

ANAPHYLAXIS IN INFANTS: CAN RECOGNITION AND MANAGEMENT BE IMPROVED?

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The true rate of occurrence of anaphylaxis in infants, defined arbitrarily as age newborn to 2 years, inclusive, is unknown; however, most anaphylaxis case series and anaphylaxis epidemiologic studies in individuals of all ages include infants, some as young as 1 month of age.¹⁻³ Fatalities in anaphylaxis, although rare in infancy, do occur, and even the first episode can be fatal.^{4,5}

CASE REPORT

A 9-month-old boy with a 2-week history of cough and wheeze suddenly developed choking, coughing, labored breathing, and apnea, followed by a respiratory arrest at home. He was resuscitated by his father and brought to a community hospital within 6 minutes. On arrival, he was afebrile, limp, and cyanotic, with decreased air entry, deep retractions, and generalized inspiratory and expiratory rhonchi. He had red, scaly areas of skin on his face, chest, and extremities, with superimposed raised red areas 0.5 to 1 cm in diameter on his face and chest. His weight was 9 kg; heart rate, 152/min; respiratory rate, 38/min; and blood pressure, 80/50mmHg. He was given supplemental oxygen, intubated, ventilated, and transferred to a pediatric intensive care unit with the diagnosis of bronchiolitis, which was epidemic in the region at the time. Chest radiograph revealed minimal peribronchial thickening. The rapid antigen detection assay for respiratory syncytial virus was negative. He responded to albuterol and was extubated within 12 hours. In view of the atypical clinical picture for bronchiolitis and the rapid improvement, the diagnosis was reconsidered.

An allergy/immunology specialist was consulted, and additional history was obtained. The infant had been almost exclusively breast-fed since birth; however, on 3 occasions, he had developed generalized hives soon after ingesting a cow's milk formula supplement. Minutes before his respiratory arrest, he had tasted ice cream for the first time. His eosinophil count was $1.08 \times 10^9/L$. Cow's milk specific IgE was 3.6 kU/L. The allergist's diagnoses were anaphylaxis to cow's milk, asthma, and atopic dermatitis. Four weeks later, the skin prick test to cow's milk was strongly positive (wheal 10 mm greater than control). Long-term risk reduction measures initiated included strict avoidance of cow's milk and related products, and optimized asthma and atopic dermatitis management. An Anaphylaxis Emergency Action Plan was developed. An epinephrine autoinjector 0.15 mg was prescribed despite recognition that this dose was not ideal for a 9-kg infant. Education sessions were held with his parents.

WHAT TRIGGERS ANAPHYLAXIS IN INFANTS?

Food is the most common trigger of anaphylaxis in this age group,⁶⁻¹⁰ through direct ingestion, breast milk, or accidental ingestion (eg, a crawling infant finds and tastes a food item); of note, skin contact with food or

food-based skin care products or inhalation of aerosolized food particles potentially sensitizes an infant but seldom causes anaphylaxis. Caregivers may be unaware of the infant's initial exposure to the food. Common culprits are cow's milk or egg, but any food can be a trigger, including those presumed innocuous (eg, cow's milk substitutes, hypoallergenic formulas⁶⁻⁸), those not traditionally given to infants (eg, sesame),⁹ or those not previously identified as being allergenic in individuals of any age (eg, caribou and whale meats).¹⁰ Less common triggers include medications (eg, β -lactam antibiotics, antipyretics such as ibuprofen, neuromuscular blockers), natural rubber latex (nipples, pacifiers, toys), insect stings, inhalant allergens, vaccinations for prevention of infectious diseases, and non-immune triggers such as cold exposure. Idiopathic anaphylaxis has been reported in infants.^{11,12}

WHICH INFANTS ARE AT INCREASED RISK FOR ANAPHYLAXIS?

Clinical risk factors and comorbid diseases that increase the risk of anaphylaxis and of fatality in anaphylaxis have not yet been optimally defined in infants. Atopy; common infant respiratory diseases such as bronchiolitis, asthma, and croup; and urticaria pigmentosa/mastocytosis are likely to be important. Comorbidities in caregivers – for example, depression, or use of sedatives, ethanol, or recreational drugs – might impede recognition of anaphylaxis in the infant for whom they are responsible.¹³

HOW CAN RECOGNITION OF ANAPHYLAXIS IN INFANTS BE IMPROVED?

