | 522 children aged 0-18 y presenting to the ED with food-induced anaphylaxis | Infants <2 y (n = 191)<br>Compared with preschoolers 2-5 y (n = 171), school-age children 6-11 y (n = 150), adolescents 12-18 y (n = 145) | Cutaneous 98%<br>Respiratory 59%*<br>GI 56%<br>CV noncalculable<br>Hives (P = .002) and vomiting (P < .001) more common in infants | Cow's milk 40%<br>Peanut 31%<br>Hen's egg 9%<br>Tree nuts 9%<br>Cow's milk (P < .001) and peanut (P = .01) more likely triggers in infants compared with other age groups | Sampson et al, <sup>31</sup><br>NIAID/FAAN<br>2006 | Not reported | Anaphylaxis: Not reported<br>Severity: Not reported | Not reported |
|---------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|--------------|-----------------------------------------------------|--------------|

AVA, Anaphylaxis; CV, cardiovascular; FAAN, Food Allergy and Anaphylaxis Network; GI, gastrointestinal; NA, not applicable/available.

\*Specific type of respiratory symptoms was not reported.

†Pouessel et al<sup>27</sup> noted that severity bias may have contributed to higher reports of CV symptoms as cases of food-induced anaphylaxis were reported voluntarily to a registry.

months old), and the remaining 75% in young or school-aged children (2 years and older).

Severity and fatalities

Besides food-induced anaphylaxis in infants being less frequent compared with older children, the evidence suggests that most reactions in infants are less severe,<sup>25,27</sup> as summarized in Table I. Of 1171 food-induced allergic reactions reported in 512 infants (age 3-15 months) with already documented or suspected milk or egg allergy, Fleischer et al<sup>34</sup> reported that most allergic reactions in infants were mild (70%), whereas the remainder had either moderate (18%) or severe symptoms (11%). In a smaller study among which 44% of infants had known food allergies, 9% of infants (12 months or younger) had anaphylactic reactions categorized as severe, which was significantly lower compared with that in children aged 1 to 17 years (32%; P = .04).<sup>25</sup>

Infants were less likely to present with respiratory and cardiovascular symptoms (Table I), which were more commonly noted in toddlers and older children.<sup>7,26,30</sup> Among children younger than 5 years presenting to the ED for any food-induced allergic reaction, infants younger than 12 months less frequently presented with respiratory symptoms compared with toddlers aged 12 to 23 months and preschoolers aged 2 to 5 years (P < .01).<sup>30</sup> These findings are further supported by Samady et al,<sup>26</sup> who noted that infants younger than 12 months were less likely to have respiratory symptoms such as cough or labored breathing (17%) compared with school children older than 6 years (49%; P < .001).<sup>26</sup> Only 2% of infants with anaphylaxis were reported to have wheezing, which was significantly lower compared with that in toddlers, young children, and school-aged children. The frequencies of cardiovascular signs and hypotension among infants presenting to the ED with food-allergic reactions were noted to be as low as 0.9% and 0.2%, respectively.<sup>30</sup>

Fatalities attributed to anaphylaxis are uncommon in infants (Table I). A meta-analysis of 10 studies reporting deaths among 0- to 19-year-olds in the general population due to food-triggered anaphylaxis calculated the incidence of fatal anaphylaxis to be approximately 1.81 per million person-years (95% CI, 0.94-3.45), which was estimated to be at least 10 times lower than the incidence of accidental death.<sup>36</sup> Among infants, fatalities due to anaphylaxis are rare, and no deaths were reported in recent studies focusing on infants.<sup>25-27,30</sup> There is 1 reported case of a 5-month-old infant with known cow's milk allergy who died secondary to an anaphylactic reaction to a breakfast cereal containing milk as an ingredient.<sup>37,38</sup> A retrospective review of death records in New York City from 2000 to 2014 reported 24 deaths from food-related anaphylaxis among children and adults, but no deaths were noted in children aged 0 to 4 years during this 15-year period.<sup>39</sup>

Biphasic reactions and hospital admissions are also uncommon among infants. Among 535 positive medically supervised oral food challenges (OFCs) to either egg, peanut, or sesame in 1-year-old infants in the HealthNuts study recruited from the general population, there were no biphasic reactions and no late or prolonged anaphylactic reactions occurring at the study clinic or at home.<sup>40-42</sup> In 3 studies, approximately 2% of infants with food-induced anaphylaxis had a biphasic reaction.<sup>27,29,30</sup> One study that was conducted within a single health system comprising multiple medical centers reported only 3 intensive

