Expertly Managing Anaphylaxis

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KEYWORDS

• Anaphylaxis • Allergy • Type-1 hypersensitivity • Mast cell disorders • Epinephrine • Antihistamines • Corticosteroids

KEY POINTS

- Anaphylaxis symptoms are more extensive than just lip/laryngeal edema and hives.
- Intramuscular epinephrine is the mainstay of anaphylaxis treatment.
- There are many triggers for anaphylaxis, including food, medications, environmental exposures, and even no known cause (idiopathic).
- A patient treated for anaphylaxis should receive a home prescription for an epinephrine autoinjector; an allergy action plan can be of benefit.
- Future reaction severity cannot be predicted by previous reaction severity.

INTRODUCTION

Anaphylaxis, a severe allergic reaction, has a worldwide prevalence of 1% to 5%, but is more common in industrialized countries.[1–3] The signs and symptoms are usually systemic, involving multiple organ systems, and can be life-threatening. Timely recognition and treatment of anaphylaxis are critical to mitigate potential complications.

EPIDEMIOLOGY

While anaphylaxis can happen in any age group, it occurs more frequently in younger children (infants and toddlers) and less often in older children and adolescents.[4,5] However, the rates of emergency department (ED) visits and hospitalizations are rising in *all* groups of children, especially for food-induced anaphylaxis (FIA).[6] These trends are happening in the United States, and in other industrialized countries.[1,7,8] Some data show up to a 200% increase over a 10-y time period in infants and toddlers, and over a 400% increase in adolescents.[4] **Table 1** details some triggers of anaphylaxis.

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Abbreviations

AAEP	allergy and anaphylaxis emergency plan
ACEI	angiotensin-converting enzyme inhibitor
BB	beta-blocker
bST	baseline serum tryptase
EAI	epinephrine autoinjector
ED	emergency department
EKG	electrocardiogram
EMS	emergency medical service
FDA	Food and Drug Administration
FIA	food-induced anaphylaxis
IgE	immunoglobulin E
IM	intramuscular
IO	intraosseous
IV	intravenous
NIAID	National Institute of Allergy and Infectious Disease
RCT	randomized control trial
SABA	short-acting, inhaled, beta-2 agonist
WAO	World Allergy Organization

Table 1
Epidemiology of anaphylaxis[2–4,9,10]

Source	Allergens	Notes
Food *Most common cause, especially in smaller children	Peanuts Tree nuts Eggs Milk Fish/Shellfish	• Highest severity from milk products • Largest hospitalization risk from peanuts, tree nuts, seeds
Medications *Second most common cause	Penicillins NSAIDs Monoclonal Antibodies ACEI Vancomycin Others	• Penicillins most common medication trigger, often severe reactions • 4% cross-reactivity from penicillins to cephalosporins • NSAIDs second most common medication trigger • Omalizumab, for severe asthma, can cause delayed anaphylaxis • Vancomycin (Red Man Syndrome) historically classified as anaphylactoid, now "non-immunologic anaphylaxis"
Perioperative	Neuromuscular blockers Blood products Latex	• Difficult to diagnose. Patients cannot communicate symptoms • Cutaneous symptoms often absent
Other	Insects Exercise-induced Vaccine-related Seminal fluid	• Test for systemic mastocytosis with a history of severe reactions to insects • Risk for exercise-induced higher with cofactors (NSAID use, high pollen counts, and certain foods) • Cholinergic urticaria (reaction to high body temperatures), is not exercise-induced anaphylaxis • Seminal fluid anaphylaxis does not affect fertility. Barrier contraceptives recommended

NSAIDs, non-steroidal anti-inflammatory medications.
Data From Refs.[2–4,9,10]

Some patients previously diagnosed with idiopathic anaphylaxis are now being found to have systemic mastocytosis. Anyone who has had anaphylaxis without an identified trigger should be tested for mastocytosis or mast cell activation syndrome.[2,3]

PATHOPHYSIOLOGY

Anaphylaxis is an immunoglobulin E (IgE)-mediated type 1 hypersensitivity reaction.[1–3] Exposure to an antigen initiates cross-linking of allergen-specific IgE molecules on mast cells and possibly basophils. Chemical mediators then flood the system from basophil and mast cell degranulation. **Fig. 1** demonstrates the anaphylaxis cascade. The coagulation and complement cascades can be triggered as well.[2]

DIAGNOSTIC CRITERIA

Multiple criteria exist for the diagnosis of anaphylaxis. The 2 generally accepted criteria are published by the National Institute of Allergy and Infectious Disease (NIAID) and the World Allergy Organization (WAO), respectively.[3] These differ on minor points and are both accepted by clinicians in the United States. Both require an acute reaction (min to h) to a known or suspected allergen, followed by several key signs and symptoms. **Table 2** shows a comparison between the two.

