

## Anaphylaxis: Unique aspects of clinical diagnosis and management in infants (birth to age 2 years)

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In this rostrum we aim to increase awareness of anaphylaxis in infancy in order to improve clinical diagnosis, management, and prevention of recurrences. Anaphylaxis is increasingly reported in this age group. Foods are the most common triggers.

Presentation typically involves the skin (generalized urticaria), the respiratory tract (cough, wheeze, stridor, and dyspnea), and/or the gastrointestinal tract (persistent vomiting). Tryptase levels are seldom increased because of infant anaphylaxis, although baseline tryptase levels can be increased in the first few months of life, reflecting mast cell burden in the developing immune system. The differential diagnosis of infant anaphylaxis includes consideration of age-unique entities, such as food protein-induced enterocolitis syndrome with acute presentation. Epinephrine (adrenaline) treatment is underused in health care and community settings. No epinephrine autoinjectors contain an optimal dose for infants weighing 10 kg or less. After treatment of an anaphylactic episode, follow-up with a physician, preferably an allergy/immunology specialist, is important for confirmation of anaphylaxis triggers and prevention of recurrences through avoidance of confirmed specific triggers. Natural desensitization to milk and egg can occur. Future research should include validation of the clinical criteria for anaphylaxis diagnosis in infants, prospective longitudinal monitoring of baseline serum tryptase levels in healthy and atopic infants during the first year of life, studies of infant comorbidities and cofactors that increase the risk of severe anaphylaxis, development of autoinjectors containing a 0.1-mg epinephrine dose suitable for infants, and inclusion of infants in prospective studies of immune modulation to prevent anaphylaxis recurrences. (*J Allergy Clin Immunol* 2014;■■■■:■■■■-■■■■.)

**Key words:** Infants (birth to 2 years), food allergy, epinephrine, adrenaline, epinephrine autoinjectors, antihistamines, clinical

*criteria for diagnosis, food protein-induced enterocolitis syndrome, natural desensitization, tryptase*

Anaphylaxis is defined as a serious generalized allergic or hypersensitivity reaction that is rapid in onset and might cause death. It typically occurs minutes to a few hours after exposure to the trigger and involves 2 or more body organ systems. This definition applies to patients of all ages regardless of the anaphylaxis trigger (cause, inducer) or mechanism (IgE-mediated, other immunologic mechanisms, or direct mast cell activation). We focus here on the infant phenotype of anaphylaxis (birth to age 2 years), with the goals of increasing awareness of anaphylaxis in this age group and improving clinical diagnosis, management, and prevention of recurrences.<sup>1-3</sup>

The true prevalence of anaphylaxis in infancy is unknown. Although it remains underdiagnosed and undercoded in this population, it is reported with increasing frequency, even in newborns. In epidemiologic studies and pediatric case series, atopic infants and boys predominate, and many episodes occur in the home. Death can occur; however, the case fatality rate in hospitalized patients is low.<sup>4-9</sup>

### RISK FACTORS AND TRIGGERS

Comorbidities that increase the risk of severe anaphylaxis, although not well defined in infants, potentially include croup, bronchiolitis, asthma, and cutaneous mastocytosis with extensive (>90%) skin involvement and/or blistering of the skin. Cofactors that amplify anaphylaxis, although also not well defined in infants, potentially include upper respiratory tract infection, fever, exertion, and emotional stress. Additionally, delayed recognition of first or subsequent episodes because of caregiver lack of awareness, depression, or substance abuse might be relevant.<sup>3,5-11</sup>

Anaphylaxis in infants can be triggered by a variety of agents, of which foods are by far the most common. Typical culprits are cow's milk, egg, and peanut, but any food can be implicated, including tree nuts, soy and other legumes, fish, vegetables, fruits, and grains, such as wheat and rice. Food-induced anaphylaxis can occur after direct ingestion or indirect ingestion through breast milk; rarely, it is triggered by skin contact with food or vomitus, or inhalation of vapors from cooking food.<sup>1,3,5-9,12,13</sup>

Drug triggers include penicillins and other antibiotics, ibuprofen and other antipyretics, and neuromuscular blockers. In infants, insect stings and bites are more likely to trigger large local reactions or urticaria than anaphylaxis. Natural rubber latex remains a potential trigger in health care and community settings, where it is found in bottle nipples, pacifiers, teethingers, and toys. Vaccinations to prevent infectious diseases; topical agents, including soaps and creams; and nonimmune triggers, such as