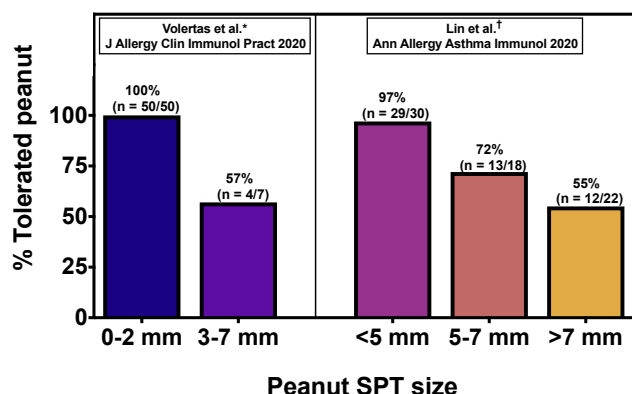


**Figure 1.** Infants tolerating peanut by SPT wheal size. \*Volertas et al.<sup>47</sup> Retrospective chart review of infants younger than 12 months. All subjects with peanut SPT wheal sizes more than 7 mm were instructed to avoid peanut. This figure includes only those subjects who underwent peanut OFC or introduced peanut at home. †Lin et al.<sup>48</sup> Retrospective chart review of infants aged 6 to 13 months who underwent OFC to 1 g of peanut.

care unit admissions (0.6% of food-induced anaphylaxis cases) between 2016 and 2018 among children younger than 5 years, and none were among infants.<sup>30</sup> Only 10 infants (2.2%) presenting to the ED with a food-induced allergic reaction were admitted for observation, and 6 of these infants were admitted as a precaution.

### Risk with early introduction of peanut

With the shift in recommendations in favor of early peanut introduction for at-risk infants, there is increasing interest in the risk of infant anaphylaxis on first-time ingestion. The current literature suggests that this risk is low. In the HealthNuts study, Koplin et al<sup>41</sup> report that there were no life-threatening reactions among 3873 “low-risk” or 751 “high-risk” infants whose parents introduced peanut at home within the first year of life or in hospital-based OFCs in infants recruited from the general population at around 1 year of age. Infants were invited for OFCs to peanut as well as egg and sesame if the skin prick test (SPT) wheal size was 1 mm or greater compared with that achieved with the negative control for either hen’s egg, peanut, sesame, shellfish, or cow’s milk.<sup>40</sup> A random sample of infants with negative SPT results was also invited to undergo the same OFCs as negative controls.<sup>41</sup> Home introduction of peanut in the first year of life was assessed by questionnaires administered to families of infants who declined to participate in SPT and possible food challenges. “Low-risk” and “high-risk” definitions were based on the LEAP study criteria in which “high-risk” infants had early moderate/severe eczema (at 6 months or less) and/or egg allergy and “low-risk” infants had neither. Among the 3873 “low-risk” infants, 0.8% had challenge-confirmed peanut allergy. Sixteen percent of the cohort was categorized as “high risk,” and 14% of these infants were allergic to peanut. Among 150 positive food challenges to peanut performed at 1 year of age, most infants presented with urticaria while anaphylaxis occurred in 4% of positive challenges (n = 6 infants). One of these 6 anaphylaxis

cases occurred in a “low-risk” infant. Infants were older in the HealthNuts study by the time of peanut OFC because they were screened from the general population at 12-month immunization visits and food challenges took place between age 12 and 18 months. There would likely be even fewer allergic reactions to peanut if it was introduced earlier in infancy. Only 0.06% of infants in this study had a possible anaphylactic reaction to peanut when introduced to peanut at home before age 12 months.

In the LEAP study, 7 high-risk infants between 4 and 11 months of age who were randomized to the consumption group (n = 319) reacted during the baseline OFC.<sup>10</sup> Symptoms during these reactions were predominately cutaneous and considered mild. Six were treated with antihistamines, and 1 was treated with an oral glucocorticoid. Based on the HealthNuts cohort and LEAP study, evidence suggests that severe anaphylactic reactions to peanut on first-time ingestion are uncommon in the general population and likely rare among infants without egg allergy or early-onset moderate/severe eczema. In Australia, early introduction of peanut is recommended in infancy without screening those infants who are high risk,<sup>19,43</sup> and its success has been demonstrated with recent evidence.<sup>44</sup> Around the world, no deaths have ever been reported on first ingestion.

Despite these low risks and the evidence behind the benefits of early peanut introduction, a previous study showed that caregivers may still be hesitant to introduce peanut early at home. In a nationwide survey conducted in April 2017, Greenhawt et al<sup>45</sup> reported that less than one-third of caregivers expressed willingness to introduce peanut before or around 6 months of life. Almost 40% preferred to wait until after 11 months, and more than half would not allow skin testing or OFC before 11 months. Even caregivers with a family history of food allergy, including those with food-allergic children, were not more likely to be willing to introduce peanut earlier. In a survey of food allergy knowledge, 52% of parents incorrectly believed young children are at a higher risk for fatal anaphylaxis than adolescents.<sup>46</sup> Allergists and pediatricians are essential in educating the caregivers of infants to encourage early peanut introduction and provide reassurance of the low risk of peanut introduction and the rarity of life-threatening reactions in this specific age group. It will also be of interest to assess whether attitudes will shift regarding early peanut introduction several years after the publication of the NIAID guidelines in January 2017 encouraging earlier introduction of peanut in high-risk infants.

