

Guiding Principles for the Recognition, Diagnosis, and Management of Infants with Anaphylaxis: An Expert Panel Consensus



Matthew Greenhawt, MD, MBA, MSc^a, Ruchi S. Gupta, MD^b, J. Allen Meadows, MD^c, Michael Pistiner, MD, MMSc^d, Jonathan M. Spergel, MD, PhD^e, Carlos A. Camargo, Jr., MD, DrPh^f, F. Estelle R. Simons, MD^g, and Philip L. Lieberman, MD^h *Aurora, Colo; Chicago, Ill; Dothan, Ala; Boston, Mass; Philadelphia, Pa; Winnipeg, Manitoba, Canada; and Memphis, Tenn*

EXECUTIVE SUMMARY

A group of 8 anaphylaxis experts developed guiding principles for clinicians in practice and for consideration in future guidelines related to the care of infants with anaphylaxis.

Key points highlighted by the panel from this work are the following:

- The working definition of anaphylaxis, as well as the 2-system criteria for anaphylaxis, as defined by National Institutes of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network, should apply for any age including infants.
- Oral exposure to foods is the major cause of anaphylaxis during infancy, and cow's milk, egg, and peanut are the most common triggers.
- Infants are uniquely less verbal, so awareness of overt versus nonspecific signs is critical to providers identifying anaphylaxis.
 - Certain findings in infants (eg, rash, vomiting, or behavioral changes that can be considered normal in infants, even after consuming a food) may not represent symptoms of a reaction *per se*.
 - Infant anaphylaxis may be characterized by cough, wheeze, stridor, lethargy/drowsiness, tachycardia, cardiovascular collapse, and/or persistent gastrointestinal symptoms, as in older children, however.
 - In some cases, persistent vomiting may be the only sign. Nonspecific central nervous system symptoms such as cessation

of play, clinging to the caregiver, drowsiness, and persistent crying are common early signs in infant anaphylaxis and must be specifically sought. Cardiovascular collapse is rare in infants.

- Epinephrine is the mainstay of treatment for anaphylaxis regardless of age, and delays in administration of epinephrine are a known risk factor for adverse outcomes, including fatality.
 - Epinephrine is safe for any age and there are no circumstances where this should not be used in an infant to treat anaphylaxis.
 - A new, Food and Drug Administration–approved 0.1 mg epinephrine autoinjector device is available for infants 7.5 kg (16.5 lbs) to 15 kg (33 lbs), where previously the only option for this age group was to use a 0.15 mg device.
 - Antihistamines, corticosteroids, or β -agonists are not appropriate first-line agents for anaphylaxis.
- Existing anaphylaxis emergency action plans could be used for this population; however, infants could benefit from a tailored version of these plans (such as the one provided in this article's Online Repository at www.jaci-inpractice.org) to account for the numerous specific considerations identified by the panel.
- Per currently available guidelines, infants with a history of anaphylaxis would strongly benefit from ongoing periodic follow-up with an allergy/immunology specialist.

Infant anaphylaxis is an emerging risk, with food allergy the most common cause. Although the presentation of anaphylaxis involves the same systems as in older children and adults, there

are real-world challenges to identifying symptoms of an allergic emergency in nonverbal children, as well as implementing optimal treatment. Recognition of anaphylaxis in infants can be

^aSection of Allergy and Immunology, Food Challenge and Research Unit, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colo

^bDepartments of Pediatrics and Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Ill

^cAlabama College of Osteopathic Medicine, Dothan, Ala

^dDepartment of Pediatrics, MassGeneral Hospital for Children, Harvard Medical School, Boston, Mass

^eDepartment of Pediatrics, The Children's Hospital of Philadelphia, Perelman School of Medicine at University of Pennsylvania, Philadelphia, Pa

^fDepartment of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Mass

^gDepartment of Pediatrics & Child Health, Department of Immunology, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

^hDivision of Allergy and Immunology, University of Tennessee Health Science Center, Memphis, Tenn

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Abbreviations used

EAI- Epinephrine autoinjector
ED- Emergency department
FAAN- Food Allergy and Anaphylaxis Network
ICD- International Classification of Diseases
NIAID- National Institutes of Allergy and Infectious Diseases

challenging because allergic symptoms and certain normal infant behaviors may overlap. Intramuscular epinephrine is the treatment of choice for infants, as it is for older children and adults, and an epinephrine autoinjector approved by the Food and Drug Administration is now available for infants weighing between 7.5 and 15 kg. A panel of experts sought to develop guiding principles for the recognition, diagnosis, and management of anaphylaxis in infants, and provide a framework for the development of new guidelines and future research. Accordingly, anaphylaxis emergency action planning for infants was addressed by the panel. In considering formation of future infant anaphylaxis guidelines, health care providers should be aware of the needs to improve the recognition, diagnosis, and management of infants with anaphylaxis. Future research should identify and validate clinical criteria for the diagnosis of anaphylaxis in infants, as well as risk factors for the most severe reactions. © 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1148-56)

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Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death.¹ First-line therapy for anaphylaxis is intramuscular epinephrine, which can rapidly reverse life-threatening cardiac and respiratory symptoms. In 2006, the National Institutes of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) (now known as the Food Allergy Research and Education organization), with representation from 9 professional medical societies, established both the definition for anaphylaxis above and joint consensus diagnostic criteria to aid in the identification of potential cases of anaphylaxis and help facilitate prompt treatment.¹ Since publication, these criteria have been validated for use in the emergency department (ED).²

Recent evidence suggests a rising prevalence of anaphylaxis in the last 10 to 15 years, exemplified by an increase in the reported

number of severe reactions, as well as in the number of cases presenting for ED care.^{3,4} Multiple factors may influence this, including an increasing incidence and prevalence of food allergy, geography, and low vitamin D status.⁵⁻⁸

With the recent update to infant feeding guidelines that emphasizes early peanut introduction for the primary prevention of peanut allergy,⁹ there is potential concern for anaphylaxis occurring in this population given new guidelines that specifically recommend peanut introduction as early as 4 months of life have given this renewed interest.⁹ Although such concern has always existed, more infants with risk for allergy will be exposed to peanut. Although available guidelines discuss anaphylaxis in young children,¹⁰⁻¹⁴ there are no recommendations that specifically deal with infants.