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**Abbreviations used**

EAI: Epinephrine autoinjector  
RCT: Randomized controlled trial

cold exposure, are uncommon triggers. In infants with apparent idiopathic anaphylaxis, novel allergens and antigens, and the possibility of a mast cell activation syndrome, should be considered.<sup>1,3,5-10,12-14</sup>

**DIAGNOSIS OF ANAPHYLAXIS**

A high index of suspicion is needed to recognize and diagnose anaphylaxis promptly in infants.<sup>3,7-9</sup>

**Clinical criteria for diagnosis**

Clinical criteria for diagnosis of anaphylaxis have been developed and validated for use in emergency departments and other health care settings and in epidemiologic studies, although not specifically for use in this age group (Fig 1).<sup>2</sup>

Infants cannot describe symptoms, such as pruritus, throat tightness, or feeling of impending doom. Some potential signs of anaphylaxis can be difficult to interpret because they also occur in healthy infants; examples include behavioral changes, such as irritability, clinging to a caregiver, inconsolable crying, and somnolence, as well as flushing, dysphonia, drooling, regurgitation, and incontinence of urine and stool. Vital signs should be recorded and interpreted by using age-specific reference ranges (rapid resting respiratory rate, rapid resting heart rate, and low baseline blood pressure in comparison with children). Oxygen saturation should be measured by using pulse oximetry.<sup>1,3</sup>

The initial presentation of anaphylaxis in infants typically involves the following organ systems: skin and subcutaneous tissue in 98% (95% CI, 94% to 100%), the respiratory system in 59% (95% CI, 47% to 71%), and the gastrointestinal system in 56% (95% CI, 44% to 67%).<sup>8</sup> Cardiovascular signs are seldom reported; however, blood pressure is not always documented. In one study only 6% of the infants who met the clinical criteria for diagnosis of anaphylaxis were assigned an emergency department discharge term that included the term “anaphylaxis.”<sup>8</sup>

**Differential diagnosis**

Congenital abnormalities of the respiratory or gastrointestinal tracts, an apparent life-threatening event, aspiration of a foreign body, food protein–induced enterocolitis syndrome with acute presentation, and intussusception are important considerations in the differential diagnosis of anaphylaxis in infants (Table I).<sup>3</sup>

**Laboratory confirmation of the clinical diagnosis**

The standardized assay for mast cell total tryptase is widely available in clinical laboratories, although not performed on an emergency basis. Tryptase levels are seldom increased in patients with food-induced anaphylaxis, even in optimally timed blood samples obtained 15 minutes to 3 hours after symptom onset. In young infants interpretation of serum tryptase levels presents additional complexities because their baseline levels can be increased, reflecting mast cell burden in the developing immune system. Median baseline levels of  $14.2 \pm 10.2$   $\mu\text{g/L}$  in atopic

infants and  $6.13 \pm 3.47$   $\mu\text{g/L}$  in healthy infants have been reported before age 3 months, after which they gradually decrease and reach the normal reference range ( $3.85 \pm 1.8$   $\mu\text{g/L}$ ) by age 9 to 12 months.<sup>1,15,16</sup>

**INITIAL TREATMENT OF ANAPHYLAXIS**

A high level of preparedness, including a written protocol, is important because life-saving initial treatment needs to be started promptly. Remove any suspected relevant trigger. Rapidly assess circulation, airway, breathing, skin, and body weight (Fig 2). Without delay, call to request help from a resuscitation team in health care settings or from emergency medical services in community settings. Place the infant supine or semireclining in a position of comfort in the caregiver's arms. Inject epinephrine (adrenaline) intramuscularly in the mid-outer thigh in a dose of 0.01 mg/kg in health care settings. Use an epinephrine autoinjector (EAI; 0.15 mg) in community settings.<sup>1-3,13,17-19</sup>

When indicated at any time, provide high-flow supplemental oxygen (8-10 L/min) through a tightly fitting infant face mask. Establish intravenous access and start fluid resuscitation with 0.9% saline, initially at a dose of 10 to 20 mL/kg over 5 to 10 minutes. Begin continuous electronic monitoring of respiratory rate, heart rate, and blood pressure with an appropriately sized blood pressure cuff and monitor oxygenation by using pulse oximetry.<sup>1-3,13</sup> When indicated, start cardiopulmonary resuscitation with chest compressions at a rate of 100 per minute and a depth of 4 cm with minimal interruptions and start rescue breaths at a rate of 15 to 20 per minute.<sup>1</sup>