Clinicians in the acute setting should not be expected to be able to recall the minutiae but should be able to recognize the constellation of symptoms diagnostic of acute anaphylaxis.

Previously, non-IgE-mediated reactions were classified as anaphylactoid reactions. The WAO, however, has recommended re-classifying reactions as *anaphylaxis* if the symptoms meet the definition, and then further classifying into immune versus non-immune reactions.[2]

CLINICAL PRESENTATION

Symptoms of anaphylaxis can include skin and mucosal changes, respiratory derangements, gastrointestinal manifestations, and cardiovascular system disruptions.[3] **Table 3** lists common, and some more obscure, symptoms indicative of anaphylaxis.

HISTORY

Patient interviews and documentation should include, but not be limited to, several key pieces of information.[2]

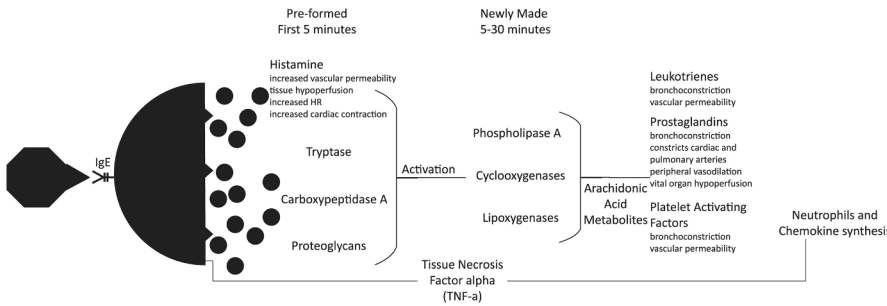

Fig. 1. Anaphylaxis cascade of chemical mediators.[1] (*Data from* McLendon K, Sternard Affiliations BT. Anaphylaxis Continuing Education Activity.; 2023. https://www.ncbi.nlm.nih.gov/books/NBK482124/?report=printable.)

Table 2
Diagnostic criteria National Institute of Allergy and Infectious Disease 2006 versus World Allergy Organization 2020[3]

NIAID 2006	WAO 2020
Anaphylaxis highly likely with any one of the 3:	Anaphylaxis highly likely with either of the 2:
Acute illness involving skin, mucosal tissue, or both, and at least 1 of the following: • Respiratory compromise • Reduced BP or evidence of end-organ dysfunction (syncope, etc.)	Acute illness involving skin, mucosal tissue, or both, and at least 1 of the following: • Respiratory compromise • Reduced BP or evidence of end-organ dysfunction (syncope, etc.) • Severe GI symptoms (especially after exposure to non-food allergens)
2 or more of the following after exposure to a likely allergen: • Skin or mucosal symptoms • Respiratory compromise • Low BP • "Persistent" GI symptoms	Acute hypotension, bronchospasm, or laryngeal involvement after exposure to a known or highly likely allergen for the patient, even without skin involvement • Excluding lower respiratory symptoms caused by inhalant allergens perceived to induce "inhalational" reaction in the absence of ingestion
Reduced BP after exposure to a known allergen for that patient, defined as: • Infants/Children: ○ Low SBP (age specific) or ○ > 30% decrease in SBP from patient's baseline • Adults ○ SBP <90 mm Hg or ○ >30% decrease in SBP from patient's baseline	

Abbreviations: NIAID, National Institute of Allergy and Infectious Disease; WAO, World Allergy Organization; BP, blood pressure; SBP, systolic blood pressure; GI, gastrointestinal.
(*From* Golden DBK, Golden DBK, Golden DBK, et al. Anaphylaxis: A 2023 practice parameter update. Ann Allergy, Asthma and Immunol 2024;132(2):124–176. doi:10.1016/j.anai.2023.09.015.)

- Time of occurrence
- Setting of reaction
- Patient location for the previous 6 to 12 h
- Exposures, ingestions, or items contacted in the previous 6 to 12 h
- Atopic status
- Relationship to onset of menses (if applicable)
- Pre-hospital treatment
- Any return of symptoms

Anaphylaxis *typically* occurs immediately, but symptoms can be delayed up to several hours, and a detailed history can be a key to finding the cause.