This panel was convened to discuss the recognition, diagnosis, and management of infants with anaphylaxis with the intention of identifying areas for clinical guidance and best-practices strategy development. Currently, there are no medical-society-sponsored guidelines for infants with anaphylaxis. The panel formulated this expert-consensus document to outline guiding principles in these areas for clinicians and to inform future development of age-tailored anaphylaxis guidelines for professional medical societies. The intended audiences of this article are clinicians who may care for an infant potentially at risk for anaphylaxis (eg, allergy/immunology, emergency medicine, pediatrics, family medicine, and neonatology), as well as other key stakeholders including those involved in the development of professional practice guidelines.

METHODS

An 8-member expert panel was convened for a 1-day in-person roundtable meeting to discuss key issues in the diagnosis and management of infant anaphylaxis. The primary objective of the meeting was to develop guiding principles and key considerations for the recognition, diagnosis, and management of anaphylaxis in infants through a physician-level consensus to assist current practice as well as future guideline development and research. Participants included board-certified allergist/immunologists, an emergency medicine physician, and pediatrician, all of whom have authored papers and/or guidelines on anaphylaxis and are considered experts in the field. Topics of discussion were broad and included epidemiology, allergic triggers, symptomatology unique to nonverbal children, as well as diagnostic workup and treatment. A modified Delphi panel was used to gain a consensus for relevant considerations, using a threshold of consensus from 6 of 8 panel members (75%) (see [Table E1](#) and [Methods](#), available in this article's Online Repository at www.jaci-inpractice.org). A key premise of this project was that these discussions would work within the framework of current guidelines,^{10,14,15} while emphasizing any infancy-related features that deserved more (or less) emphasis in an effort to

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Corresponding author: Matthew Greenhawt, MD, MBA, MSc, Children's Hospital Colorado, 13123 East 16th Avenue, Aurora, CO 80045. E-mail: matthew.greenhawt@childrenscolorado.org.

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improve the recognition, diagnosis, and management of infants with anaphylaxis.

INFANT ANAPHYLAXIS: NONCLINICAL GAPS IN PRACTICE

Definition

The panel unanimously agreed that when considering anaphylaxis in very young children, both infants and toddlers should be considered together, distinct from older children with more advanced verbal skills. The term “infant” defines a child under the age of 12 months, and “toddler” a child between the age of 12 and 36 months. The panel unanimously agreed that weight should be less of a consideration in this delineation, though most of these children would likely weigh 15 kg or less. It was felt that defining this population by weight may cross lines for particular epinephrine autoinjector (EAI) product indications, and not focus on more critical issues such as a child’s developmental skills. In addition, the panel unanimously agreed that the working definition of anaphylaxis, as defined by NIAID/FAAN, should apply for any age (Table I),¹ and that an infant-specific anaphylaxis definition was unnecessary at this juncture. Rather, it was agreed that there should be a broader understanding and awareness of age-related differences in symptom presentation (eg, frequent skin manifestations, behavioral changes such as withdrawal or inconsolability) that distinguish the presentation of anaphylaxis in infants from older children who have verbal skills. Moreover, it was unanimously agreed that certain findings in children (eg, rash, vomiting, or behavioral changes that can be considered normal in infants, even after consuming a food) may not represent symptoms of a reaction *per se*, and cautious use of a broad differential diagnosis is needed when interpreting these findings.¹⁶

Epidemiology

Data suggest that the prevalence of food-related anaphylaxis has increased in children, paralleling the rise in food allergy over the past 20 years. There is a paucity of infant-specific data, as most describe older children and adolescents. Approximately 5.9 million US children under the age of 18 are estimated to have food allergies,⁵ and food allergy is the leading cause of anaphylaxis in young children.¹⁷ The prevalence of food-related anaphylaxis in children age 6 months to 18 years increased 50% between 2007 and 2012, mirroring an observed 18% rise in food allergy in US children between 1997 and 2007.^{18,19} In Illinois alone, there was an annual increase in ED visits and hospitalizations for food-induced anaphylaxis of 27% in children 0 to 4 years of age between 2008 and 2012, highlighting infants/toddlers as a potentially vulnerable age subgroup.²⁰ Between 2005 and 2014, ED visits for anaphylaxis increased 129% in children under 5 years.⁴ Although a 2014 study noted 84 deaths in children 17 years or younger,²¹ fatalities due to food-induced anaphylaxis are rare in young children.²²

Challenges posed by billing and coding issues

The panel identified inconsistencies in the age ranges used in large data sets and how anaphylaxis is defined across studies, with grouping of data by discharge coding (ie, not at the level of the presenting symptoms). These are limitations affecting the interpretation of these data, complicating the use of large health care data sets. The panel unanimously agreed that discharge coding can be inaccurate and misrepresentative of actual chart-documented

TABLE I. NIAID/FAAN clinical criteria for a diagnosis of anaphylaxis

Anaphylaxis is highly likely when any *one* of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

- a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

OR

2. Two or more of the following that occur rapidly after exposure to a *likely allergen* for that patient (minutes to several hours):

- a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
- b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
- d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

OR

3. Reduced BP after exposure to *known* allergen for that patient (minutes to several hours):

- a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
- b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