Antihistamines and glucocorticoids are commonly given; however, these medications should not be used as initial treatment or as monotherapy because they do not rapidly reverse laryngeal edema, bronchospasm, or hypotension.<sup>1,2,20-22</sup> Biphasic anaphylaxis can occur in infants.<sup>23</sup> Recommendations for pharmacologic treatment of anaphylaxis in this age group are extrapolated from recommendations for treatment of anaphylaxis in older patients.<sup>1,2,17,20-22</sup>

Infants who do not respond to initial anaphylaxis treatment should, if possible, be transferred promptly to the care of a pediatric emergency medicine team that is trained, experienced, and equipped to provide skilled airway management and ventilation, and optimal shock management guided by continuous electronic monitoring of respiratory and cardiovascular outcomes.<sup>1</sup>

**MANAGEMENT AFTER RESOLUTION OF AN ANAPHYLACTIC EPISODE**

Long-term management focuses on treatment and prevention of anaphylaxis recurrences in community settings. The importance of follow-up with a physician, preferably an allergy/immunology specialist, should be emphasized (Fig 3).<sup>1,12,13,17-34</sup>

**Management at discharge after treatment of anaphylaxis in a health care setting**

Caregivers should be trained how to recognize anaphylaxis and inject 0.15 mg of epinephrine in the mid-outer thigh with an EAI.<sup>1-3,12,13,24-27</sup> A personalized written anaphylaxis emergency action plan that lists common symptoms and signs of anaphylaxis in infants and outlines prompt initial treatment should be provided.

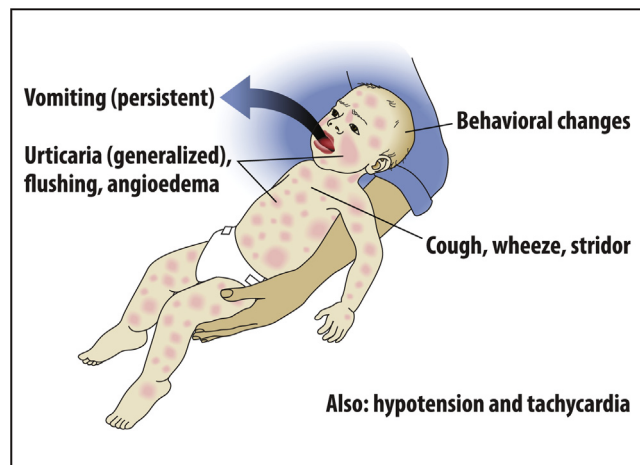
**Anaphylaxis in infants: Potential symptoms and signs**

**FIG 1.** Clinical diagnosis of anaphylaxis in infants is based on sudden onset of characteristic symptoms and signs in 2 or more body organ systems. Typical symptoms and signs can include generalized urticaria, cough, wheeze, stridor, and/or persistent vomiting. In infants with anaphylaxis, respiratory compromise is more likely than hypotension or shock, and shock is more likely to manifest initially as tachycardia rather than hypotension.<sup>1-3</sup>

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

|                                                                                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Skin: Urticaria; urticaria pigmentosa/mastocytosis; hereditary angioedema                                                                                                                                                                        |
| Respiratory (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 |
| Gastrointestinal tract: Obstruction, congenital, including pyloric stenosis and malrotation, or acquired, including food protein–induced enterocolitis syndrome with acute presentation, and intussusception                                     |
| Shock: Septic, cardiogenic, hypovolemic, distributive                                                                                                                                                                                            |
| Central nervous system: Seizure, postictal state, stroke, trauma, child abuse, increased intracranial pressure                                                                                                                                   |
| Metabolic disorders                                                                                                                                                                                                                              |
| Infectious diseases, such as pertussis, gastroenteritis, meningitis                                                                                                                                                                              |
| Ingestion of poison or toxin (eg, food, drug, or plant); drug overdose                                                                                                                                                                           |
| Munchausen syndrome by proxy                                                                                                                                                                                                                     |
| Sudden infant death syndrome, apparent life-threatening event                                                                                                                                                                                    |
| Other                                                                                                                                                                                                                                            |