To help shift these attitudes, recently there has been real-world data on reaction risks (rate and severity) at first ingestion during implementation of NIAID guidelines to help with scenarios such as more than 4 mm SPT wheal sizes that data from randomized studies do not address. Volertas et al<sup>47</sup> reviewed 84 infants who underwent screening, and among 16 who had peanut SPT wheal sizes 3 to 7 mm, 7 received peanut OFC (Figure 1). Of these, 3 (43%) reacted at OFC, with none having a severe reaction or needing epinephrine (most only had hives). As expected, among 50 infants who had peanut SPT wheal sizes 0 to 2 mm, 100% tolerated peanut on first ingestion. Lin et al<sup>48</sup> reviewed a larger number of peanut OFC outcomes, in 70 higher-risk infants (>75% had eczema and roughly 50% had egg sensitization) who received 1 g peanut protein OFCs following

**TABLE II.** Symptoms and signs of anaphylaxis in infants \*

| Anaphylaxis symptoms that infants cannot describe                                                                                      | Anaphylaxis signs that are potentially difficult to interpret in infants, and why                                                                                                                                                                                                                                                                                                                             | Anaphylaxis signs in infants: obvious but may be nonspecific                                                                                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| General: feeling of warmth, weakness, anxiety, apprehension, impending doom                                                            | General: nonspecific behavioral changes such as persistent crying, fussing, irritability, fright                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                     |
| Skin/mucus membranes: itching of lips, tongue, palate, uvula, ears, throat, nose, eyes, and so forth; mouth-tingling or metallic taste | Skin/mucus membranes: flushing (may also occur with fever, hyperthermia, or crying spells)                                                                                                                                                                                                                                                                                                                    | Skin/mucus membranes: rapid onset of hives (potentially difficult to discern in infants with acute atopic dermatitis; scratching and excoriations, as such, will be absent in young infants); angioedema (face, tongue, oropharynx) |
| Respiratory: nasal congestion, throat tightness; chest tightness; shortness of breath                                                  | Respiratory: hoarseness, dysphonia (common after a crying spell); drooling, increased secretions (common in infants)                                                                                                                                                                                                                                                                                          | Respiratory: rapid onset of coughing, choking, stridor, wheezing, dyspnea, apnea, cyanosis                                                                                                                                          |
| Gastrointestinal: dysphagia, nausea, abdominal pain/cramping                                                                           | Gastrointestinal: spitting up/regurgitation (common after feeds), loose stools (normal in infants, especially if breast-fed); colicky abdominal pain                                                                                                                                                                                                                                                          | Gastrointestinal: sudden, profuse vomiting                                                                                                                                                                                          |
| Cardiovascular: feeling faint, presyncope, dizziness, confusion, blurred vision, difficulty in hearing, palpitations                   | Cardiovascular: hypotension; measured with an appropriate-size blood pressure cuff, low systolic blood pressure for infants is defined as <70 mm Hg from age 1 mo to 1 y, and <(70 mm Hg + [2 × age in y]) in the first and second years of life; tachycardia, defined as >120-130 beats/min from the third month to second year of life inclusive; loss of bowel and bladder control (ubiquitous in infants) | Cardiovascular: weak pulse, arrhythmia, diaphoresis/sweating, pallor, collapse/unconsciousness                                                                                                                                      |
| Central nervous system: headache                                                                                                       | Central nervous system: drowsiness, somnolence (common in infants after feeds)                                                                                                                                                                                                                                                                                                                                | Central nervous system: rapid onset of unresponsiveness, lethargy, or hypotonia; seizures                                                                                                                                           |

Reproduced with permission, from Table 1 in Simons.<sup>21</sup>

\*More than 1 body system involved.

screening SPT (Figure 1). Impressively, 25 of 40 (63%) with peanut SPT wheal sizes more than 4 mm tolerated peanut on first ingestion at OFC, which included 13 of 18 (72%) with SPT wheal sizes 5 to 7 mm and 12 of 22 (55%) with SPT wheal sizes more than 7 mm. As expected, 29 of 30 (97%) with SPT wheal sizes 4 mm or less tolerated peanut. Among the 16 of 70 (23%) who reacted at OFC, 9 infants were given epinephrine as a precaution for mild to moderate symptoms, and none of the infants had any significant respiratory, cardiovascular, or neurologic symptoms. Taken together, these highly anticipated real-world data are very reassuring because they have finally shed light on infants excluded from the LEAP study. Not only have they affirmed the safety of first ingestion among infants at even higher risk than those in the general population (most had eczema or egg sensitization), they provide much needed evidence that even infants with more than 4 mm SPT wheal sizes at first ingestion either completely tolerate peanut or at most typically experience mild to moderate symptoms. With these new data that include a full spectrum of at-risk infants, it is hoped that both practitioners and caregivers will finally be reassured that the risk of severe anaphylaxis on first ingestion during infancy (<12 months) is extremely remote.