BP, Blood pressure; FAAN, Food Allergy and Anaphylaxis Network; NIAID, National Institutes of Allergy and Infectious Diseases; PEF, peak expiratory flow. Reproduced with permission from Sampson et al.¹

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 mo to 1 y, less than (70 mm Hg + [2 × age]) from 1 to 10 y, and less than 90 mm Hg from 11 to 17 y.

events, and there was shared concern that certain key symptoms could be overlooked for infants/toddlers, who are nonverbal or minimally verbal compared with older children. Therefore, it was acknowledged that accurate assessment of symptoms in infants could be difficult. Though International Classification of Diseases (ICD)-10 coding is more specific than ICD-9, potentially enabling better description and tracking of anaphylaxis, coding is often an automated function of electronic medical record systems and too often may be inaccurate and prone to variability. For example, it is possible to code an event under an “acute allergic reaction,” yet this may not have accurately captured that there were signs of 2 or more organ systems, which would most accurately be coded as anaphylaxis. Proposals have been submitted to the World Health Organization to help improve the accuracy of future ICD-11 coding for anaphylaxis, including for a code to be included on death certificates.²³

Routes of exposure

The panel unanimously agreed that oral exposure to foods is the major cause of anaphylaxis during infancy, and that cow’s milk, egg, and peanut are the most common triggers.^{5,16} However, any food item could potentially trigger anaphylaxis. Nonoral exposure to food is very unlikely to trigger a reaction.²⁴⁻²⁶ The panel agreed that with early peanut introduction in children beginning as early

as age 4 months to prevent peanut allergy, there is an emerging concern about the increased potential that this could result in cases of infant anaphylaxis. However, data from the Learning Early About Peanut allergy study, the Enquiring About Tolerance study, and the Health Nuts study indicate that this early introduction of food is safe, with anaphylaxis rarely reported as an outcome of early introduction (for peanut and other foods).^{9,27-29} Foods are not the only trigger of anaphylaxis during infancy—insect stings, latex, vaccines, topicals (eg, natural rubber latex, chlorhexidine, soaps), and medications (β -lactam and other antibiotics, ibuprofen and other antipyretics, and neuromuscular blockers) are also potential but less common causes in this age range. Data from the Vaccine Adverse Events Reporting System suggest that anaphylaxis rates from vaccines range from 0.65 to 1.31 per million doses.³⁰ Thus, although food is the most likely cause among infants, a detailed history is essential to probe for these other potential triggers.

Risk factors for anaphylaxis

There are multiple studies exploring the developmental origins of atopy, and risk factors that predispose to atopic conditions. However, there is a poor understanding of what predisposes risk of anaphylaxis in these conditions. The panel discussed numerous potential comorbidities and cofactors relevant to infants in considering plausible risks, compared with known risks at other ages. Although known food allergy, drug allergy, or venom allergy can be associated with a potential risk of anaphylaxis, no studies have identified if other common infant conditions such as bronchiolitis, congenital heart disease, recurrent viral induced wheezing, eczema without known food allergy, or isolated allergic sensitization may have potential risk or associations for developing anaphylaxis. Both severe anaphylaxis and biphasic reactions in this age group are thought to be quite rare, though both can occur.¹⁶ Furthermore, it is unknown if such conditions are cofactors for severe anaphylaxis, or biphasic reactions (though these are rarely reported in infants). Moreover, although exercise is a known cofactor for severe allergic reactions in older individuals, it is not established if vigorous activity and/or tantrums in this age (felt by the panel to be an exercise equivalent) are potential cofactors. It also remains unclear (at any age) if racial/ethnic, genetic factors, or social determinants (eg, socioeconomic, insurance, access to health care) could predispose to risk of anaphylaxis. Thus, the panel agreed that there are numerous areas requiring further investigation to better specify what may increase the risk of anaphylaxis in infants.

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Symptoms of infant anaphylaxis

There was unanimous agreement that specific symptoms most likely to be present in an infant needed clearer delineation to facilitate prompt diagnosis but would most likely include cutaneous, respiratory, cardiovascular, and/or gastrointestinal systems, as well as behavioral changes (Figure 1).¹⁶

It was also determined that there was a need to emphasize the differences in presenting symptoms that could differentiate between an “allergic reaction” and “anaphylaxis” in this age group. Data from challenge-based infant studies have noted most anaphylactic reactions in this age present with skin findings.^{29,31,32} However, the panel unanimously agreed that caution is needed to avoid misinterpretation of simple rashes as more concerning than warranted. For example, urticaria is a common

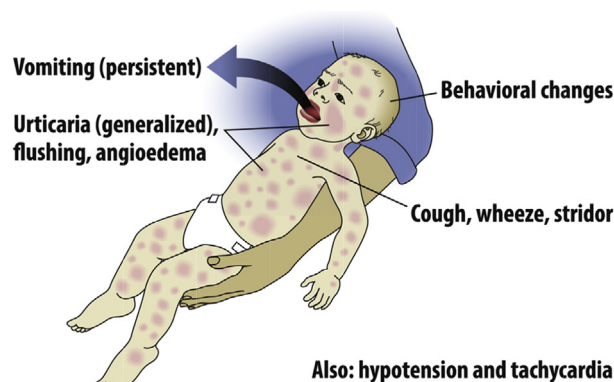


FIGURE 1. Anaphylaxis in infants: potential signs and symptoms. Reproduced with permission from Simons and Sampson.¹⁶

viral exanthema during infancy, and in combination with respiratory symptoms from an upper respiratory infection, such presentation could be misinterpreted as a 2-organ system event indicating anaphylaxis. Facial erythema and perioral hives (eg, perioral contact reactions) from mild transient contact irritation from food are also common in this age but are often non-bothersome and self-limiting in nature. Such contact irritation could happen at other spots on the body where food may inadvertently make contact. This mild contact reaction would be in stark contrast to a pruritic urticarial rash that erupts on the torso and back within minutes of food exposure. Coughing in infants with food ingestion could be developmental as the child is still learning how to negotiate the texture and coordination of solid food. Vomiting and abdominal pain in this age are also multifactorial and could represent reflux, constipation, or many other nonallergic etiologies. Tachycardia can be secondary to crying, febrile illness, and discomfort. These exemplify common scenarios, when scrutiny is put on new food ingestion early in life (in particular, high-risk foods), that can lead to misdiagnosis of anaphylaxis.

