

Management of Anaphylaxis in Infants and Toddlers



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KEYWORDS

• Infant • Toddler • Anaphylaxis • Food allergy • Prevention • Management

KEY POINTS

- Anaphylaxis in infants typically has good outcomes and lower severity than other age groups.
- The mainstay of treatment of anaphylaxis is intramuscular epinephrine. In the community setting, a weight-appropriate autoinjector should be used when available.
- Long-term management of anaphylaxis in infants and toddlers includes allergy testing and routine follow-up, epinephrine autoinjector prescription, and maintenance of an age-appropriate allergy emergency plan.

INTRODUCTION

Anaphylaxis is a potentially serious, systemic reaction, either immunologic or nonimmunologic, that is usually rapid in the onset, of variable severity, and may cause death.¹ Anaphylaxis is estimated to affect 1.5 to 757 per 100,000 persons/year worldwide.^{2–4} The global prevalence of anaphylaxis over a lifetime has been rising according to studies reported in the United States (US), Europe, Australia, and Asia in recent years, by 1.89- to 3.3-fold.^{5–7} One systematic review of fatal anaphylaxis cited fewer cases in France and Canada when compared with increased rates in Finland and Australia, and stable rates in the United Kingdom, the US, and Brazil.⁸ Recent studies have also found that anaphylaxis rates are rising in the infant and toddler age group, specifically.³ In a large US database, from 2006 to 2015, emergency department (ED) visits for infants and toddlers with anaphylaxis increased, whereas hospitalizations remained stable or decreased.^{3,9}

Epidemiologic studies on anaphylaxis are based on different parameters, including diagnosis codes from ED visits and hospitalizations, epinephrine use, and voluntary registries of physicians. Unfortunately, these estimators are limited by a 60% to 64% positive predictive value for diagnosis code-based estimates,¹⁰ and

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documentation of epinephrine use does not equate to an anaphylaxis diagnosis.^{11–14} Limitations of using epinephrine as a surrogate marker for anaphylaxis include that epinephrine may not always be available for an initial allergic reaction, it may sometimes be used preemptively before criteria are met, and underutilization of epinephrine by both providers and caregivers to treat anaphylaxis is common.¹⁵

Allergic reactions in infants and toddlers are most often triggered by foods, and less often by drugs or insect stings. Food allergens are associated with 91% to 93% of infant anaphylaxis cases presenting in the hospital setting, including ED visits, inpatient, and outpatient encounters, according to 2 studies.^{16,17} Egg and milk are the most common triggers of allergic reactions in infants, though the frequency may vary based on geographic locations and feeding practices.^{8,15–18} In 2 European studies and a Korean study, milk was the most common food trigger in infants (44%–61%).^{8,16,17} Another 2 studies in the US reported that egg was the most common food trigger in infants (33% and 38%).^{15,18} In toddlers, peanut is the most common triggering food for allergic reactions in the US^{15,18} and tree nuts were noted as the most common trigger in toddlers in a European study.¹⁹

Infants and toddlers also present with a distinct pattern of allergic symptoms and severity of reactions. Evidence suggests decreased severity of allergic reactions among infants when compared with other pediatric age groups.^{8,15,16,18,20,21} Among 512 infants from 3 to 15 months old with milk or egg allergy, Fleischer and colleagues reported that 70% of reactions were mild, 18% were moderate, and 11% were severe.²² In addition to lower rates of systemic involvement, death and biphasic reactions were also less frequently reported.^{8,21,23–27}

CLINICAL PRESENTATION IN INFANTS AND TODDLERS

Context of reactions

In infants and toddlers who have been diagnosed with food allergy, allergic reactions are mainly due to accidental exposures.²² This age group is more likely to have accidental exposure to allergens due to crawling on the ground and mouthing of hands, fingers, and objects. However, in some cases, caregivers have reported intentional exposures causing reactions. Reasons cited by caregivers include determining whether the child has outgrown the allergy or giving a larger amount of an allergen than previously tolerated, in particular to milk, egg, and peanut.²² Limited studies have identified that cofactors may increase the likelihood of an allergic reaction in infants and toddlers including upper respiratory infection at the time of reaction.^{8,28}