DIFFERENTIAL DIAGNOSIS

The symptoms seen in anaphylaxis are not specific to IgE-mediated type 1 hypersensitivity reactions but can manifest during many other syndromes that should be

Table 3
Signs and symptoms of anaphylaxis[2,3,8]

Skin/Mucosa	• Urticaria
	• Pruritis without a rash
	• Diffuse skin flushing
	• Periorbital edema
Pulmonary	• Dyspnea
	• Wheezing • Reduced peak expiratory flow • Hypoxemia
	• Cough
	• Upper airway angioedema
	• Rhinitis
Cardiovascular	• Hypotension
	• Distributive shock
	• Bezold-Jarish reflex
	• Chest pain
	• Arrhythmia
Airway	• Angioedema
	• Stridor
	• Hoarse voice
	• Lip swelling
	• Tongue edema • Uvular edema
	• Laryngeal edema
	• Persistent clearing of the throat
	• Feeling of fullness in the throat
Gastrointestinal	• Abdominal pain or cramping
	• Nausea
	• Repetitive vomiting
	• Diarrhea
Other	• Diaphoresis
	• Dizziness
	• Headache
	• Hypotonia
	• Incontinence
	• Seizures
	• Somnolence
	• Syncope

From Refs[2,3,8]

considered. Differentiation between anaphylaxis and other diagnoses can often be achieved with a thorough history.

Mastocytosis and Mast Cell Activation Syndromes

These may be the true cause of many cases of idiopathic anaphylaxis. Testing includes baseline serum tryptase (bST) levels and bone marrow biopsies. The Red Espanola MAstocytosis score and/or the National Institutes of Health Idiopathic Clonal Anaphylaxis Score assess the risk of an underlying mast cell disorder.[3]

Alpha Gal Hypersensitivity

Alpha-1,3-galactose, or "alpha-gal", is an oligosaccharide on the cells of non-primate mammals.[2,3] Reactions can cause an IgE antibody response up to several hours after a meal. Those with a tick bite history may be at higher risk. Avoidance of mammalian meats can prevent subsequent reactions.

Hereditary α-tryptasemia

Hereditary α-tryptasemia causes a reaction that looks like classic anaphylaxis. This should be considered if the bST level is elevated greater than 8 ng/mL.[2,3]

Table 4 lists other diagnoses to consider when a patient presents with anaphylactic symptoms.

LABORATORY TESTING

No single test can definitively confirm anaphylaxis. It is a clinical diagnosis. Serum tryptase, plasma histamine, and C1 esterase inhibitor levels can be helpful, but one should not wait for these to guide treatment decisions.[2] There are many tests that can differentiate anaphylaxis from other diagnoses, but they are beyond the scope of what is practical in the ED.[2]

Serum tryptase can differentiate anaphylaxis from an undiagnosed mast cell disorder.[3] It peaks between 60 to 90 min after exposure and can stay elevated for 5 h. However, it can be elevated in other conditions, including systemic mastocytosis, hereditary α-tryptasemia, complement activation-related pseudoallergy, myeloid neoplasms and other malignancies, hypereosinophilic syndrome, helminth infections, and end-stage renal disease.[2,3] Patients with a history of recurrent, severe, or idiopathic anaphylaxis reactions should have a bST level measured to consider alternative diagnoses.

Plasma histamine levels are more sensitive but not typically useful.[2] They peak quickly and only remain elevated for 30 to 60 min. Levels may return to normal by the time a patient presents for emergency care. Urine collection for 24 h is more likely to show an elevated level. Plasma histamine has higher associations with urticaria, skin erythema, abdominal symptoms, and wheezing.

TREATMENT IN THE HEALTH CARE SETTING

Epinephrine

Mechanism of action

Epinephrine is a sympathomimetic catecholamine that acts as an agonist at alpha- and beta-adrenergic receptors.[1–3,13] **Table 5** demonstrates epinephrine's role in treatment of anaphylaxis by its action on adrenergic receptors.