## FOOD TRIGGERS AND CONTEXT OF REACTIONS

### Most common food triggers

In multiple studies, hen's egg and cow's milk were identified as the top food triggers of anaphylaxis among infants, causing

**TABLE III.** Differential diagnosis of anaphylaxis in infants

|                                                                                                                                                                                                                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Skin:</b> Urticaria; urticaria pigmentosa/mastocytosis; hereditary angioedema                                                                                                                                                                        |
| <b>Respiratory</b> (upper or lower respiratory tract): Obstruction, congenital (eg, laryngeal web, vascular ring, or malacias) or acquired (eg, aspiration of foreign body,* croup, bronchiolitis, or asthma); asphyxiation/suffocation; breath holding |
| <b>Gastrointestinal tract:</b> Obstruction, congenital, including pyloric stenosis and malrotation, or acquired, including food protein–induced enterocolitis syndrome with acute presentation, and intussusception                                     |
| <b>Shock:</b> Septic, cardiogenic, hypovolemic, distributive                                                                                                                                                                                            |
| <b>Central nervous system:</b> Seizure, postictal state, stroke, trauma, child abuse, increased intracranial pressure                                                                                                                                   |
| <b>Metabolic disorders</b>                                                                                                                                                                                                                              |
| <b>Infectious diseases,</b> such as pertussis, gastroenteritis, and meningitis                                                                                                                                                                          |
| <b>Ingestion of poison or toxin</b> (eg, food, drug, or plant); drug overdose                                                                                                                                                                           |
| <b>Munchausen syndrome by proxy</b>                                                                                                                                                                                                                     |
| <b>Sudden infant death syndrome,</b> apparent life-threatening event                                                                                                                                                                                    |
| <b>Other</b>                                                                                                                                                                                                                                            |

Reproduced with permission from Simons et al.<sup>23</sup>

\*Peanuts and tree nuts account for one-third of foreign body aspirations, as well as being common triggers of anaphylaxis.

between 53% and 80% of food-induced allergic reactions.<sup>25-27,30</sup> A summary of these studies is presented in Table I. In 2 studies in the United States, egg was identified as the most common food triggering anaphylaxis or allergic reactions in infants presenting to the ED.<sup>26,30</sup> In other countries, cow's milk was the most common food trigger of anaphylaxis likely due to differences in cultural

**TABLE IV.** Select attributes of currently FDA-approved epinephrine devices in the United States

| Attribute                                   | Auvi-Q                                | EpiPen                 | Adrenaclick             | Generic EAI            | SYMJEPI (prefilled syringe) |
|---------------------------------------------|---------------------------------------|------------------------|-------------------------|------------------------|-----------------------------|
| Manufacturer                                | Kaleo                                 | Mylan                  | Amedra                  | Teva                   | Adamis                      |
| Dosages (mg)                                | 0.10, 0.15, 0.30                      | 0.15, 0.30             | 0.15, 0.30              | 0.15, 0.30             | 0.15, 0.30                  |
| Trainer                                     | Yes                                   | Yes                    | No                      | Yes                    | No                          |
| Supplied                                    | 2-pack                                | 2-pack                 | 2-pack                  | 2-pack                 | 2-pack                      |
| Exposed needle length<br>for pediatric EAIs | 0.29" for 0.1 mg<br>0.50" for 0.15 mg | 0.51" for 0.15 mg      | 0.51" for 0.15 mg       | 0.63" for 0.15 mg*     | 0.63" for 0.15 mg*          |
| Injection hold time                         | 2-s hold, no massage                  | 3-s hold, 10-s massage | 10-s hold, 10-s massage | 3-s hold, 10-s massage | 2-s hold, 10-s massage      |
| Needle guard                                | Yes                                   | Yes                    | No                      | Yes                    | Yes (manual)                |
| Retractable needle                          | Yes                                   | No                     | No                      | No                     | No                          |
| Vocalized audio prompts                     | Yes                                   | No                     | No                      | No                     | No                          |

FDA, Food and Drug Administration.

Adapted with permission from Greenhawt et al.<sup>22</sup>

\*As reported by company on inquiry.

dietary preferences.<sup>25,27,29</sup> Samady et al<sup>26</sup> analyzed cases of anaphylaxis in infants presenting to the ED between June 2015 and June 2017 and found egg (38% vs 1%;  $P < .001$ ) and cow's milk (17% vs 7%;  $P = .03$ ) were significantly more common in infants than in school-aged children older than 6 years.

As infants become toddlers, peanut surpasses milk and egg as the most likely trigger of anaphylaxis (Table 1). Both studies by Samady et al<sup>26</sup> and Ko et al<sup>30</sup> similarly found that peanut- and tree nut-induced allergic reactions were more common in older age groups. Infants less frequently presented with anaphylaxis to peanut compared with toddlers aged 12 to 23 months (13% vs 33%;  $P = .02$ ).<sup>26</sup> In an anaphylaxis registry, peanut and tree nuts were more common triggers for anaphylaxis in children aged 1 to 6 years.<sup>27</sup> With time, additional studies are needed to determine whether peanut may become a more or less likely trigger for anaphylaxis in the years following the 2017 NIAID guidelines recommending earlier peanut introduction for high-risk infants.