Physicians need to have a high index of suspicion to diagnose anaphylaxis promptly in infants, because it may be difficult to recognize in this age group for a variety of reasons. Parents, caregivers, and even health care professionals may not be aware of the possibility that anaphylaxis can occur in infancy. Many anaphylaxis episodes in infancy are 'first' episodes. Subjective symptoms of anaphylaxis such as itching cannot be described by infants (Table I). Some signs of anaphylaxis (for example, regurgitation and loose stools after feeding) also occur in healthy infants. The differential diagnosis of anaphylaxis is age-dependent (Table II).

Laboratory tests to support the clinical diagnosis of anaphylaxis may or may not be helpful.¹³ Histamine levels need to be measured in a blood sample obtained within 1 hour of symptom onset. Total tryptase levels need to be measured in a sample obtained within 3 hours of symptom onset. Even if the sample is optimally timed, tryptase levels are seldom elevated in food-induced anaphylaxis. Moreover, if fatality occurs and an elevated postmortem tryptase level is found, interpretation can be difficult because elevated tryptase levels have also been reported in some infants with sudden infant death syndrome.¹⁴

WHAT ARE THE BARRIERS TO OPTIMAL MANAGEMENT OF ANAPHYLAXIS IN INFANTS?

Acute management in health care settings

The universal principles of prevention, prompt diagnosis, rapid assessment (airway, breathing, circulation,

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Table 1. Symptoms and signs of anaphylaxis in infants*

Anaphylaxis symptoms that infants cannot describe	Anaphylaxis signs that are potentially difficult to interpret in infants, and why	Anaphylaxis signs in infants: obvious but may be nonspecific
General: feeling of warmth, weakness, anxiety, apprehension, impending doom	General: nonspecific behavioral changes such as persistent crying, fussing, irritability, fright	
Skin/mucus membranes: itching of lips, tongue, palate, uvula, ears, throat, nose, eyes, and so forth; mouth-tingling or metallic taste	Skin/mucus membranes: flushing (may also occur with fever, hyperthermia, or crying spells)	Skin/mucus membranes: rapid onset of hives (potentially difficult to discern in infants with acute atopic dermatitis; scratching and excoriations, as such, will be absent in young infants); angioedema (face, tongue, oropharynx)
Respiratory: nasal congestion, throat tightness; chest tightness; shortness of breath	Respiratory: hoarseness, dysphonia (common after a crying spell); drooling, increased secretions (common in infants)	Respiratory: rapid onset of coughing, choking, stridor, wheezing, dyspnea, apnea, cyanosis
Gastrointestinal: dysphagia, nausea, abdominal pain/cramping	Gastrointestinal: spitting up/regurgitation (common after feeds), loose stools (normal in infants, especially if breast-fed); colicky abdominal pain	Gastrointestinal: sudden, profuse vomiting
Cardiovascular: feeling faint, presyncope, dizziness, confusion, blurred vision, difficulty in hearing, palpitations	Cardiovascular: hypotension; measured with an appropriate size blood pressure cuff, low systolic blood pressure for infants is defined as less than 70 mmHg from age 1 month to 1 year, and less than $(70 \text{ mmHg } 1 + [2 \times \text{age in y}])$ 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

*More than 1 body system involved.

responsiveness, skin, and weight), and prompt treatment apply.¹ The evidence base for the treatment of anaphylaxis in infants is largely empirical. Epinephrine is the initial medication of first choice; however, the recommended initial dose of 0.01 mg/kg intramuscularly is based entirely on tradition, because no prospective epinephrine clinical pharmacology study has been conducted in infants with, or at risk of, anaphylaxis.¹⁵ If intravenous epinephrine is needed, care should be taken to calculate the dose accurately, dilute the epinephrine solution accurately, and avoid an overly rapid infusion rate. If epinephrine overdose occurs, infants cannot report symptoms; signs include pallor, tremor, and pulmonary edema that, like anaphylaxis itself, may be manifest by cough and respiratory distress.¹⁵ In addition to epinephrine, supplemental oxygen should be given. The airway should be established and maintained. An intravenous line should be established. Continuous monitoring should be instituted. Additional medications should be administered as needed.¹