Evidence for use

A 2009 Cochrane review could not definitively provide recommendations for epinephrine use in acute anaphylaxis due to a lack of sufficient randomized control trial (RCT)

Table 4
Differential diagnoses to consider for anaphylaxis reactions[2,3,9]

Mast cell disorders	• Mastocytosis
	• Mast cell activation syndrome
	• Hereditary α-tryptasemia
Vasodepressor reactions	• Vasovagal event
Flushing reactions	• Rosacea
	• Autonomic epilepsy (SeLEAS or Panayiotopoulos syndrome)[11,12]
	• Pheochromocytoma
	• Tumors
	• Vancomycin reaction (Red Man Syndrome)
	• Niacin reaction
	• Catecholamine surge
	• Nicotine reaction
	• Ethanol reaction
Ingestion syndromes (aka Restaurant syndromes)	• Scombroid[2]
	• Monosodium glutamate (MSG)
Non-organic syndromes	• Vocal cord dysfunction
	• Factitious anaphylaxis
	• Panic attacks
Not otherwise classified	• Alpha-1,3-galactose (Alpha-gal) hypersensitivity • Dysautonomia
	• Capillary leak syndrome
	• C1 esterase deficiency/Hereditary angioedema with rash

From Refs[2,3,9]

data.[14] This is likely due to the ethical implications of withholding epinephrine, a life-saving medication, in anaphylaxis. Despite the lack of RCT data regarding its efficacy, virtually all professional organizations and expert consensus guidelines recommend the use of epinephrine as a first-line treatment for anaphylaxis.[3,15]

Table 5
Epinephrine effects on anaphylaxis[1,13]

α1	β1	β2
Vasoconstriction	Increases cardiac output	Bronchodilation
Decreases vascular permeability	Increases inotropy	Decreases histamine release from mast cells and basophils
	Increases chronotropy	Decreases tryptase release from mast cells and basophils

Simons FER. Anaphylaxis. Journal of Allergy and Clinical Immunology. 2010;125(2 SUPPL. 2). doi:10.1016/j.jaci.2009.12.981

Adverse effects

Severe adverse events related to epinephrine administration are more common in intravenous (IV) administration versus intramuscular (IM). The rate of serious cardiovascular events, such as arrhythmia, cardiac ischemia, stroke, angina, or hypertension is low, especially in children.[16] The most common adverse effects are pallor, tremors, anxiety, hypertension, and tachycardia (**Table 6**).[17,18,19]

Adjunctive Medications

Intravenous fluids

Anaphylaxis causes fluid redistribution to the skin, pulmonary, and gastrointestinal tissues, leading to distributive shock. In hypotensive patients, fluid administration increases cardiac stroke volume within 10 min of administration.[23] Crystalloid administration is associated with faster resolution of abdominal cramping and pain. The recommended dose of crystalloid is 20 mL/kg in children and 500 to 1000 mL in adults. Colloid administration is no more effective than crystalloid and is not currently recommended.[23]

Oxygen

Oxygen administration may be warranted in anaphylaxis, as pulmonary mucosal edema and bronchospasm may cause hypoxemia. Use of non-invasive positive pressure ventilation has not been well-studied in anaphylaxis.

Antihistamines

H1 antagonists. Antihistamines are a mainstay of treatment in anaphylaxis. However, a 2007 Cochrane review found no RCTs comparing H1 antihistamines to placebo for treatment of anaphylaxis and concluded that there was no substantial evidence to support their use.[24]

H1 antagonists do not[24]:

- Relieve airway obstruction
- Alleviate hypotension or shock
- Affect the release of allergic components from basophils and mast cells

Of note, they can be associated with cardiovascular side effects or worsening hypotension.

Administration of H1 antagonists should not delay treatment with epinephrine. They can/should be used to decrease discomfort associated with itching and hives.[25,26]

H2 antagonists. As with H1 antagonists, systematic reviews show no demonstrable benefit in anaphylaxis with H2 blockers.[27,28] Despite this, H2 antagonists have shown some benefit in treating urticaria, with minimal side effects (**Table 7**).

Bronchodilators

Short-acting, inhaled, beta-2 agonists (SABAs), such as albuterol, are frequently used to treat respiratory distress in anaphylaxis. There is a paucity of literature specific to SABAs in anaphylaxis, but expert consensus recommends them for treatment of bronchospasm.[17,31]

Dosing is the same as in asthma—2.5 to 5 mg inhaled, repeated every 20 min via metered-dose inhaler or nebulization. Continuous nebulization can be considered if there is positive clinical response and ongoing bronchospasm.