### Context of reactions

Allergic reactions in infants are most likely caused by accidental exposure. In a prospective study, 87% of allergic reactions in infants aged 3 to 15 months were due to accidental exposure among 834 allergic reactions to milk, egg, or peanut despite the infants already having a diagnosis of food allergy.<sup>34</sup> Reasons for accidental ingestion included forgetfulness, decreased supervision, not checking labels or label reading error, cross-contamination, and error in preparation. Infants may also be more susceptible because of behaviors that include crawling on the ground, picking up foods on the ground, and mouthing of objects or hands/fingers. Caregivers were also responsible for nonaccidental exposures in which they may have intentionally given the known food allergen to their infant to determine whether the infant had outgrown the allergy. The large number of accidental and nonaccidental exposures involving the caregiver suggests a need to reinforce the importance of strict avoidance. It also highlights the need to educate all caregivers taking care of the infant to prevent accidental exposures.

Compared with older children, infants are less likely to have a diagnosed food allergy, and the allergic reaction typically occurs with first-time ingestion.<sup>30</sup> However, Ko et al reported that among children presenting to the ED for any food-induced allergic reaction, most infants who were treated with epinephrine

before arriving at the hospital were previously diagnosed with food allergies (74%). Only 1 infant in the study without a previous history of food allergies received prehospital epinephrine at home. Because infants more commonly presented with milder symptoms and were not more likely to require hospital admission in this study, the authors concluded that there is likely no benefit in prescribing epinephrine autoinjectors (EAIs) to infants without a history of food allergies.

Cofactors for anaphylactic reactions have been previously reported in a small number of infants including proton pump inhibitors (esomeprazole) ( $n = 2$ ) and viral upper respiratory tract infection ( $n = 1$ ) at the time of anaphylaxis.<sup>27</sup> More studies are needed to assess other cofactors or comorbidities that increase the risk for anaphylaxis specifically in infants including bronchiolitis, croup, reactive airway disease, congenital heart disease, fever, or emotional stress.<sup>22,23</sup> Comorbidities also include factors that may impair caregiver decision making such as alcohol, drugs, depression, sedatives, or sleep deprivation.<sup>23</sup>

## CLINICAL PRESENTATION AND DIAGNOSIS

### Clinical criteria and presentation in infants

The clinical criteria for the diagnosis of anaphylaxis have been established by NIAID and the Food Allergy and Anaphylaxis Network<sup>31</sup> (currently known as Food Allergy Research Education). With the exception of reduced blood pressure after exposure to a known allergen, anaphylaxis presents with multi-system involvement, and urticaria or angioedema alone do not fulfill the criteria for anaphylaxis. There are no specific criteria for infants,<sup>23</sup> while a working consensus expert panel concluded that the clinical criteria for diagnosing anaphylaxis should be applied to all ages as opposed to a separate set of criteria for infants.<sup>22</sup> However, it was recommended that there should be increased awareness of key differences in how infants may present with anaphylaxis.

Studies on infants with anaphylaxis or allergic reactions report that infants most commonly present with skin and/or gastrointestinal symptoms (Table 1).<sup>7,25-27,29,30</sup> A retrospective review of food-induced anaphylaxis presenting to the ED in the United States found that infants (<12 months old) and toddlers (12-23 months old) were significantly more likely to present with skin involvement (94% and 91%) compared with school-aged

children (>6 years old) (62%;  $P < .001$ ).<sup>26</sup> In particular, urticaria was more likely to occur in infants ( $\leq 12$  months) compared with preschool children aged 1 to 6 years as reported in a French-speaking anaphylaxis registry ( $P = .02$ ).<sup>27</sup> In comparison to toddlers (12–23 months), infants were also significantly more likely to have gastrointestinal symptoms (89%;  $P = .003$ ).<sup>26</sup> A smaller study similarly found that persistent vomiting occurred more frequently in 23 infants ( $\leq 12$  months) compared with children aged 1 to 17 years presenting to the ED with anaphylaxis due to any trigger ( $P = .023$ ).<sup>25</sup>

Infants are less likely to present with severe symptoms, and respiratory and cardiovascular symptoms are less commonly reported (Table I) as previously discussed above.<sup>7,26,30</sup> Topal et al<sup>25</sup> noted that blood pressure was measured in significantly fewer infants 12 months or younger (22%) versus 54% of children aged 1 to 17 years ( $P = .005$ ). The underreporting of blood pressure measurements may be attributed to the challenges of measuring blood pressure in a crying or irritable infant or due to the unavailability of appropriately sized blood pressure cuffs.<sup>22,23</sup> When obtaining a blood pressure measurement is not possible in an infant, Bird et al<sup>49</sup> suggest examining for signs of hypotension. Signs and symptoms such as pale or mottled skin, delayed capillary refill, or lethargy can be indicators for hypotension.

Additional challenges exist when diagnosing anaphylaxis in infants as outlined in Table II. However, there is a lack of published evidence that these challenges have resulted in morbidity or mortality. Moreover, the recent evidence above suggesting that infant anaphylaxis appears to be milder than anaphylaxis in older children suggests that even if recognition of some cases of infant anaphylaxis is delayed, the consequences are not as profound as missing anaphylaxis in older children.