Similarly, care must be taken to confirm a true provoking trigger versus a “suspected” trigger, raising the issue of diagnostic sensitivity. This is crucial given more recent trends in food anaphylaxis management that advocate an option for epinephrine administration in instances of suspected but not definitely confirmed ingestion of an item, which may be an area of controversy. The value of this option is unproven at any age but may warrant potential higher scrutiny in infants. Thus, although hives and vomiting are frequently documented symptoms of anaphylaxis in infants,³³ the precise symptomatology of anaphylaxis for infants is not well defined, and the context within which these symptoms are interpreted must always be considered.¹⁶ On the basis of clinical experience, panel members also noted that infant anaphylaxis may be characterized by cough, wheeze, stridor, lethargy/drowsiness, tachycardia, cardiovascular collapse, and/or persistent gastrointestinal symptoms, as in older children (Figure 1). In some cases, persistent vomiting may be the only sign. Nonspecific central nervous system symptoms such as cessation of play, clinging to the caregiver, drowsiness, and persistent crying are common early signs in infant anaphylaxis and must be specifically sought.^{16,34} Cardiovascular collapse is infrequently reported in infants and is typically a late sign.¹⁶

TABLE II. Potential signs and symptoms 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 less than 70 mm Hg from age 1 mo to 1 y, and less than $(70 \text{ mm Hg} + [2 \times \text{age in y}])$ in the first and second years of life; tachycardia, defined as greater than 120-130 beats per minute 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 Simons.³⁴

*More than 1 body system involved.

Unique challenges in assessing infants

The panel unanimously agreed that infants are uniquely less verbal, so awareness of overt versus nonspecific signs is critical to providers identifying anaphylaxis (Table II).³⁴ For example, changes in skin color and subtle behaviors such as scratching and drooling that can signify itching and difficulty swallowing, respectively, may indicate anaphylaxis depending on the context.³³ Behavioral changes such as irritability, inconsolability and dysphonia, regurgitation, and incontinence may also indicate anaphylaxis,¹⁶ though again, the context is crucial, as many of these are normal behaviors during infancy. These symptoms are more significant in combination with other potential symptoms, or within close temporal proximity to a potential allergen ingestion/exposure. The panel unanimously agreed that accurately assessing blood pressure and cardiovascular changes during infancy can be difficult. Proper cuff size is essential, and automated machines may struggle to obtain valid readings in fussy infants. Tachycardia is common during infancy, so heart rate must be interpreted in context of the child's age, and subtle elevations in an otherwise upset infant must be considered as a possible sign for compensated shock in certain contexts. Lastly, the panel unanimously agreed that the role of decreased basal body temperature should be more robustly explored as a possible marker of anaphylaxis (see Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Few data are available to more broadly categorize the diversity of presenting symptoms. Rudders et al³³ detailed

presenting symptoms in children 0 to 2 years of age from 2 large northeast EDs (Table III). The panel unanimously agreed that a firmer consensus to itemize specific organ-system symptoms that may or may not signify anaphylaxis would be of high value to providers in assessing these patients and would be of use to inform the development of future clinical guidelines. As with all allergy assessments, timing is crucial to corroborate symptoms with the likelihood that a reaction could be anaphylaxis.

Diagnosis

The panel unanimously supported the current NIAID/FAAN definition of anaphylaxis in terms of specific criteria to define cases.¹ The panel also unanimously agreed that the applicability of existing anaphylaxis criteria to these younger extremes of age would require further study, in particular to validate the 2-organ system paradigm as being sensitive and specific in infants,^{11,14} versus certain stand-alone symptoms that may better fit as diagnostic of anaphylaxis.

Differential diagnosis

The differential diagnosis of anaphylaxis in infants, which differs from the differential diagnosis in children and adults, should be reviewed and novel allergens and other age-unique causes should be considered. Congenital abnormalities (eg, respiratory or gastrointestinal), foreign body aspiration, acute food protein-induced enterocolitis syndrome, and folding of the

TABLE III. Symptoms and system involvement identified in infants ≤ 2 y old (n = 191)

Reported in infants by symptom	Percent of infants (95% CI)
Hives	88 (79-97)
Nausea/vomiting	53 (41-65)
Swelling	53 (41-65)
Trouble breathing/shortness of breath	37 (26-48)
Wheezing	29 (20-39)
Itching	19 (10-29)
Stridor	5 (3-7)
Reported in infants by system	Percent of infants (95% CI)
Cutaneous	98 (94-100)
Respiratory	59 (47-71)
Gastrointestinal	56 (44-67)

Data excerpted from Rudders et al.³³

small bowel are important considerations in the differential diagnosis of anaphylaxis in infants (Table IV).¹⁶

Workup: acute setting

Previously published guidelines review recommendations on the workup of suspected cases of anaphylaxis, and the panel unanimously agreed that these should be followed, as this workup is similar across most ages.^{11,13} In the acute setting, the panel identified that it is crucial to assess the infant quickly and thoroughly, including taking a comprehensive set of vital signs and thorough history. This history should try to identify specific potential exposures (in particular foods, but also new medications or a potential venom-containing insect sting/bite) and the likely timing of this exposure in relation to the onset of symptoms. The panel emphasized the importance of probing for subtle, less overt changes in the infant's baseline, such as unusual fussiness or shifts in behavior apart from more obvious symptoms. If treatment was given before presentation, it is important to document medication dosing and timing of symptom response. Timing of onset of symptoms is critical because reactions fitting an IgE-mediated mechanism typically have rapid onset within minutes of ingestion but are unlikely to occur beyond 2 hours. If anaphylaxis is confirmed or strongly suspected, families/caretakers of these infants/toddlers should be recommended to avoid offending triggers, prescribed an EAI, trained how to use it, and given an outpatient anaphylaxis emergency action plan to use in case of another allergic emergency (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org for a sample plan). Most importantly, the infant should be referred to an allergy/immunology specialist trained in the diagnosis and management of anaphylaxis.