The greatest number of new food exposures occurs during the infant and toddler ages. As such, allergic reactions due to first-time exposures are more likely in infants and toddlers than in older children.¹⁵ As an example of one solid food introduction practice that is recommended, infant peanut introduction guidelines may affect the rate and timing of first-time exposures and therefore reactions. The Learning Early About Peanut (LEAP) clinical trial, a landmark study published in 2015, showed that the early introduction of peanut between 4 and 11 months was linked to a decrease in the development of peanut allergy in high risk infants.²⁹ The 2017 National Institute of Allergy and Infectious Diseases (NIAID) Addendum Guidelines to Prevent Peanut Allergy which followed, recommends that high-risk infants (with egg allergy or severe eczema) be evaluated for peanut and introduced to peanut between 4 and 6 months of age and that infants with mild to moderate eczema start peanut around 6 months.³⁰ A retrospective cohort study of 561 patients in California found an increase in the rate of ED visits and epinephrine prescriptions in infants between 2016 and 2018, from 2.2 to 5.7 per 1000, which may represent an impact of these published guidelines in the short term.³¹

Assessing allergic reactions in infants and toddlers

Allergic reactions consist of a constellation of symptoms that present on a continuum from mild reactions (grade 1-cutaneous or upper respiratory without cutaneous) to cardiovascular collapse and/or respiratory distress (grade 4 or 5 – anaphylaxis, **Fig. 1, Table 1**).³² Studies have shown that infants present most commonly with skin and/or gastrointestinal (GI) symptoms, and cardiovascular, and respiratory symptoms are less frequent.^{15–18,20,33,34}

Some differences in anaphylaxis presentation are also noted when comparing infants and toddlers. One study of 374 caregivers reported that infants more frequently experience skin reactions, mottling, ear pulling/scratching, or putting fingers in ears, whereas toddlers experienced throat itching and coughing/wheezing more frequently.³⁴ Also, GI symptoms are more common in infants than in all other age groups and respiratory symptoms were more common in toddlers than in infants, according to a retrospective study of 357 ED visits.¹⁸ A similar pattern of symptoms was noted in a retrospective European study, with cutaneous and neurologic symptoms also increased in infants of this group of 314 anaphylaxis cases.¹⁹

Assessments of infants and toddlers can be challenging. Blood pressure measurement in an acutely reacting child can be especially difficult as this requires an appropriate cuff size to be available and behaviors such as fussiness or crying can present barriers to obtaining an accurate measure. The lack of this data point in many cases precludes the use of hypotension as a parameter for assessing the severity of anaphylaxis.^{16,35,36} As a surrogate measure, signs and symptoms of hypotension can be assessed by examining for mottled or pale skin, delayed capillary refill, or lethargy. Two other complicating factors related to the assessment of allergic reactions in infants and toddlers include their inability to communicate subjective symptoms and challenges in recognizing nonspecific signs and symptoms as potential markers of



Fig. 1. Potential signs and symptoms of anaphylaxis in infants. (From Simons FE, Sampson HA. Anaphylaxis: Unique aspects of clinical diagnosis and management in infants (birth to age 2 years). *J Allergy Clin Immunol.* 2015 May;135(5):1125 to 31.)

Table 1
Modified WAO grading system

Grading System for SARs				
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anaphylaxis				
Symptom (sign(s) from 1 organ system present	Symptom(s)/sign(s) from ≥ 2 organ symptoms listed in grade 1	Lower airway	Lower airway	Lower or upper airway
Cutaneous		• Mild bronchospasm. for example, cough, wheezing, shortness of breath which responds to treatment	• Severe bronchospasm, for example, not responding or worsening in spite of treatment	• Respiratory failure and/or Cardiovascular
• Urticaria and/or erythema-warmth and/or pruritus, other than localized at the injection site		And/or Gastrointestinal	And/or	• Collapse/hypotension*
And/or		• Abdominal cramps* and/or vomiting/diarrhea	Upper airway	And/or
• Tingling, or itching of the lips* or		Other	• Laryngeal edema with stridor	Loss of consciousness (vasovagal excluded)
• Angioedema (not laryngeal)*		• Uterine cramps	• Any symptom(s)/sign(s) from grades 1 or 3 would be included	• Any symptom(s)/sign(s) from grades 1, 3, or 4 would be included
Or		• Any symptom(s)/sign(s) from grade 1 would be included		
Upper respiratory				
• Nasal symptoms (eg, sneezing, rhinorrhea nasal pruritus, and/or nasal congestion) And/or				
• Throat-clearing (itchy throat)* And/or				
or				
• Cough not related to bronchospasm				
Or				
Conjunctival				
• Erythema, pruritus, or tearing				
Or				
Other				
• Nausea				
• Metallic taste				

From Cox LS, Sanchez-Borges M, Lockey RF. World Allergy Organization Systemic Allergic Reaction Grading System: Is a Modification Needed? J Allergy Clin Immunol Pract. 2017 Jan-Feb;5(1):58 to 62.e5.