### Differential and lab confirmation

The differential of anaphylaxis is unique for infants compared with older children, as presented in Table III. Other differential diagnoses may present similarly to an allergic reaction such as aspiration of a foreign body, septic shock, or a congenital disorder and should also be considered.<sup>23</sup>

Anaphylaxis remains a clinical diagnosis, while laboratory testing for mast cell mediators such as tryptase level may be helpful if the clinical presentation of anaphylaxis is unclear. Mast cell tryptase level must be measured within 2 to 4 hours of the onset of symptoms<sup>9,50</sup> and should be interpreted with caution because tryptase levels may not always be elevated during an episode of food-induced anaphylaxis.<sup>51</sup> An additional barrier for tryptase level measurement is that blood draws can be more challenging in infants, in particular symptomatic infants. Tryptase levels have also been noted to be higher for infants at baseline, which has been attributed to the developing immune system.<sup>52</sup> These levels decrease with age and reflect normal levels by age 9 to 12 months. Therefore, tryptase levels in infants need to be interpreted in the context of age-specific reference values. A consensus panel of experts concluded that a test or biomarker to confirm anaphylaxis with high specificity and sensitivity is still needed.<sup>22</sup>

## ACUTE MANAGEMENT

### Initial treatment and epinephrine

Guidelines have been published on the acute treatment of anaphylaxis, and the initial assessment and workup is similar

among all ages.<sup>9,50,53</sup> These recommendations are based on previous evidence and studies on older children and adults,<sup>22</sup> which includes measuring vitals, performing a complete physical examination, and taking a detailed history. Simons and Sampson<sup>23</sup> and Bird et al<sup>49</sup> have published figures to guide management of anaphylaxis in infants.

Irrespective of age, the initial treatment of choice is epinephrine at 0.01 mg/kg of a 1:1000 [1 mg/mL] solution injected intramuscularly into the mid-outer thigh with a maximum dose of 0.3 mg in children and 0.5 mg in adults.<sup>3,31,50,53</sup> The infant should be placed in a supine or semireclining position.<sup>23</sup> EAI is available by prescription for use in the community.<sup>3,22,23</sup> On recognition of anaphylaxis, epinephrine should be administered immediately without delay.<sup>3,9,50</sup> Of note, there are no previous pharmacology studies on administration of epinephrine in infants.<sup>27</sup> Regardless, a consensus panel of experts advises that epinephrine is safe to use at any age including infants when appropriately dosed and administered intramuscularly.<sup>22</sup> Even among infants with congenital heart disease, the benefits of treating anaphylaxis with epinephrine outweigh the risks.

Among recent studies evaluating infants presenting to the ED with anaphylaxis, use of more than 1 epinephrine injection among infants was infrequent, again suggesting that anaphylaxis in infants is milder than in older children. Topal et al<sup>25</sup> reported that among 104 cases of anaphylaxis, no infants ( $\leq 12$  months) received more than 1 epinephrine dose, while 4 children (4.9%) presenting to the ED with anaphylaxis were treated with 2 doses of epinephrine and admitted to the intensive care unit.<sup>25</sup> At most, 1 infant (<12 months) requiring a second epinephrine injection was reported in 2 other studies.<sup>26,30</sup>

Although not first-line therapy for anaphylaxis, H1 antihistamines, steroids, and sometimes beta-agonists are administered before or instead of epinephrine.<sup>23,25</sup> However, these medications are adjunctive, and use of these should not delay the administration of epinephrine. Intravenous fluids may be indicated because of hypotension or dehydration, and oxygen can be considered for respiratory symptoms.<sup>31</sup> These treatments should not be used alone without epinephrine to treat anaphylaxis.

### Epinephrine autoinjectors

EAI is primarily sold in 2 doses, 0.15 mg for children above 15 kg or 0.3 mg for children above 30 kg. Since 2018, a lower dose 0.1 mg autoinjector with a shorter needle was approved by the Food and Drug Administration in the United States and is recommended for children weighing between 7.5 kg and 15 kg.<sup>50</sup> A comparison of different brands of EAI and devices is presented in Table IV.

The 0.1 mg autoinjector device for infants may not be available or affordable for all families and is currently available only in the United States. If this lower dose is not available for children in the 7.5-kg to 15-kg weight range, off-label use of the 0.15 mg autoinjector is recommended, taking into account that the benefits of having an autoinjector ready for immediate use may outweigh the risks of delaying or not treating with epinephrine.<sup>3,50</sup> This higher 0.15 mg EAI dose is preferable to drawing up epinephrine from an ampule with a syringe in particular among caregivers without any medical background, which has been shown to be associated with treatment delay and inaccurate dosing.<sup>54</sup> For similar reasons, a consensus expert panel

strongly agreed that off-label use of the 0.1 mg EAI would be safe in these infants weighing less than 7.5 kg.<sup>22</sup> More studies on the use of EAI in infants weighing less than 7.5 kg are needed.

Needle length is another concern regarding EAI use in infants. Previous studies have demonstrated using ultrasound that the needle length in some autoinjectors runs the risk of injecting the bone.<sup>55-58</sup> An estimate of the ideal needle length for children weighing 7.5 to 15 kg is between 7.0 mm (0.28 in) and 8.0 mm (0.31 in).<sup>56</sup> Only the 0.1 mg autoinjector is within this range, which has a needle length of 0.29 in (Table IV). In a study on the EpiPen device, the preferred hold time of an EAI device was noted to be no more than 3 seconds to avoid lacerations in a moving child.<sup>59</sup> Specific recommended hold times for different EAI devices are presented in Table IV.