Glucocorticoids

Glucocorticoids are used quite frequently in acute anaphylaxis, despite epinephrine being the recommended first-line medication.[32] Many clinicians believe they prevent

Table 6
Epinephrine route of administration[8,17,20–22]

Route	Concentration	Dose	Notes
Intramuscular (IM) (*standard-of-care)	1:1000 (1 mg/mL)	0.01 mg/kg *max dose 0.3 mg prepubertal child *max dose 0.5 mg adolescent	• Higher/faster peak plasma concentration vs SQ
Intravenous (IV) (*use with extreme caution, only in special circumstances)	1:10,000 (0.1 mg/mL) (*DO NOT use 1:1000 or 1 mg/mL concentration through IV) (*may need pharmacist to make 1:100,000 or 1:250,000 concentration)	1 mcg/kg slow push over 2 – 5 min (*For continuous infusion, 0.1 – 1 mcg/kg/min) Adolescents 50 – 100 mcg	• NOT first line • Delay in treatment due to needing IV access • Higher risk severe adverse events • Useful for shock or severe refractory anaphylaxis • Recommended only for those who utilize and titrate vasopressors routinely
Intranasal (IN)	1 mg/0.1 mL/spray 2 mg/0.1 mL/spray	1 or 2 mg once into one nostril, may repeat after 5 min	• FDA has approved Neffy ® (ARS Pharmaceuticals, Inc.) 1 mg for children 15-20 kg and 2 mg for those >30 kg • Favorable results vs 0.3 mg IM epi • Faster time of onset/time to peak concentration

Abbreviations: SQ, subcutaneous; mg, milligrams; mL, milliliters; kg, kilogram; min, minute; FDA, Food and Drug Administration; epi, epinephrine.
From Refs[8,17,20–22]

Table 7
Antihistamines in anaphylaxis[26,29,30]

Antihistamine type	Examples	Dose	Benefits
First generation H1 antagonists	Diphenhydramine Hydroxyzine Chlorpheniramine	Diphenhydramine 1 mg/kg (max 50 mg) q6-8 h (*max daily dose 5 mg/kg or 200 mg/)	• Alleviates pruritis/urticaria • Decreases progression to anaphylaxis in local reactions
Second generation H1 antagonists	Cetirizine Loratidine	>6 mo to 2 y: 2.5 mg daily 2 – 5 y old: 2.5 – 5 mg daily >5 y old: 5 – 10 mg daily	• Alleviates pruritis/urticaria • Less sedating
H2 antagonists	Famotidine Ranitidine Cimetidine	Famotidine 0.25 mg/kg (max 20 mg) once or twice daily	• Alleviates urticaria • Use with H1 antagonist

q, every; mg, milligrams; kg, kilogram; max, maximum.
From Refs[26,29,30]

biphasic reactions; however, a large Cochrane review and multiple propensity analyses have shown no significant benefit of glucocorticoids in preventing biphasic reactions or ED revisits in patients receiving epinephrine in the ED for anaphylaxis.[32,33] Glucocorticoids did have an inverse relationship to hospital length-of-stay in hospitalized children given epinephrine.[34]

Corticosteroid treatment. The most current guidelines do not strongly recommend the routine use of corticosteroids.[3] Corticosteroids may have more benefit in children with a history of asthma. They should only be administered based on clinician judgment.

Dosing. Dosing of steroids is the same as in asthma:

- Dexamethasone 0.6 mg/kg (max 16 mg), oral, IM, or IV
- Prednisolone 1 mg/kg (max 60 mg), oral
- Methylprednisolone 1 mg/kg (max 125 mg), IV

Medications for Refractory Anaphylaxis

Vasopressors

Epinephrine. The currently recommended vasopressor for shock in the setting of anaphylaxis is epinephrine. IV administration should only be considered for hypotension that is unresponsive to fluids and IM epinephrine.

Vasopressin. Vasopressin has been described in anaphylaxis for refractory shock. Retrospective reviews report a dose of 0.17 to 8.0 milliUnits/kg/min. Vasopressin increases arterial blood pressure and urine output.[35] The only double-blinded, placebo-controlled study of children with vasodilatory shock found no significant difference in the time to hemodynamic stability and demonstrated an association with increased mortality in the vasopressin group.[36]

Glucagon. Glucagon has been described in treating refractory bronchospasm and hypotension in patients on beta-blockers (BBs) with anaphylaxis. No data support its routine use. If clinically indicated based on clinician judgment, however, dosing is[2]:

- 20 to 30 μg/kg (max. 1 mg) in small children
- 1 to 5 mg in adolescents
- Administer IV over 5 min, followed by an infusion of 5 to 15 μg/min

  Glucagon can induce vomiting, so care should be taken to protect the airway.