Long-term risk reduction

Assessment. Most episodes of anaphylaxis in infants are IgE-mediated. Sensitization to allergens – for example, to foods – can be determined by using skin prick tests or by quantitative measurement of allergen-specific IgE levels.⁶ Selection of allergens for testing should be based on the history. Positive skin tests have a different appearance in infants compared with older

individuals. Like elevated allergen-specific IgE levels, they denote sensitization, but are not themselves diagnostic of anaphylaxis or any other allergic disease. In infants with food allergy, physician-monitored oral incremental challenges may be helpful if the diagnosis is in doubt or if there is minimal or no evidence of sensitization to the suspect allergen. A challenge is strictly contraindicated in an infant such as the one reported here, who has a strong clinical history of anaphylaxis and is highly sensitized to the suspect allergen.⁶

Equipping the infant's caregivers for management of anaphylaxis in the community. Risk reduction involves vigilant allergen avoidance, which can be stressful for families.^{13,16} Relevant comorbidities in the infant and the caregiver should be managed optimally. Caregivers should be equipped with injectable epinephrine for first aid treatment in the context of an Anaphylaxis Emergency Action Plan, which can be downloaded from www.aaaai.org and readily adapted for use in infants.¹³

Epinephrine

Most infants weigh less than 15 kg. No epinephrine autoinjector currently available provides a dose of <0.15 mg,^{15,17} presenting a dilemma for physicians prescribing epinephrine autoinjectors for this vulnerable population (see Case Report). Although experienced pediatric nurses draw up and measure infant doses from an ampule of epinephrine rapidly and accu-

Table III. 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, malacias) or acquired (eg, aspiration of foreign body,* croup, bronchiolitis, asthma); asphyxiation/suffocation; breath-holding
Gastrointestinal tract [†] : obstruction, congenital (eg, pyloric stenosis, malrotation) or acquired (eg, intussusception)
Shock: septic, cardiovascular, hypovolemic
Central nervous system: seizure, post-ictal state, stroke, trauma, child abuse, increased intracranial pressure
Metabolic disorders
Infectious diseases: eg, pertussis, gastroenteritis, meningitis
Ingestion of poison or toxin (eg, food, drug, plant): drug overdose
Munchausen syndrome by proxy
Sudden infant death syndrome
Other

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

[†]Infants with gastrointestinal anaphylaxis present with abdominal pain/ cramps and vomiting with or without diarrhea minutes to a few hours after ingestion of the culprit food.

rately, caregivers without medical training find this extremely difficult to do.¹⁸

H₁-antihistamines

In anaphylaxis, H₁-antihistamines might relieve skin symptoms and signs but they do not relieve upper or lower airway obstruction or shock. They therefore are not drugs of choice, are not life-saving, and do not replace epinephrine.

The onset of action of orally administered H₁-antihistamines takes at least 1 to 2 hours. First-generation H₁-antihistamines in usual doses potentially cause sedation and unresponsiveness that can impede the recognition of anaphylaxis, and they can also lead to respiratory arrest in infants.^{19,21}

Medical identification

At-risk infants who are in the care of a babysitter or other third party should be protected by wearing accurate medical identification,¹³ such as a T-shirt or Velcro patch on clothes (Velcro USA Inc, Manchester, NH) with a specific allergy alert message, for example, "Do not give cow's milk to this baby." Medical identification bracelets made of cloth are available for older infants.

Anaphylaxis education. Caregivers of infants report high anxiety levels with regard to taking responsibility for the recognition and management of an anaphylaxis episode, particularly the possibility of having to inject epinephrine.^{13,16} Individualized instruction and coaching help to diminish this anxiety.

SUMMARY

Anaphylaxis is likely underrecognized in infancy. Many episodes are 'first' episodes. Infants cannot report symptoms. Diagnosis therefore depends on a high index of suspicion and on physical signs. The differential diagnosis of anaphylaxis in infancy includes age-unique entities such as congenital or metabolic disorders, child abuse,

Munchausen syndrome by proxy, and sudden infant death syndrome. Management is based on empirical evidence. A prospective systematic study of anaphylaxis in infancy is needed.

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Declaration of conflict of interest

The author declares no conflict of interest.

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