Although undertreatment with epinephrine is a common and persistent problem, it is not specific to infants. Ko et al<sup>30</sup> reported that 12% of all children younger than 5 years and 10% of infants were treated with epinephrine in the ED.<sup>30</sup> No significant difference in epinephrine use was noted between infants and older age groups.<sup>25,27,30</sup> Ko et al also reported a trend of increased use of epinephrine before arriving to the hospital for preschoolers (13%) and toddlers (12%) versus infants younger than 12 months (4%;  $P = .12$ ); however, this was not statistically significant.<sup>30</sup> As with all age groups, more education is needed among all caregivers to identify anaphylaxis and emphasize the importance of administering epinephrine in a timely manner. Caregivers should receive regular training on how to use EAI because studies have shown that this ability may be forgotten with time.<sup>60,61</sup>

## LONG-TERM MANAGEMENT

### Allergy referral and education

After an anaphylactic reaction has resolved, specific anaphylaxis counseling and education should take place ideally before discharge from the hospital or ED.<sup>50,53</sup> The caregivers of the infant should receive instructions on what to avoid, an EAI prescription, and a referral to a board-certified allergy/immunology specialist. They should also be taught how to use an EAI and receive an emergency action plan that provides details on when epinephrine should be administered.<sup>62,63</sup> Reassurance should be provided that epinephrine is safe to use in infants and is the treatment of choice in anaphylaxis. Health care providers using the more general emergency action plan applicable to all ages should emphasize with caregivers the different symptoms to monitor for in a nonverbal infant. A specific infant/toddler emergency action is available, which lists potential symptoms tailored toward an infant with more objective signs and symptoms.<sup>22</sup>

In the outpatient setting, the history and details of circumstances surrounding an anaphylactic reaction are crucial for diagnosing anaphylaxis and identifying potential triggers.<sup>22</sup> The history is also important for differentiating IgE-mediated food allergies from other allergic conditions such as food protein-induced enterocolitis syndrome, which most commonly presents in infancy.<sup>64</sup> The allergy specialist may consider SPT and/or serum IgE testing to determine allergic sensitization to confirm suspected triggers. If sensitization is negative for a highly suspected food trigger, repeat SPT should be considered at least

4 to 6 weeks later due to possible temporary depletion of mast cells after a severe allergic reaction.<sup>22</sup> Testing to large panels of allergens is strongly discouraged because sensitization may not always be clinically relevant.<sup>23</sup> A consensus panel of experts agreed that there is no minimum age for allergy evaluation and testing.<sup>22</sup> If indicated (eg, infants sensitized to foods that have not been tried before), physician-supervised OFCs performed by experienced staff should be considered in an appropriately equipped medical facility.<sup>23</sup> Specific guidance on conducting OFCs to peanut in infants has been reported by Bird et al.<sup>49</sup> Similar to children of any age, infants with a history of anaphylaxis should routinely follow with an allergy specialist in accordance with current guidelines.<sup>9,50</sup>

### Challenge of preventing reaction recurrence

Current guidelines recommend strict avoidance of food allergens to prevent recurrence of allergic reactions. However, strict avoidance may be difficult for caregivers and can become a source of stress and anxiety.<sup>21,50</sup> In a prospective study, caregivers of infants aged 3 to 15 months were provided standardized advice to strictly avoid milk, egg, and/or peanut if allergic.<sup>34</sup> Despite these specific instructions, 72% of infants had an allergic reaction, with an annualized rate of reaction of 0.81 per year (95% CI, 0.76-0.85). More than half (53%) of these infants had more than 1 allergic reaction during the median follow-up period of 36 months. In addition, previous presentation to the ED for food-induced anaphylaxis does not confer experience. Jeon et al<sup>29</sup> reported that 15% of infants younger than 2 years had subsequent anaphylactic reactions. Huang et al<sup>6</sup> observed that 20 children had more than 1 ED visit for anaphylaxis, which did not increase the likelihood of treatment with epinephrine during subsequent reactions. These findings imply that improvements are warranted in educating and reinforcing how to strictly avoid allergens and when to use epinephrine, and also suggest that avoidance may be inferior to emerging therapies for the infant age group as described in the next section.