Other. In refractory anaphylaxis, if there is evidence that the coagulation or complement cascades have been triggered, consider administering *tranexamic acid* for intravascular coagulation or *methylene blue* for refractory hypotension.[2]

Unfortunately, clinicians still find it challenging to identify and properly treat anaphylaxis. Anaphylaxis is often underrecognized and is miscoded as simple "allergic reactions".[8,37] One study showed only 1/5 of the study population received epinephrine to treat anaphylaxis. Patients were more likely to receive steroids and antihistamines and up to ¼ of patients did not even receive those. Very few patients, even after hospitalization for anaphylaxis, were prescribed epinephrine autoinjectors (EAIs).[37] It is important to consider the diagnosis of anaphylaxis so the patient can receive proper treatment.

DISPOSITION

Various organizations differ on indications for discharge, admission, and critical care unit needs. **Table 8** describes some evidence-based recommendations for disposition from the acute care setting.

Table 8
Factors to guide disposition[3,8,38,39]

Disposition	Factors/Symptoms/Presentations to Guide Disposition
Admission to general floor or progressive unit	• Lack of access to emergency medical services or emergency medical care • Risk for biphasic, protracted, or fatal anaphylaxis • History of biphasic reactions • Unknown trigger or drug trigger • History of severe asthma • Severe anaphylactic reaction or history of such • Possible continued exposure to allergen • Lack of access to epinephrine autoinjector • Hypotension at any time • Persistent bronchospasm or systemic involvement without improvement • 3 or more doses of IM epinephrine
Admission to ICU	• Airway edema (angioedema, stridor) • Continued need for continuous albuterol • Continued need for vasopressors
Discharge after ED observation	• All symptoms completely resolved and asymptomatic after at least 1-h observation • History of biphasic reaction or risk factors for fatality = observe 6 h or longer

Abbreviations: ICU, intensive care unit; ED, emergency department; IM, intramuscular.
From Refs.[3,8,38,39]

Emergency Department Discharge Plan

Allergen avoidance and reaction prevention

Allergen avoidance should be counseled after anaphylaxis. In one case series, 90% of fatalities were caused by peanut or tree nut exposure.[40] If the child has a peanut or tree nut allergy, strict avoidance of oral ingestion is recommended. Skin contact or inhalation is unlikely to cause a reaction.[41]

Epinephrine autoinjectors

Over 50% of parents hesitate to use an EAI due to fear of injury or a bad medication outcome.[42] One survey showed only 55% of families had an unexpired EAI.[43] This infrequent use, paired with the increasing incidence of EAI injuries, demonstrates clear need for thorough EAI training and written instructions.[44–46] Children and parents should be taught how to administer EAIs prior to discharge. If feasible, an EAI trainer should be available for in-person training.

Approximately 1 in 10 anaphylactic reactions require multiple doses of epinephrine.[47] Consider prescribing 2 EAIs for children at risk for severe, persistent, or refractory reactions. There are 3 Food and Drug Administration (FDA)-approved EAI doses:

- 0.1 mg, 7.5 *to* 15 kg
- 0.15 mg, 15 to 30 kg
- 0.3 mg, $\geq$30 kg

Based on clinical experience, infants tolerate doses of epinephrine higher than 0.01 mg/kg. The Joint Task Force on Practice Parameters 2020 anaphylaxis update supports the 0.15 mg EAI for children less than 15 kg.[48]

Anaphylaxis action plan

To best support children and families after discharge, an allergy and anaphylaxis emergency plan (AAEP) can be beneficial. The AAEP guides caregivers to treat allergic reactions outside of the hospital. The American Academy of Pediatrics' AAEP is at the following link: www.aap.org/aaep.

The AAEP should include[49]:

- Weight for proper medication dosing
- Known allergic triggers
- ± history of asthma
- Prior anaphylaxis
- If child may self-administer EAI (anywhere from 6 – 14 y old)
- Pathways for treatment of mild allergic reactions and anaphylaxis
  - Medications to be given
  - Doses of each medication
- Clearly list symptoms of anaphylaxis and severe reactions
- Clearly indicate when and how to give EAI

If the child has a history of severe anaphylaxis, consider telling the caregiver to "pretreat" after an exposure, even in the absence of immediate symptoms, to prevent a severe reaction.[49] A clear plan with medication dosages empowers the child and caregiver to deliver timely interventions.

Discharge Instructions

Parents and adolescents should be counseled on the signs and symptoms of anaphylaxis, when and how to give epinephrine, when to observe, and when to give a second dose of epinephrine and/or activate emergency medical services (EMSs).

If symptoms resolve without recurrence within minutes of EAI administration, if remaining symptoms are minimal, and if the symptoms do not persist beyond 10 to 20 min after epinephrine administration, the child may be observed at home.[3] This is conditional upon the development of no new symptoms or worsening of residual symptoms.