Workup: outpatient setting

The outpatient workup in the primary care office, occurring after a resolved event, should largely follow the same principles as in the acute setting in terms of history taking. The panel unanimously agreed that the patient's history in the outpatient setting is unequivocally the most important piece of information to help determine the likelihood of a recent reaction being consistent with anaphylaxis, and to properly investigate suspected allergic triggers. As recommended in current anaphylaxis guidelines, primary care providers should prescribe an EAI, provide an

TABLE IV. 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

Reproduced with permission from Simons and Sampson.¹⁶

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

anaphylaxis emergency care plan, recommend avoidance of the offending trigger(s), and refer these patients to the aforementioned specialist for more detailed evaluation.^{11,14}

Outpatient workup should be conducted by a board-certified allergist/immunologist and may include performing skin testing to determine sensitization to potentially relevant triggers, if so directed by the history (given testing itself is not diagnostic of allergy). The specialist, as well as the primary care provider, can also assess for sensitization in the serum. The panel unanimously agreed with current recommendations that if sensitization is negative, but there is still a strong suspicion that a potential trigger caused an event, the infant should be advised to avoid the item and be retested in 4 to 6 weeks. There can be transient mast cell depletion after a severe reaction that could create a window where results could be “falsely negative” on skin prick testing.^{14,35} Furthermore, the panel unanimously agreed that in a child with a suspected anaphylactic reaction, no patient is ever “too young” for referral and allergy testing, which may be a falsely held anecdotal belief. Though a prescription for an EAI and anaphylaxis management training should ideally be provided before referral to a specialist, this should be reinforced, and provided if not previously.

In terms of other testing, the panel unanimously agreed that there is no other test of demonstrated value in the workup of anaphylaxis. There is no biomarker with high sensitivity and specificity for anaphylaxis, though it was agreed that one is needed (see Table E1 available in this article's Online Repository at www.jaci-inpractice.org). Mast cell tryptase may be considered, but only in the acute setting. Unless obtained within 2 to 4 hours of the event, tryptase will not reflect acute mast cell degranulation as part of an anaphylactic reaction and will only reflect the resting burden of mast cells, which could be of use in evaluating conditions with abnormal mast cell aggregation.¹⁵ Eosinophilia is neither sensitive nor specific for anaphylaxis and therefore not of use.¹⁵ Basophil activation testing and newer generation allergen component testing have shown promise in research settings (in determining phenotypes of food allergy that

may be associated with anaphylaxis), but these findings still lack widespread validation and are not ready for clinical use.¹⁵

Treatment

There was unanimous consensus that epinephrine is the mainstay of treatment for anaphylaxis regardless of age, and that delay in administration of epinephrine is a known risk factor for adverse outcomes, including fatality.^{13,14} The panel furthermore agreed that infants may be at even greater risk for delayed epinephrine administration because symptoms may be harder to recognize in this patient population.³⁶ In infants with a known allergy and potential risk for anaphylaxis, outpatient anaphylaxis management plans can help guide prehospital treatment. The panel agreed that for clear symptoms of anaphylaxis or a severe reaction (significant respiratory symptoms, cardiovascular symptoms, or 2-organ system presentations), epinephrine should unequivocally be given immediately per current guidelines. In some instances, there is rationale to administer epinephrine to an infant for any symptom of a reaction to a known allergen in cases where families are not near to an urgent/emergency care facility that can help prevent the progression of symptoms. Caregivers should identify the nearest urgent/emergency care facility that is set up for the care of infants. Emergency medical services responding to cases of likely or potential anaphylaxis should strongly consider giving epinephrine as early as possible, following the recommendations detailed here and in current guidelines. Lastly, the panel unanimously agreed that there are few data regarding treatment of infants with anaphylaxis, and most treatment recommendations are based on extrapolation from data in older children and heavily subject to expert opinion. In particular, it should be emphasized that past reactions have no/limited value as a predictive measure for the severity of future reactions in any age. Thus, there is a critical need for more studies of any type to better inform opinion and clinical decision making.

The panel was more split on the utility of adjunct therapies but unanimously agreed that antihistamines, corticosteroids, or β -agonists were not appropriate first-line agents. However, there was disagreement and no clear consensus regarding their use as adjunct therapies. Some panel members disfavored their use entirely, and recommended epinephrine only for any and all symptoms of an allergic reaction for infants (mild or severe), whereas others either supported their use as adjunct therapies or for milder reactions so long as epinephrine was available in the event of symptom escalation or poor response. The panel acknowledged the lack of evidence on this issue, as well as the fact that certain anaphylaxis emergency action plans have variable instructions with regard to the use of nonepinephrine therapies.

Safety

The panel unanimously agreed that epinephrine is safe for any age and there are no circumstances where this should not be used in an infant to treat anaphylaxis. The panel could not identify situations where the risks of epinephrine in anaphylaxis would outweigh the benefits, even in children with certain congenital heart diseases. Epinephrine is well tolerated and quickly metabolized, and as long as it is properly dosed by weight (and administered intramuscularly), the drug itself is not associated with many risks. Based on data obtained in a randomized, blinded, parallel group study in young children, epinephrine is

optimally injected into the vastus lateralis muscle, compared with subcutaneous administration.³⁷ The advent of the EAI has facilitated preset dosing and relative ease of administration compared with drawing up epinephrine with a needle and syringe from an ampule. However, administration with an EAI has distinct issues.