Adapted from Simons.<sup>3</sup>

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

EAI is underprescribed and underused in the treatment of anaphylaxis.<sup>1,3,7-9,25</sup> Inability to use an EAI correctly is common, even when assessed immediately after one-on-one instruction.<sup>27</sup> When competence is acquired after instruction, it is not permanent.<sup>28</sup> In a study in which only 29.9% of infants with severe anaphylaxis received epinephrine injections, reasons for not injecting it included the following: reactions were not recognized, EAI was unavailable, caregivers were too afraid to inject, caregivers were waiting for more symptoms to develop, and/or caregivers were unsure whether epinephrine was needed.<sup>25</sup>

The epinephrine dose of 0.15 mg contained in EAI is high for many infants (a 3-fold dose for those weighing 5 kg and a 2-fold dose for those weighing 7.5 kg) but is recommended by many physicians because of the lack of availability of a more

appropriate EAI dose for infants and the favorable benefit/risk ratio of epinephrine in this potentially fatal disease. Caregivers without a medical background who are taught how to draw up an optimal infant dose from an ampule of epinephrine containing 1 mg/mL using a 1-mL syringe can take several minutes to prepare the dose, which can be inaccurate; as an example, if the epinephrine solution has been ejected along with the air, the syringe contains no epinephrine dose at all.<sup>18</sup>

Cloth medical identification bracelets or clothing (eg, T-shirts) imprinted with allergen avoidance alerts are recommended to protect infants at risk of anaphylaxis from being exposed to their triggers.<sup>3</sup>

**Confirmation of anaphylaxis triggers**

Selection of allergens for skin prick tests should be based on the history of the anaphylactic episode and performed at least 4 to 6 weeks afterward. Infants with negative skin test results and a convincing history of anaphylaxis should be retested weeks or months later. Intradermal tests with foods are contraindicated. Allergen-specific serum IgE levels can be measured at any time after the episode. The reference ranges above which there is a 95% to 99% chance of clinical reactivity to some specific foods are lower in infants than in older patients; as examples, the milk-specific IgE level highly predictive of clinical reactivity is 5 kU<sub>A</sub>/L in infants and 15 kU<sub>A</sub>/L in older patients, and the egg-specific IgE level highly predictive of clinical reactivity is 2 kU<sub>A</sub>/L in infants and 7 kU<sub>A</sub>/L in older patients.<sup>1,3,12,13</sup>

Skin tests and specific IgE measurements confirm sensitization to the allergens tested, although they are not diagnostic of anaphylaxis. Testing to large panels of allergens is unnecessary and potentially misleading because many infants are sensitized to allergens without being clinically reactive to them. Although skin prick test wheal sizes and levels of allergen-specific IgE can suggest the likelihood of future allergic reactions, they do not predict the severity of such reactions.<sup>1,3,12,13,29</sup>

In sensitized infants, additional investigations, including relevant allergen component tests to, for example, casein in milk, ovomucoid in egg, or Ara h 2 in peanut, can be helpful in assessing the risk of future clinical reactivity to these foods.<sup>12,29</sup> If indicated, a medically supervised incremental challenge/provocation test to rule out clinical reactivity to a relevant allergen should be conducted in a well-equipped medical setting staffed by health care professionals who are trained and experienced in performing challenges and diagnosing and treating anaphylaxis. Standardized approaches to performing food challenges have been developed.<sup>12,13,30</sup>

Infants with drug-induced anaphylaxis should be assessed by using history and skin tests. Although validated reagents for skin testing are available only for penicillins, other medications, including other antibiotics, can be tested by using nonirritating concentrations of the relevant drug. Intradermal tests with drugs are performed less frequently in infants compared with older patients. If indicated, medically supervised incremental challenge tests should be performed.<sup>1,3</sup>

Infants with Hymenoptera sting–induced anaphylaxis should have skin tests and measurement of specific IgE levels to standardized yellow jacket, honeybee, hornet, and wasp venoms. Sensitization to fire ants is confirmed by testing with whole-body extract. Intradermal tests are performed less frequently in this age group.<sup>1,3</sup>

## Anaphylaxis in infants: Initial treatment

- 1) Have a written emergency protocol for anaphylaxis recognition and treatment.
- 2) If possible, remove exposure to the trigger, e.g. stop IV medication.
- 3) Assess circulation, airway, breathing, skin, and body weight (mass).
- 4) Promptly and simultaneously, call to request help from a resuscitation team in a healthcare setting or from emergency medical services in a community setting (eg. 911).