EMS activation and a second dose of epinephrine should be *strongly considered* if patients have residual globus sensation, nausea, cough, or stomach pain after the first epinephrine administration.[3] EMS should be *activated immediately*, and a second dose of epinephrine should be strongly considered if the child has respiratory distress, stridor, altered mental status, syncope, cyanosis, or incontinence. This also includes if the child has worsening non-skin symptoms, such as vomiting, hoarseness, cough, dysphagia, wheezing, or lightheadedness.[3]

Follow-up

All children should be referred to their primary care clinician upon discharge, especially after the first episode. The primary care clinician can take further history to elucidate potential allergens and provide prescriptions for EAIs. Allergist referral should be considered. An allergist can coordinate allergy testing and have conversations with the family about therapeutic options and avoidance measures.[9] No child is too young for referral to allergy testing when anaphylaxis is suspected.[10]

SPECIAL POPULATIONS

Infants and Toddlers

From 2006 to 2015, the incidence of anaphylaxis in infants and toddlers increased from 20/100,000 to 50/100,000.[50] Anaphylaxis in this population is a challenge to diagnose, as young children have difficulty communicating their symptoms, and subtle signs and symptoms may go unnoticed. Hence, the clinician must have a high index of suspicion. There is a paucity of evidence in this special age group, so the current NIAID or WAO anaphylaxis criteria should be used for diagnosis.[3,10]

Signs and symptoms

The most common presenting symptoms in infantile anaphylaxis are[5,10,51]:

- Skin symptoms (88%)—urticaria, erythema, and skin mottling
- Nausea (53%)
- Persistent vomiting
- Cough, wheeze, and stridor
- Drowsiness, lethargy, and persistent crying
- Cessation of play, clinginess
- Tachycardia, cardiovascular collapse
- Less commonly
  - Trouble swallowing
  - Respiratory distress
  - Drooling or angioedema

The emergency clinician must also consider alternative diagnoses when evaluating an infant or toddler with suspected anaphylaxis. **Table 9** summarizes some alternative diagnoses.

Medications

Except in extreme circumstances, an EAI should be administered in the anterolateral thigh (vastus lateralis) in children.[52] Using the deltoid region is associated with increased risk of intraosseous (IO) injection, especially in infants.[53] Due to its shorter needle length, the 0.1 mg EAI, trade name Auvi-Q (kaleo, Inc. CM-US-AQ-3662), has a lower risk of IO injection, but may have higher rates of subcutaneous administration.[52]

There is no recommendation for the use of glucocorticoids or antihistamines in anaphylaxis in infants and toddlers.[10] Cetirizine has not been well-studied in children younger than 6 mo. Diphenhydramine is not recommended for children less than 12 mo old due to risk of sedation. Clinicians should treat with these adjunctive medications at their discretion.

Patients on Beta-blockers and/or Angiotensin-converting Enzyme Inhibitors

Children may be on BBs or angiotensin-converting enzyme inhibitors (ACEIs). A systematic review and meta-analysis showed that both BBs and ACEIs were associated with significantly increased *severity* of anaphylaxis (odds ratio = 2.19 and 1.56, respectively), but the *incidence* of anaphylaxis was not significantly increased (odds ratio = 1.40 and 1.38, respectively).[54] The most current practice parameter for anaphylaxis recommends shared decision-making for those with severe anaphylaxis regarding continuing BB or ACEIs but favor continuing if systemic disease is severe.[3] A clinician should consult with the child's other specialists when discussing long-term medication management of anaphylaxis in this population.

Table 9
Anaphylaxis differential diagnoses and mimics for infants and toddlers[10]

Symptoms	Alternative Diagnoses to Consider
Erythema, urticaria and angioedema	• Mastocytosis • Hereditary angioedema
Wheezing or stridor	• Laryngomalacia • Laryngeal web • Vascular ring • Aspirated foreign body • Croup
Nausea, vomiting and/or pain	• Obstruction • Pyloric stenosis • Malrotation with/without volvulus • Food protein enterocolitis • Intussusception
Urticarial rash	• Viral upper respiratory infections ±vomiting/diarrhea in acute gastroenteritis
Perioral erythema, intraoral hives	• Food contact dermatitis
Coughing while eating	• Aspiration • Uncoordinated swallow

Greenhawt M, Gupta RS, Meadows JA, et al. Guiding Principles for the Recognition, Diagnosis, and Management of Infants with Anaphylaxis: An Expert Panel Consensus. Journal of Allergy and Clinical Immunology: In Practice. 2019;7(4):1148-1156.e5. doi:10.1016/j.jaip.2018.10.052