anaphylaxis.³⁷ Infants and toddlers cannot clearly express symptoms such as anxiety, itchiness, congestion, nausea, or dizziness. Some signs that may be difficult to attribute to an allergic reaction in this age group include behavioral changes (fussiness and fear are common in a health care setting), flushing (may occur with fever or crying), drooling (common in infants), and drowsiness (common after feeds or around nap-time). Therefore, additional descriptors for anaphylaxis signs and symptoms may help caregivers identify reactions in infants and toddlers (**Table 2**).^{34,38}

Differential diagnosis

Although the differential diagnosis of anaphylaxis is addressed in detail in Section 2, an expanded differential needs to be considered in this young age group. For an infant or toddler, infectious, respiratory, GI, and toxicology-related etiologies should also be considered during assessment. Infectious conditions causing septic shock may be considered given the shared symptoms of hypotension, flushing, and coughing symptoms. For infants and toddlers presenting with respiratory symptoms of wheezing and cough, obstruction, congenital abnormalities, and aspiration of a foreign body may be considered. Notably, aspiration of peanuts and tree nuts make up one-third of foreign body aspirations in toddlers.³⁹ In the GI system, syndromes such as pyloric stenosis, malrotation, and intussusception could cause symptoms of vomiting, abdominal pain, or diarrhea which could be misattributed to an allergic reaction. Non-IgE-mediated food allergies such as food protein-induced enterocolitis syndrome may need to be considered if delayed GI symptoms are observed.⁴⁰

Discernment of anaphylaxis with testing of the mast cell enzyme, tryptase, may be used to support the diagnosis. This enzyme can be measured within a 2 to 4-hour window of allergic reaction onset, but may not always be elevated in food-induced anaphylaxis.^{41–43} Blood sampling for tryptase levels may be challenging to obtain in an ill infant, and results should be interpreted with caution as younger patients have higher tryptase levels at baseline.⁴⁴

ACUTE MANAGEMENT

The World Allergy Organization, Joint Task Force of Practice Parameters (US), and European Academy of Allergy and Clinical Immunology have all published guidelines on the acute management of anaphylaxis.^{41,43,45} These guidelines are similar across ages and are based on studies performed in older children and adults.^{46–48} Epinephrine is the mainstay of treatment in anaphylaxis and should be administered without delay.

Initial treatment in the medical setting

Once there is a concern for anaphylaxis, standard procedures should be followed, including the removal of allergen trigger and administration of intramuscular (IM) epinephrine to the anterolateral thigh (0.01 mg/kg of a 1:1000 [1 mg/mL] solution⁴⁹). The benefits of using epinephrine in anaphylaxis outweigh the risks. In infants and toddlers, epinephrine underuse can be attributed to factors such as lack of access in patients without a previous diagnosis, difficulty with identifying symptoms in this age group, and caregiver or provider hesitancy.

In the clinical setting, after epinephrine administration, the provider should call for help, and position the patient in a supine or semi-reclining manner.^{36,50} Next, the patient should be assessed for any disturbances in the airway, breathing, or circulation. If cardiopulmonary arrest is identified, resuscitation should be initiated without delay. Adjunctive medications, such as antihistamines, steroids, beta-agonists, intravenous

Table 2 Alternative, age-specific symptoms/signs used in this study to help identify anaphylaxis in infants/toddlers	
Language Used in Current Diagnostic Criteria*	Language Used in AAFA Infant Toddler Anaphylaxis Study
Pruritis	Tongue thrusting, tongue pulling, repetitive lip licking, or licking of hands or objects. Throat itching ear pulling, scratching, or putting fingers in the ears. Eye rubbing, eye itching
Dyspnea	Belly breathing, fast breathing, nasal flaring, chest or, neck "tugging"
Stridor	Hoarse voice, hoarse cry. Barky/croup-like cough
Reduced PEF	<i>(Currently, no appropriate and practical way to get FEV₁ in this population in an acute setting)</i>
Reduced BP (low systolic BP [age specific] or >30% decrease in systolic BP)	<i>(Blood pressure in this population can be challenging to acquire and interpret. Hypotension is also t late phase cardiovascular symptom in this age group. Tachycardia may be an earlier vital sign change)</i> Wobbly appearance, lethargic, floppy, poor head control, difficult to wake up. Crankiness, withdrawn or clingy, inconsolable crying, subdued or less active, limp. Mottling of the skin or blue/gray skit (cyanosis) around mouth/lips or hands/feet
Hypotonia (collapse), syncope	Wobbly appearance, lethargic, floppy, poor head control, difficult to wake up. Crankiness, withdrawn or clingy, inconsolable crying, subdued or less active, limp
Incontinence	<i>(Can be challenging to differentiate in diaper wearing population)</i>
Persistent gastrointestinal symptoms	Abdominal pain, diarrhea, hiccups, spitting up, back arching, vomiting

Abbreviations: AAFA, asthma and allergy foundation of America; BP, blood pressure; PEF, peak expiratory flow.