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- 5) Place the infant supine or semi-reclining in a position of comfort in the caregiver's arms.



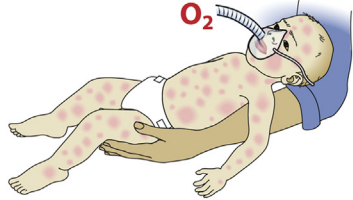

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- 6) Inject epinephrine (adrenaline) intramuscularly in the mid-outer thigh in a dose of 0.01 mg/kg in healthcare settings, or use an epinephrine auto-injector (EAI), 0.15 mg in community settings.



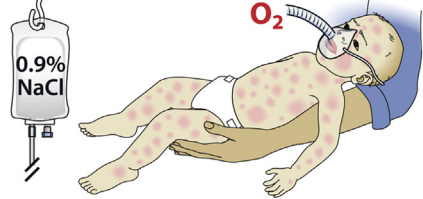

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- 7) When indicated at any time, provide high-flow supplemental oxygen (8-10/L) using a tightly-fitting infant face mask.



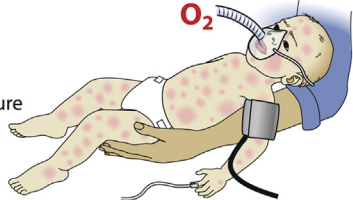

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- 8) Establish intravenous access and start fluid resuscitation with 0.9% saline, initially in a dose of 10-20 mL/kg over 5-10 minutes.




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- 9) Monitor respiratory rate, heart rate, and blood pressure using continuous electronic monitoring if possible. Monitor oxygenation using pulse oximetry.




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- 10) When indicated, perform cardiopulmonary resuscitation (CPR) at a rate of 100 chest compressions per minute and a depth of 4 cm, with minimal interruptions, and perform rescue breaths at a rate of 15-20/minute.

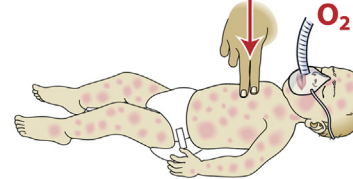


**FIG 2.** The protocol for initial treatment of anaphylaxis in infants should be posted and rehearsed regularly. As soon as anaphylaxis is diagnosed, steps 4, 5, and 6 should be performed promptly and simultaneously.<sup>1-3</sup> IV, Intravenous.

## Prevention of anaphylaxis recurrences

Strict avoidance of exposure to culprit allergens to which infants are sensitized and clinically reactive prevents anaphylaxis recurrences; however, consistently maintaining high-level vigilant avoidance for months and years is stressful for caregivers.<sup>1,3,12,13</sup>

In a prospective longitudinal observational study, advice and written instructions were provided to the families of 512 infants with milk or egg allergy who were age 3 to 15 months at study entry. During a median follow-up of 36 months (range, 0-48 months), allergic reactions were reported in 53% of the babies. Reactions were associated not only with misreading food