COMPLICATIONS

Misdiagnosis and Delayed Treatment

The timely diagnosis of anaphylaxis is crucial, as delays and misdiagnosis contribute to significant morbidity and mortality. Early treatment of FIA in children was associated with a lower risk of hospitalization.[55] Delaying administration of epinephrine has been linked to higher rates of biphasic reactions.[48] No high-level evidence supports an association between delayed or untreated anaphylaxis and death, but multiple case series demonstrated that most patients who died from anaphylaxis did not receive timely epinephrine.[3]

Persistent, Biphasic, and Refractory Anaphylaxis

Biphasic anaphylaxis is a recurrence of symptoms after a period of complete symptom resolution of ≥1 h, without re-exposure or continued exposure to an allergen. The pediatric prevalence ranges between 5% and 6%, but can be up to 20%.[2,3] It is only clinically significant in 4% to 5% of patients. Peak onset is usually around 8 to 11 h after the initial reaction. Recurrent reaction is unlikely when anaphylaxis is not severe. Several factors are associated with higher risk of biphasic anaphylaxis[3,48,56]:

- Greater severity of anaphylaxis
- Delay of epinephrine administration
- ≥1 dose of epinephrine
- Oral ingestion of antigens

Persistent anaphylaxis is continued anaphylaxis despite appropriate pharmacologic management for greater than or equal to 4 h. In a single-center study, protracted anaphylaxis was seen in 1% of cases, with fatalities occurring in 2%.[57]

Refractory anaphylaxis is a reaction that is unresponsive to maximal therapy with epinephrine. It is associated with increased risk of fatality (26.2% vs 0.35%).[58]

Understanding the predictive factors for these 3 types of reactions, as well as the associated morbidity, is important in the care of patients with anaphylaxis.

Kounis Syndrome

Kounis Syndrome, or "allergic angina", is a rare coronary hypersensitivity resulting from anaphylaxis and/or its treatment with epinephrine.[59,60] This can cause vasospasm, myocardial infarction, or stent thrombus formation.[60] Consider Kounis Syndrome in patients with anaphylaxis and persistent chest pain. Electrocardiogram (EKG) changes support the diagnosis. Corticosteroids and antihistamines plus epinephrine (with caution) can treat this. Calcium channel blockers or nitrates may treat vasospasm (with caution) in patients without hypotension. Pain can be treated with fentanyl, which causes less mast cell and histamine activation than morphine.

DISCUSSION

With such a variety of presentations and symptoms and wide range of severity, anaphylaxis and its treatments are difficult to study. Evidence does not strongly support the historic standard-of-care medications, though it is difficult to imagine that epinephrine or antihistamines would be withheld in a child with anaphylaxis due to lack of RCT support. Ultimately the clinician must tailor treatments to what is deemed most beneficial for the patient's symptoms, erring on the side of treating early and with epinephrine at minimum. The clinician must also anticipate potential side effects or adverse reactions to medications and be attentive to complications of anaphylaxis. Standardized protocols for identification, treatment, and disposition of children with anaphylaxis can be beneficial for clinicians and can improve patient-care.

SUMMARY

Anaphylaxis is a (frequently underdiagnosed) type 1 hypersensitivity reaction, and the astute clinician must remain vigilant to recognize it, especially in children. Many triggers may precipitate anaphylaxis. The multi-system manifestations may be confused with other diagnoses. Timely treatment with appropriately dosed epinephrine is essential to prevent complications or recurrent symptoms. Clinicians may consider using antihistamines, steroids, beta-agonists, fluids, or even vasopressors if deemed appropriate. Once symptoms are mitigated, patients require EAI prescriptions and education, and a clear anaphylaxis emergency plan. Close follow-up with primary care and/or an allergy specialist is prudent.

CLINICS CARE POINTS

- Take a thorough history to elucidate the offending anaphylaxis trigger. The exposure may have been several hours prior to presentation.
- IM epinephrine is strongly recommended when a patient has anaphylaxis involving 2 or more body systems. Multiple doses may be necessary.
- It is reasonable to treat with antihistamines to make your patient comfortable, but these alone are inadequate in anaphylaxis.
- Monitor for an appropriate time for biphasic or recurrent reactions. Consider admission for those at risk of severe or persistent symptoms.

DISCLOSURES

The authors have nothing to disclose. Dr Magill and Dr Gibson do not report any financial conflicts of interest.

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