From Pistiner M, Mendez-Reyes JE, Eftekhari S, Carver M, Lieberman J, Wang J, Camargo CA Jr. Caregiver-Reported Presentation of Severe Food-Induced Allergic Reactions in Infants and Toddlers. J Allergy Clin Immunol Pract. 2021 Jan;9(1):311 to 320.e2.

fluids, or oxygen supplementation may be considered, but only after epinephrine is administered.

Management in the community setting

In the community setting, a weight-appropriate epinephrine autoinjector (EAI) should be used, if available. Some patients may need more than one EAI administration if symptoms do not resolve soon after the first dose. For caregivers, a patient-specific emergency action plan can help guide management during an acute reaction as it reminds caregivers of signs and symptoms that can occur and provides instructions for additional steps after epinephrine has been administered (aap.org/anaphylaxis).

Epinephrine autoinjectors

In the US, EAI's are currently available in 3 doses, 0.1 mg, 0.15 mg, and 0.3 mg. A summary of the differences between these devices in terms of indication and other parameters can be found in [Table 3](#). The 0.1 mg device is not as widely available due to insurance coverage and regulatory approval in many countries. If it is available, the

Table 3
Attributes of 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 for pediatric EAIs	0.29 ⁰⁰ for 0.1 mg 0.50 ⁰⁰ for 0.15 mg	0.51 ⁰⁰ for 0.15 mg	0.51 ⁰⁰ for 0.15 mg	0.63 ⁰⁰ for 0.15 mg ^a	0.63 ⁰⁰ for 0.15 mg ^a
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

Abbreviations: FDA, food and drug administration.

^a As reported by the company on inquiry.

From Tsuang A, Chan ES, Wang J. Food-Induced Anaphylaxis in Infants: Can New Evidence Assist with Implementation of Food Allergy Prevention and Treatment? J Allergy Clin Immunol Pract. 2021 Jan;9(1):57-69.

package insert states that dosing is 0.1 mg for children between 7.5 kg and 15 kg, whereas the 0.15 mg is for children weighing 15 kg and 25 kg, and 0.3 mg for anyone more than 25 kg. Expert consensus recommends the 0.1 mg dose of EAI for children under 7.5 kg, given the benefits of treatment over delay in treatment or lack of treatment.³⁵ Based on the same perspective, if the 0.1 mg is unavailable, the 0.15 mg is recommended for young children weighing 7.5 to 15 kg.^{41,49}

Another element of EAI for consideration is the needle length. In smaller infants, there is a theoretical concern of accidentally injecting beyond the muscle to the bone, based on the applied pressure.^{51,52} The ideal IM injection needle length, based on studies measuring the distance between skin, muscle, and bone, using ultrasound, is 7 to 8 mm (0.28–0.31 inches) in children 7.5 to 15 kg.⁵¹ Considering the currently available EAI, only the 0.1 mg EAI fits this range. However, a follow-up study reported the increased risk of subcutaneous injection when any age patient wears winter clothes.⁵³ These considerations are noteworthy for optimal treatment; according to a randomized, double-blind, placebo-controlled, prospective study in adult males, peak plasma concentrations are highest when epinephrine is injected intramuscularly in comparison with subcutaneous injection.⁵⁴

LONG-TERM MANAGEMENT

Allergy referral and education

In the acute setting, before discharge from the hospital or ED, education and counseling should be provided regarding allergen avoidance and management of future allergic reactions. If the trigger is identifiable, the family should be instructed about the identification and avoidance of specific foods, medications, or insects.⁴¹ Also, a weight-appropriate EAI should be prescribed and a demonstration of how to use the EAI using a device trainer or training video can be beneficial. A referral to an allergist is advisable to evaluate and confirm potential triggers and receive additional education and management guidance. In terms of allergic reaction management, an allergy emergency plan should be provided to the family with guidance on what medications should be administered based on the patient's symptoms.^{55,56} An allergy and anaphylaxis emergency plans are available from the American Academy of Pediatrics (both English and Spanish).⁵⁶ Emergency plans should also be updated and reviewed with the family at each follow-up visit to reinforce the management of allergic reactions and ensure appropriate medication dosing for the growing child. Annual follow-up is advised for any child with food allergy to ensure that the family has updated medications and emergency plans.⁵⁶