### Emerging therapies

There is increasing interest in the effectiveness of food allergen oral immunotherapy (OIT) in younger children for peanut, milk, and egg.<sup>65-68</sup> A study on peanut OIT in 37 infants and young children aged 9 to 36 months reported that 78% achieved sustained unresponsiveness to peanut 4 weeks after discontinuing peanut OIT.<sup>65</sup> The authors hypothesize that the increased success and safety profile of immunotherapy in this younger age group are due to lower baseline serum IgE levels to peanut as well as the immature immune system, which may be more susceptible to immunomodulation. The real-world safety of preschool OIT was confirmed in a Canadian study of 270 preschoolers who were started on peanut OIT with a goal maintenance dose of 300 mg peanut protein, and only 0.4% experienced a severe reaction during build-up.<sup>69</sup> Indeed, the recently published first-ever Canadian guidelines on OIT permit its use outside of the research setting for patients where the benefits outweigh the risks.<sup>70</sup> More data will be forthcoming as well, as a phase II trial was recently completed assessing peanut OIT in children aged 1 to less than 4 years (Oral Immunotherapy for Induction of Tolerance and Desensitization in Peanut-Allergic Children

[IMPACT]—NCT01867671), and a phase III clinical trial in this same age group is underway (Peanut Oral Immunotherapy Study of Early Intervention for Desensitization [POSEIDON]—NCT03736447). The earlier regular ingestion is initiated, the greater the likelihood of achieving sustained unresponsiveness and tolerance, because what we have learned from the Persistence of Oral Tolerance to Peanut (LEAP-On) study<sup>71</sup> is likely directly applicable to OIT in infants and preschoolers. Treatment in preschoolers has the added advantage of preventing psychosocial consequences of longstanding food allergy such as anxiety, diminished quality of life, and bullying.<sup>72</sup>

Epicutaneous immunotherapy has similarly demonstrated an increase in peanut tolerance in younger children aged 4 to 11 years accompanied by changes in the immune system including a decrease in sensitization and an increase in IgG<sub>4</sub>.<sup>73</sup> A phase III clinical trial is underway in younger children aged 1 to 3 years on peanut epicutaneous immunotherapy (Safety and Efficacy Study of Viaskin Peanut in Peanut-allergic Young Children 1-3 Years of Age [EPITOPE]—NCT03211247). The safety and efficacy of epicutaneous immunotherapy is also being studied for milk (Efficacy and Safety of Viaskin Milk in Children with IgE-Mediated Cow's Milk Allergy [MILES]—NCT02223182).

## CONCLUSIONS

The most common food triggers for infant anaphylaxis are egg and milk, and the most likely presenting symptoms are cutaneous or gastrointestinal. Although infant anaphylaxis may be underrecognized and undertreated by caregivers and health care professionals, there is no clear evidence of the magnitude of underrecognition and it does not appear to impact morbidity or mortality. Most research studies on infant anaphylaxis are composed of retrospective case series often with small numbers, which only capture infants presenting to the ED.<sup>7,25,26,29,30</sup> Other studies may rely on the recall of caregivers, and registries of anaphylaxis are susceptible to severity bias.<sup>27</sup> Therefore, more prospective studies will be necessary to further understand and more accurately characterize infant anaphylaxis.

New evidence suggests that infant anaphylaxis is less severe than in older children, and fatalities are rare, knowledge of which could assist with improved implementation of food allergy prevention and emerging treatments. Clinical trial and new real-world data demonstrate that the risk of severe anaphylaxis on first ingestion of an allergen during infancy (<12 months) is remote even among higher-risk infants with eczema and/or egg sensitization. For prevention, we have an opportunity to inspire more confidence in practitioners and caregivers for early allergen introduction than ever before, with or without screening. For treatment, OIT in infants and preschoolers holds exceptional promise due to better safety and efficacy, with additional advantages such as prevention of long-term psychosocial consequences such as anxiety, bullying, and poor quality of life. The future for interventions in infants that focus on regular, long-term ingestion rather than avoidance is brighter than it has ever been based on recent evidence.

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# Food-Induced Anaphylaxis in Infants: Can New Evidence Assist with Implementation of Food Allergy Prevention and Treatment?

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### Learning objectives:

1. To list the most common food triggers of anaphylaxis in infants compared with older children.
2. To describe the unique clinical presentation of food-induced anaphylaxis in infants.
3. To counsel caregivers regarding the risk and severity of food-induced anaphylaxis in infants.
4. To identify challenges in the diagnosis of food allergies and the status of potential food allergy treatment therapies in infants.

### CME items

*Question 1.* Which of the following food allergens are more likely triggers of anaphylaxis in infants compared with older children?

- A. Wheat and soy
- B. Peanut and tree nuts
- C. Cow's milk and hen's egg
- D. Sesame

*Question 2.* Which of the following symptoms of a food-induced allergic reaction are more common among infants than among older children?

- A. Mucocutaneous
- B. Respiratory
- C. Gastrointestinal
- D. Cardiovascular

*Question 3.* The severity of anaphylaxis in infants is best summarized by which of the following statements?

- A. Similar to toddlers/preschool children
- B. Similar to adolescents
- C. Less severe compared with older children
- D. More severe compared with older children

*Question 4.* Which of the following percentages of infants had possible anaphylaxis to peanut in the HealthNuts study when introduced to peanut at home before age 12 months?

- A. 10.6%
- B. 6.0%
- C. 0.6%
- D. 0.06%

*Question 5.* Recent studies on peanut oral immunotherapy (OIT) in infants and preschoolers have concluded that it is which of the following?

- A. Safe but ineffective
- B. Safe and effective
- C. Unsafe and not recommended
- D. Unsafe but effective