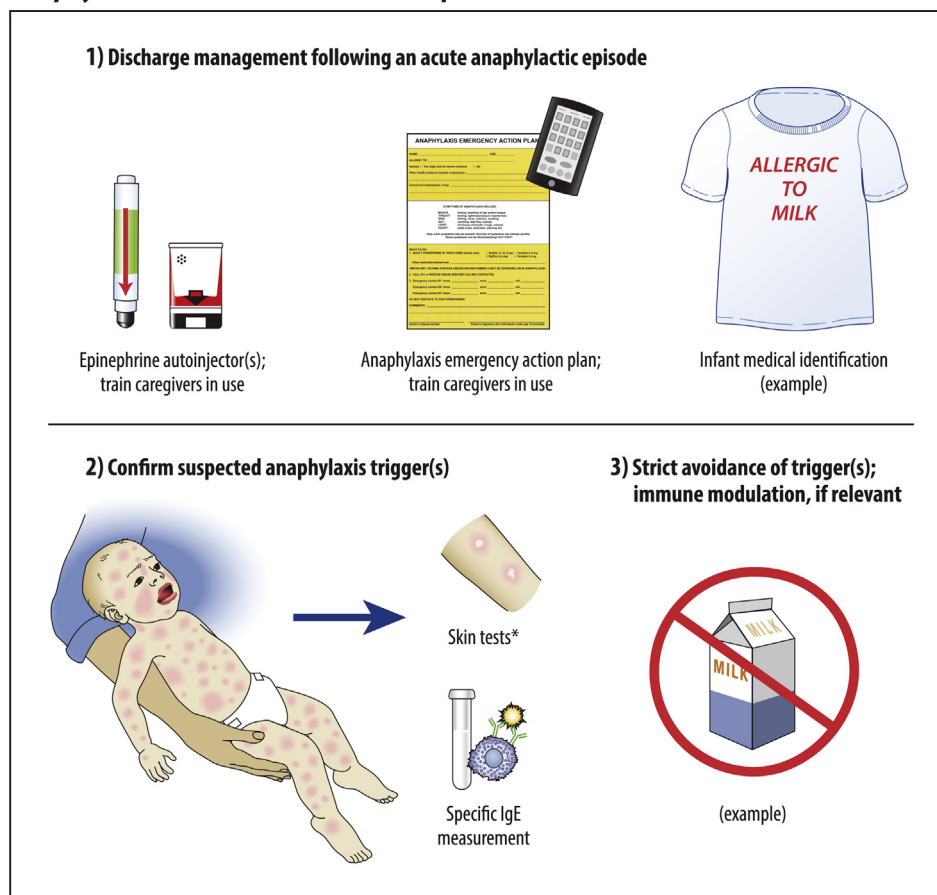
**Anaphylaxis in infants: Treatment and prevention of recurrences**

**FIG 3.** After treatment of anaphylaxis in a health care setting, subsequent management includes providing an EAI (or a prescription for an EAI) and an action plan and training the caregiver to recognize anaphylaxis symptoms and use the EAI promptly (*top panel*). Long-term management involves risk assessment, preferably by an allergy/immunology specialist, to confirm the anaphylaxis triggers and risk reduction and prevention of recurrences through allergen avoidance and immune modulation (*bottom panel*).<sup>1-3</sup>

labels and food cross-contamination but also with intentional exposure to foods to which the infants were sensitized and with infants being fed by persons other than their parents.<sup>25</sup>

Natural desensitization occurs in many infants and children with clinical reactivity to some foods, such as milk or egg.<sup>12,13,31,32</sup> Baseline characteristics that predict resolution include relatively low allergen-specific IgE levels, small skin prick test wheal sizes, and the characteristics of the initial reaction. Infants in whom natural desensitization is likely to occur can also be identified by their history of tolerating small amounts of unintentionally ingested extensively heated (baked) milk or egg, a marker of transient IgE-mediated allergy. Addition of baked milk or egg to the diet of these infants seems to accelerate the development of tolerance to unheated milk or egg. In contrast, ongoing reactivity to small amounts of baked milk or egg suggests a more severe phenotype and the need for continued strict dietary avoidance of these allergens, even in trace amounts. Strategies for improved screening of new hypoallergenic infant formulas are being developed and will potentially help prevent symptoms in infants with milk allergy.<sup>12,13,33-35</sup>

Randomized controlled trials (RCTs) of oral or sublingual immunotherapy with some foods, such as milk, egg, or peanut, have confirmed that clinical tolerance (desensitization) can be achieved; however, immunologic tolerance is more elusive, and adverse effects are frequent. These approaches are not yet ready for widespread clinical use.<sup>12,17,36-39</sup>

For infants with drug-induced anaphylaxis, if no suitable therapeutic alternative (preferably from a different class) is available, desensitization to the culprit drug conducted by experienced health care professionals is safe and effective for one uninterrupted course of treatment.<sup>1</sup>

In the rare infants with stinging insect venom-induced anaphylaxis, recurrences can be prevented by subcutaneous immunotherapy with the relevant standardized Hymenoptera venom. To date, few infants have been enrolled in RCTs of immune modulation to any allergens.<sup>17</sup>

Infants with the uncommon history of anaphylaxis after vaccination to prevent infectious disease should be evaluated by an allergy/immunology specialist by using skin tests to the suspected culprit vaccine and the excipients it contains, such as

ovalbumin, gelatin, or neomycin. If skin test results are negative, the vaccine can be administered in usual doses, and the infant should be observed. If skin test results are positive, the vaccine should be administered in graded doses, and the infant should be observed. Infants with egg allergy and no history of anaphylaxis to egg or reaction to influenza vaccine can receive an intramuscular injection of an influenza vaccine with low ovalbumin content in a medical setting in which they can be observed for 30 minutes and in which anaphylaxis can be promptly recognized and treated. They should not receive live attenuated influenza vaccines.<sup>14</sup>