The first issue is needle length. Recent studies have shown that certain devices may be associated with needle lengths that risk penetration into bone, as measured using ultrasound (skin-to-bone distance).^{38,39} One recent case series also detailed a risk of lacerations from the combination of a long needle held in place where a young child suddenly jerked his or her leg, which emphasizes the importance of training families to apply optimal pressure with the device, and to position the child with his or her legs secured to prevent flailing or jerking motions.⁴⁰ Optimal needle length for children between 7.5 and 15 kg has been suggested to be between 7.0 and 8.0 mm (eg, 7.5 mm = 0.29 inch),³⁹ and the device held against the skin for no longer than 3 seconds to minimize these risks.^{41,42}

The second issue is dose. Although the recommended weight-based epinephrine dosing is 0.01 mg/kg,^{15,43} there was consensus among the panel that, despite widespread use, this dose is not evidence based. However, the panel also agreed that trials to establish an optimal dose would face ethical concerns and logistical difficulties. EAI's are currently sold in 2 fixed doses, 0.15 mg for children over 15 kg (33 lbs) and 0.3 mg for children over 30 kg (66 lbs). A third dose, 0.1 mg, produced by one EAI manufacturer, was approved by the Food and Drug Administration (FDA) in November 2017 and is now available for children 7.5 kg (16.5 lbs) to 15 kg (33 lbs).^{14,15} The panel unanimously agreed that the current recommendation for weight-based dosing was the best available guidance in practice, given the unlikelihood of future trials and lack of evidence that current dosing conventions do not work. However, in acknowledging this, the panel also felt that there was little risk posed to a child under 30 kg (66 lbs) if he or she was administered the 0.3 mg dose, or the child under 15 kg (33 lbs) being given the 0.15 mg dose, given no alternative options. The panel also felt that although it remains unclear precisely at what weight the transition from the 0.15-mg dose to the 0.3-mg dose should occur, it was appropriate to consider this for a child weighing between 20 and 30 kg. Available FDA-approved EAI's and select attributes, including needle length, hold time, and available dosing, are shown in Table V.

Long-term management

The panel unanimously agreed that per current guidelines,^{13,14} infants with a history of anaphylaxis would strongly benefit from ongoing periodic follow-up with an allergy/immunology specialist. The panel discussed that this ongoing management and follow-up should encompass: (1) a periodic assessment of changes in sensitization to established triggers; (2) annual updating of the EAI prescription and verification of the technique through the use of a trainer when available; and (3) updating and re-education regarding the anaphylaxis emergency action plan. The panel agreed that this was likely already being done by most specialists with patients who have suffered past anaphylaxis, and this can be incorporated for infants. The panel felt that it was particularly important for health care providers to offer (and document) education to caregivers regarding allergic trigger avoidance, how to follow the anaphylaxis emergency

TABLE V. Select attributes of currently FDA-approved epinephrine autoinjectors in the United States

Attribute	Auvi-Q	EpiPen	AdrenaClick
Manufacturer	Kaléo	Mylan	Amedra
Dosages (mg)	0.10, 0.15, 0.3	0.15, 0.3	0.15, 0.3
Trainer	Yes	Yes	No
Supplied	2-pack	2-pack	2-pack
Exposed needle length for available pediatric EAI	0.29" for 0.1 mg 0.50" for 0.15 mg	0.51" for 0.15 mg	0.51" for 0.15 mg
Injection hold time	2-s hold, no massage	3-s hold, 10-s massage	10-s hold, 10-s massage
Needle guard	Yes	Yes	No
Retractable needle	Yes	No	No
Vocalized audio prompts	Yes	No	No

EAI, Epinephrine autoinjector; FDA, Food and Drug Administration.

action plan, how to use and care for the EAI, and how to properly position the infant for administration. Anaphylaxis management guidelines recommend prescription of 2 EAI, and this has been facilitated in recent years by the advent of the “two-pack” as the unit of dispensing.

The panel unanimously agreed that although the existing anaphylaxis plans could be used for infants, children in this age range would benefit from a tailored version of these plans that account for the numerous specific considerations that have been discussed throughout this document (see [Figure E1](#) in this article’s Online Repository at www.jaci-inpractice.org for a sample plan). It was also felt that these plans would benefit from the addition of pictures of typical symptoms in infants, or at least their description, to assist in the diagnosis. Most importantly, the panel agreed that when available, for children 7.5 kg (16.5 lbs) to 15 kg (33 lbs), the EAI with the 0.1-mg epinephrine dose may be considered/recommended. For infants less than 7.5 kg (16.5 lbs), the panel discussed considerations for a dose recommendation in this age, considering that any dose in an EAI would be “off-label.” There was strong consensus that a 0.1-mg EAI would be safe to use in this population, though this could be problematic with some providers given the potential stigma of off-label use. However, there was consensus that the off-label option was likely superior to providing parents and caregivers of infants with anaphylaxis a needle and syringe containing a more “precise” dose, which is much more difficult to administer in real-world settings.⁴⁴

FUTURE RESEARCH NEEDS

The panel unanimously agreed that specific guidelines and recommendations for the recognition, diagnosis, and management of anaphylaxis in infants are needed. It was also decided that this was best handled by individual professional allergy societies that could best consider regional/national issues that may be specific to their constituencies. The panel identified multiple research priorities that could facilitate the diagnosis and management of anaphylaxis in this population, including:

- Relationship between reaction severity and specific IgE levels in this population
- Temperature changes in an infant with anaphylaxis
- Effect on health care utilization once more people start early introduction of peanuts
- Identification and developments of biomarker(s) for infant anaphylaxis

- Risk/differential risk versus other age in delayed epinephrine administration for infants/toddlers, specific to the pre-hospital and hospital environments.