In the allergist's office, a detailed history of reactions to foods, insects, and medications will be taken to help guide targeted testing for possible allergen triggers.³⁵ In the case of food allergic responses, the history can help distinguish between IgE and non-IgE-mediated reactions. To help confirm a diagnosis, the allergist may perform skin prick testing, allergen-specific IgE measurement, and/or oral food challenge (OFC). These tests provide information about sensitization and support an IgE-mediated allergy diagnosis. If there is a high suspicion and negative test, repeat skin prick testing could be considered at least 4 to 6 weeks after the initial reaction, to avoid the depletion of mast cell mediators after a severe reaction.³⁵ There is no minimum age for allergy evaluation and testing according to recommendations from a recent consensus panel of experts.³⁵ Allergy testing panels are strongly discouraged as they often lead to unnecessary avoidance of foods, or EAI prescription, due to the common occurrence of sensitization in the absence of clinically relevant allergy, especially in atopic individuals.⁵⁷ If a low level of sensitization is noted in the absence of ever eating the

food, home introduction or, physician-supervised OFCs may be considered. An infant peanut OFC guide is available from Bird and colleagues.⁵⁰ Annual follow-up is typical in the course of food, drug, and venom allergy management.

Preventing recurrence

Allergen avoidance is the standard of care for the management of most allergic triggers in infants and toddlers. Even in the setting of allergen avoidance, accidental exposures can occur and can trigger symptoms that may require epinephrine.^{22,58} Fleischer and colleagues noted that among 512 preschool-aged children, the annualized reaction rate was 0.81 per year, with 87.4% due to accidental reactions, 11.4% of cases classified as severe, and 29.9% requiring treatment with epinephrine.²² Therefore, caregivers should always be prepared to recognize and manage unexpected allergic reactions.

Emerging therapies for food allergy

Allergen avoidance can be effective, but has been associated with increased stress and anxiety and decreased quality of life in some patients.⁵⁹ Therefore, there have been ongoing efforts to develop treatments for food allergies. Treatment approaches focus on incremental trigger desensitization or immune dampening using a biologic medication. Oral (OIT) and epicutaneous immunotherapy (EPIT) are both promising approaches to food allergy treatment in infants and toddlers. Currently, there is one FDA-approved product available for peanut OIT, Palforzia that may help prevent or minimize reactions to accidental peanut exposures, by increasing peanut thresholds for patients 4 to 17 years of age.⁶⁰ OIT has shown to be efficacious in infants in 2 early studies, and there is an ongoing phase 3 study underway (NCT03736447).^{61–63} Another mode of treatment, EPIT, is also being studied in this age group. One study in 1 to 3-year-old children with peanut allergy (EPITOPE) is currently underway (NCT03211247),⁶⁴ and another in 2 to 11-year-old children with IgE-mediated milk allergy (MILES) was recently completed (NCT02223182).^{65,66} The MILES study showed an increase in milk tolerated, after 1 year of treatment.⁶⁵ Biologic medications, such as omalizumab (anti-IgE monoclonal antibody), are also being studied. Currently, an NIH-sponsored Consortium of Food Allergy trial is investigating omalizumab as monotherapy and as adjunctive to OIT for food allergy (NCT03881696)⁶⁷ and includes children 1 year and older.

SUMMARY/DISCUSSION

Lifetime anaphylaxis cases are increasing over time and infant and toddler cases are no exception, particularly regarding ED visits. Notably, this increase in ED visits was documented before the NIAID Addendum Guidelines to Prevent Peanut Allergy in 2017.⁵

Anaphylaxis in infants and toddlers should be treated according to established guidelines, and epinephrine is the mainstay of treatment. Epinephrine is a safe and life-saving medication, and its use should never be hesitated. Long-term management of anaphylaxis includes trigger avoidance and follow-up testing and evaluation with an allergy/immunology specialist.

Recent studies have demonstrated that infant and toddler anaphylaxis has good outcomes, is less severe than other age groups, and primarily presents with cutaneous and GI symptoms. This evidence could allay concerns and support the implementation of food allergy prevention guidelines and emerging treatments.

CLINICS CARE POINTS

- Pearls
 - In infants and toddlers, food is the most common trigger of anaphylaxis. In infants, the most common trigger is milk or egg, whereas, in toddlers, the most common trigger is peanuts.
 - Infants and toddlers have favorable outcomes in anaphylaxis.
- Pitfalls
 - Infants and toddlers should be treated with epinephrine without delay; epinephrine is underutilized and this may be due to the lack of access, difficulty identifying symptoms, or caregiver/provider hesitancy.
 - Due to challenges in recognizing signs and symptoms of anaphylaxis in infants and toddlers, age-specific descriptors may be considered to aid caregivers in recognizing anaphylaxis.

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