## FUTURE DIRECTIONS

Further research is needed with regard to the diagnosis, management, and prevention of infant anaphylaxis, with potential focus on the following:

- validation of the clinical criteria for anaphylaxis diagnosis in infants;
- prospective longitudinal studies in which baseline serum tryptase levels are monitored in healthy and atopic infants throughout the first year of life;
- study of infant comorbidities and amplifying cofactors that increase the risk of severe anaphylaxis;
- development of autoinjectors containing a 0.1-mg epinephrine dose suitable for infants; and
- enrollment of infants in RCTs of immune modulation to prevent anaphylaxis recurrences.

Infants are included in the proposed international research agenda for anaphylaxis.<sup>40</sup> Research in this vulnerable age group is critical to provide high-quality evidence to support future age-appropriate recommendations for the diagnosis and treatment of anaphylaxis and prevention of recurrences.

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## REFERENCES

1. Simons FER, Arduoso LRF, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. *J Allergy Clin Immunol* 2011;127:587-93. e1-22.
2. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
3. Simons FER. Anaphylaxis in infants: can recognition and management be improved? *J Allergy Clin Immunol* 2007;120:537-40.
4. Lin RY, Anderson AS, Shah SN, Nuruzzaman F. Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990-2006. *Ann Allergy Asthma Immunol* 2008;101:387-93.
5. Huang F, Chawla K, Jarvinen KM, Nowak-Węgrzyn A. Anaphylaxis in a New York City pediatric emergency department: triggers, treatments, and outcomes. *J Allergy Clin Immunol* 2012;129:162-8.e3.
6. Vetander M, Helander D, Flodstrom C, Ostblom E, Alfvén T, Ly DH, et al. Anaphylaxis and reactions to foods in children—a population-based case study of emergency department visits. *Clin Exp Allergy* 2012;42:568-77.
7. Topal E, Bakirtas A, Yilmaz O, Ertoy Karagöl IH, Arga M, Demirsoy MS, et al. Anaphylaxis in infancy compared with older children. *Allergy and Asthma Proc* 2013;34:233-8.
8. Rudders SA, Banerji A, Clark S, Camargo CA Jr. Age-related differences in the clinical presentation of food-induced anaphylaxis. *J Pediatr* 2011;158:326-8.
9. Jacobs TS, Greenhawt MJ, Hauswirth D, Mitchell L, Green TD. A survey study of index food-related allergic reactions and anaphylaxis management. *Pediatr Allergy Immunol* 2012;23:582-9.
10. Alvarez-Twose I, Vano-Galvan S, Sanchez-Munoz L, Morgado JM, Matito A, Torrelo A, et al. Increased serum baseline tryptase levels and extensive skin involvement are predictors for the severity of mast cell activation episodes in children with mastocytosis. *Allergy* 2012;67:813-21.
11. Wolbing F, Fischer J, Koberle M, Kaesler S, Biedermann T. About the role and underlying mechanisms of cofactors in anaphylaxis. *Allergy* 2013;68:1085-92.
12. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol* 2014;133:291-307.
13. Boyce JA, Assa'ad AH, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126(suppl):S1-58.
14. Kelso JM, Greenhawt MJ, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol* 2012;130:25-43.
15. Belhocine W, Ibrahim Z, Grandne V, Buffat C, Robert P, Gras D, et al. Total serum tryptase levels are higher in young infants. *Pediatr Allergy Immunol* 2011;22:600-7.
16. Komarow HD, Hu Z, Brittain E, Uzzaman A, Gaskins D, Metcalfe DD. Serum tryptase levels in atopic and nonatopic children. *J Allergy Clin Immunol* 2009;124:845-8.
17. Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilo MB, et al. Management of anaphylaxis: a systematic review. *Allergy* 2014;69:168-75.
18. Simons KJ, Simons FER. Epinephrine and its use in anaphylaxis: current issues. *Curr Opin Allergy Clin Immunol* 2010;10:354-61.