CONCLUSIONS

This expert panel identified multiple considerations that may help guide current practice and facilitate future practice guideline development for infant anaphylaxis. The use of consensus techniques such as the Delphi method can be helpful in establishing guiding principles where no professional guidelines currently exist. There are inherent limitations to using this technique including the notion that although a clinical consensus statement may be based on high-level evidence in many cases, some are based on clinical experience and logic alone because many questions in anaphylaxis cannot be answered in clinical trials for ethical or logistical reasons. Also, with a limited panel of experts, personal biases based on one’s own practice habits (eg, local or regional differences in patient populations or care) may be difficult to account for in this expert panel report.

Although children defined as infants (age less than 12 months) were the focus of this work, the panel recognizes that many of these concepts would also apply to toddler-aged children (age between 12 and 36 months). Moving forward, assessments and treatments should be better tailored to the needs of infants and toddlers, to enhance the safety and efficacy of how we manage anaphylaxis in the youngest of children. Appropriate and adequate epinephrine dosing, EAI needle size, and optimal discrimination of specific symptoms that indicate anaphylaxis are all important to achieving good outcomes. Moreover, we have identified barriers at the research level, such as issues pertaining to coding, that can be enhanced to enable better determination of anaphylaxis-related outcomes.

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ONLINE REPOSITORY

METHODS

Inclusion/exclusion criteria

An expert panel was selected by prominence from among known key opinion leaders and experts in the allergy and anaphylaxis, pediatric, or emergency medicine literature to discuss and draft a paper to help establish a methodological perspective for future guidelines. A total of 15 physicians were considered for the project, with 12 invited. From this, a final panel of 8 physicians was chosen to attend the 1-day, in-person meeting. All panel members are considered experts in anaphylaxis.

Format

The panel used the modified Delphi method (round number and face-to-face engagement—a written questionnaire was not

used) technique to reach consensus on issues in infant anaphylaxis that were identified from existing guidelines for older children and adults.^{E1-E4} A single-group, single-round method was chosen for developing consensus on all statements. Feedback was given on each statement via live, real-time responses. Responses were tallied and discussed among the wider group. The tally was then either confirmed or revised based on panel member insights from the discussion.

Consensus threshold definition

Consensus threshold was defined *a priori* as agreement on a given statement by 6 of 8 panel members (75%). This threshold was chosen based on the existing literature and agreed upon as an appropriate level by the experts.^{E3} Questions were developed before the meeting between Hybrid Health team members and the meeting chair after review of the literature, and no topic was dropped from the discussion during the meeting.

TABLE E1. Modified Delphi method and results of the panel consensus

Statement	Panel results	Consensus
Consider children less than 12 mo and toddler-aged children up to 3 y of age for all recommendations on “infant” anaphylaxis	8 Agree 0 Disagree	100%
Weight should not be a consideration in the delineation of age in young children at risk for anaphylaxis	8 Agree 0 Disagree	100%
The working definition of anaphylaxis, as defined by NIAID/FAAN, should apply for any age	8 Agree 0 Disagree	100%
Certain findings in infants (eg, rash, vomiting, or behavioral changes that can be considered normal in infants, even after consuming a food) may not represent symptoms of a reaction <i>per se</i>	8 Agree 0 Disagree	100%
Issues with current medical coding systems may not accurately capture the nature of an allergic reaction/anaphylaxis in infants	8 Agree 0 Disagree	100%
Oral exposure to foods is the major cause of anaphylaxis during infancy, and cow’s milk, egg, and peanut are the most common triggers	8 Agree 0 Disagree	100%
Early peanut introduction as early as age 4 mo is an emerging concern because of the potential that this could result in cases of infant anaphylaxis	8 Agree 0 Disagree	100%
It is not known which conditions, common or other, in infancy may increase the risk of anaphylaxis and more work is needed in this area	8 Agree 0 Disagree	100%
Specific symptoms most likely to be present in an infant need clearer delineation to facilitate prompt diagnosis	8 Agree 0 Disagree	100%
There is a need to emphasize the differences in presenting symptoms that could differentiate between an “allergic reaction” and “anaphylaxis” in this age group	8 Agree 0 Disagree	100%
Infants are uniquely less verbal, so awareness of overt vs nonspecific signs is critical to providers identifying anaphylaxis	8 Agree 0 Disagree	100%
Accurately assessing blood pressure and cardiovascular changes during infancy can be difficult but may not be necessary during an assessment for anaphylaxis	8 Agree 0 Disagree	100%
The role of decreased basal body temperature should be more robustly explored as a possible marker of anaphylaxis	8 Agree 0 Disagree	100%
A firmer consensus to itemize specific organ-system symptoms that may or may not signify anaphylaxis would be of high value to providers in assessing these patients and would be of use to inform the development of future clinical guidelines	8 Agree 0 Disagree	100%
The applicability of existing anaphylaxis criteria to these younger extremes of age requires further study, in particular to validate the 2-organ system paradigm as being sensitive and specific in infants	8 Agree 0 Disagree	100%
Previously published guidelines on the workup of suspected cases of anaphylaxis should apply to infants as well	8 Agree 0 Disagree	100%
It is crucial to assess an infant quickly and thoroughly, including taking a comprehensive set of vital signs	8 Agree 0 Disagree	100%
The patient’s history in the outpatient setting is the most important piece of information to help determine the likelihood of a recent reaction being consistent with anaphylaxis	8 Agree 0 Disagree	100%

(continued)

TABLE E1. (Continued)