19. Sheikh A, Simons FER, Barbour V, Worth A. Adrenaline auto-injectors for the treatment of anaphylaxis with and without cardiovascular collapse in the community. *Cochrane Database Syst Rev* 2012;8:CD008935.
20. Sheikh A, ten Broek V, Brown SGA, Simons FER. H<sub>1</sub>-antihistamines for the treatment of anaphylaxis: Cochrane systematic review. *Allergy* 2007;62:830-7.
21. Nurmatov UB, Rhatigan E, Simons FER, Sheikh A. H<sub>2</sub>-antihistamines for the treatment of anaphylaxis with and without shock: a systematic review. *Ann Allergy Asthma Immunol* 2014;112:126-31.
22. Choo KJ, Simons FER, Sheikh A. Glucocorticoids for the treatment of anaphylaxis. *Cochrane Database Syst Rev* 2012;4:CD007596.
23. Mehr S, Liew WK, Tey D, Tang MLK. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. *Clin Exp Allergy* 2009;39:1390-6.
24. Grossman SL, Baumann BM, Garcia Pena BM, Linares MYR, Greenberg B, Hernandez-Trujillo VP. Anaphylaxis knowledge and practice preferences of pediatric emergency medicine physicians: a national survey. *J Pediatr* 2013;163:841-6.
25. Fleischer DM, Perry TT, Atkins D, Wood RA, Burks AW, Jones SM, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. *Pediatrics* 2012;130:e25-32.
26. Chad L, Ben-Shoshan M, Asai Y, Cherkaoui S, Alizadehfard R, St-Pierre Y, et al. A majority of parents of children with peanut allergy fear using the epinephrine auto-injector. *Allergy* 2013;68:1605-9.
27. Brown J, Tuthill D, Alfaham M, Spear E. A randomized maternal evaluation of epinephrine autoinjection devices. *Pediatr Allergy Immunol* 2013;24:173-7.
28. Arga M, Bakirtas A, Catal F, Derinoz O, Harmanci K, Razi CH, et al. Training of trainers on epinephrine autoinjector use. *Pediatr Allergy Immunol* 2011;22:590-3.
29. Ford LS, Bloom KA, Nowak-Węgrzyn AH, Shreffler WG, Masilamani M, Sampson HA. Basophil reactivity, wheal size, and immunoglobulin levels distinguish degrees of cow's milk tolerance. *J Allergy Clin Immunol* 2013;131:180-6.
30. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 2012;130:1260-74.
31. Wood RA, Sicherer SH, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of milk allergy in an observational cohort. *J Allergy Clin Immunol* 2013;131:805-12.
32. Peters RL, Dharmage SC, Gurrin LC, Koplin JJ, Ponsonby AL, Lowe AJ, et al. The natural history and clinical predictors of egg allergy in the first 2 years of life: a prospective, population-based cohort study. *J Allergy Clin Immunol* 2014;133:485-91.
33. Kim JS, Nowak-Węgrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. *J Allergy Clin Immunol* 2011;128:125-31.
34. Lemon-Mule H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Węgrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. *J Allergy Clin Immunol* 2008;122:977-83.
35. van Esch BCAM, Knipping K, Jeurink P, van der Heide S, Dubois AEJ, Willemsen LEM, et al. In vivo and in vitro evaluation of the residual allergenicity of partially hydrolysed infant formulas. *Toxicol Lett* 2011;201:264-9.

36. Brozek JL, Terracciano L, Hsu J, Kreis J, Compalati E, Santesso N, et al. Oral immunotherapy for IgE-mediated cow's milk allergy: a systemic review and meta-analysis. *Clin Exp Allergy* 2012;42:363-74.
37. Nurmatov U, Venderbosch I, Devereux G, Simons FER, Sheikh A. Allergen-specific immunotherapy for peanut allergy. *Cochrane Database Syst Rev* 2012;9: CD009014.
38. Jones SM, Burks AW, Dupont C. State of the art on food allergen immunotherapy: oral, sublingual, and epicutaneous. *J Allergy Clin Immunol* 2014;133:318-23.
39. Wood RA, Sampson HA. Oral immunotherapy for the treatment of peanut allergy: is it ready for prime time? *J Allergy Clin Immunol Pract* 2014;2:97-8.
40. Simons FER, Arduso LRF, Bilo MB, Cardona V, Ebisawa M, El-Gamal Y, et al. International consensus on (ICON) anaphylaxis. *World Allergy Organ J* 2014;7:9.