Statement	Panel results	Consensus
If sensitization to a trigger is initially negative, but there is still a strong suspicion that a potential trigger caused an event, the infant should be advised to avoid the item and be retested in 4–6 wk	8 Agree	100%
	0 Disagree	
A child with a suspected anaphylactic reaction is never “too young” for specialty referral and allergy testing	8 Agree	100%
	0 Disagree	
There is no test of demonstrated value in the workup of anaphylaxis due to a lack of biomarkers	8 Agree	100%
	0 Disagree	
Mast cell tryptase may be considered as a test, but only in the acute setting	6 Agree	75%
	2 Disagree	
Epinephrine is the mainstay of treatment for anaphylaxis regardless of age, and delay in administration of epinephrine is a known risk factor for adverse outcomes, including fatality	8 Agree	100%
	0 Disagree	
There are few data describing treatment of infants with anaphylaxis, and most treatment recommendations are based on extrapolation from data in older children and heavily subject to expert opinion	8 Agree	100%
	0 Disagree	
Antihistamines, corticosteroids, or β -agonists are not appropriate first-line agents for anaphylaxis	8 Agree	100%
	0 Disagree	
Epinephrine is safe for any age and there are no circumstances where epinephrine should not be used in an infant to treat anaphylaxis	8 Agree	100%
	0 Disagree	
Weight-based epinephrine dosing is not evidence based; however, there is little rationale to change what is currently done in practice	8 Agree	100%
	0 Disagree	
Per currently available guidelines, infants with a history of anaphylaxis would strongly benefit from ongoing periodic follow-up with an allergy/immunology specialist	8 Agree	100%
	0 Disagree	
Existing anaphylaxis emergency action plans could be used for infants; however, infants could benefit from a tailored version of these plans to account for the numerous specific considerations discussed by the panel	8 Agree	100%
	0 Disagree	
A 0.1 mg EAI would be safe to use in infants less than 7.5 kg (16.5 lbs), although this would be “off-label” use	8 Agree	100%
	0 Disagree	
Specific guidelines and recommendations for the recognition, diagnosis, and management of anaphylaxis in infants are needed	8 Agree	100%
	0 Disagree	

EAI, Epinephrine autoinjector; FAAN, Food Allergy and Anaphylaxis Network; FDA, Food and Drug Administration; NIAID, National Institutes of Allergy and Infectious Diseases.

INFANT/TODDLER ANAPHYLAXIS EMERGENCY ACTION PLAN*This plan is intended for infants and toddler (0-3 years of age) with a diagnosis of anaphylaxis.*

Child's Photo

PATIENT NAME _____ DOB _____ AGE _____ DATE OF PLAN _____

HEIGHT _____ inches (____ cm) WEIGHT _____ lbs. (____ kg)

CHILD DEVELOPMENT: ☐ APPROPRIATE FOR AGE ☐ DELAYED VERBAL ☐ YES ☐ NO**KNOWN ALLERGENS:**

- ☐ Tree nut, specify _____
- ☐ Peanuts, specify _____ ☐ Fish/shellfish, specify _____
- ☐ Milk, specify _____ ☐ Grains, specify _____
- ☐ Egg, specify _____ ☐ Other _____

PREVIOUS ALLERGIC SYMPTOMS TO KNOWN ALLERGENS:

- ☐ Skin _____ ☐ Breathing _____
- ☐ Stomach/intestinal _____ ☐ Tongue/throat _____
- ☐ Heart _____ ☐ Other _____

IF THE CHILD SHOWS ANY OF THE FOLLOWING SYMPTOMS WITHIN MINUTES TO A FEW HOURS AFTER EXPOSURE TO A KNOWN ALLERGEN, GIVE EPINEPHRINE:

- **Skin:** raised red rash in more than one small area; swelling of the lips/mouth; blue skin around the mouth/lips
- **Breathing:** difficulty breathing (wheezing, coughing, gasping, turning blue)
- **Stomach/intestinal:** repeat vomiting; persistent diarrhea
- **Tongue/throat:** pushing out the tongue; drooling, scratching at mouth
- **Heart:** unconscious, weak pulse, sweating, pale color, fast heart beat (greater than 120-130 beats per minute)
- **Symptoms that can look like normal behaviors but may not be if exposed to known allergen:** behavioral changes such as fussiness, clinginess, sleepiness and unable to wake

HOW TO ADMINISTER EPINEPHRINE TO THE INFANT/TODDLER:

1. Place the child in a secure position (reverse hug in lap if possible)
2. Hold the child's legs from moving before to using their prescribed epinephrine auto-injector
3. Use the child's prescribed epinephrine auto-injector in the outer thigh muscle
4. Assess child, and if necessary, call 911 (discuss when to call 911 with your child's allergist)
5. Contact others in the order listed here:

Parent's # _____; Pediatrician's # _____; Allergist's # _____

PRESCRIBED MEDICATIONS*

- ☐ 0.1 mg epinephrine auto-injector[†] ☐ Auvi-q 0.1 mg
- ☐ 0.15 mg epinephrine auto-injector[‡] ☐ Generic 0.15 mg ☐ EpiPen, Jr 0.15 mg ☐ Auvi-q 0.15 mg

☐ Other medications to administer: _____

Instructions: _____

*For anaphylaxis, epinephrine is always the first choice of therapy. [†]Consider alternative forms of epinephrine for children weighing less than 16.5 lbs., since this device is indicated for infants and toddlers 16.5 lbs. to 33 lbs. [‡]If the child weighs more than 33 lbs., consider using a 0.15-mg epinephrine auto-injector.

PARENT NAMES/NUMBERS _____

PEDIATRICIAN NAME/NUMBER _____

ALLERGIST NAME/NUMBER _____

FIGURE E1. Sample infant anaphylaxis action plan.

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