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Epinephrine for First-aid Management of Anaphylaxis

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Anaphylaxis is a severe, generalized allergic or hypersensitivity reaction that is rapid in onset and may cause death. Epinephrine (adrenaline) can be life-saving when administered as rapidly as possible once anaphylaxis is recognized. This clinical report from the American Academy of Pediatrics is an update of the 2007 clinical report on this topic. It provides information to help clinicians identify patients at risk of anaphylaxis and new information about epinephrine and epinephrine autoinjectors (EAs). The report also highlights the importance of patient and family education about the recognition and management of anaphylaxis in the community. Key points emphasized include the following: (1) validated clinical criteria are available to facilitate prompt diagnosis of anaphylaxis; (2) prompt intramuscular epinephrine injection in the mid-outer thigh reduces hospitalizations, morbidity, and mortality; (3) prescribing EAs facilitates timely epinephrine injection in community settings for patients with a history of anaphylaxis and, if specific circumstances warrant, for some high-risk patients who have not previously experienced anaphylaxis; (4) prescribing epinephrine for infants and young children weighing <15 kg, especially those who weigh 7.5 kg and under, currently presents a dilemma, because the lowest dose available in EAs, 0.15 mg, is a high dose for many infants and some young children; (5) effective management of anaphylaxis in the community requires a comprehensive approach involving children, families, preschools, schools, camps, and sports organizations; and (6) prevention of anaphylaxis recurrences involves confirmation of the trigger, discussion of specific allergen avoidance, allergen immunotherapy (eg, with stinging insect venom, if relevant), and a written, personalized anaphylaxis emergency action plan; and (7) the management of anaphylaxis also involves education of children and supervising adults about anaphylaxis recognition and first-aid treatment.

INTRODUCTION

Anaphylaxis is defined as a serious, generalized allergic or hypersensitivity reaction that is rapid in onset and potentially fatal.

abstract

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Clinical presentation and severity can vary among patients and in the same patient from 1 anaphylactic episode to another.[1–3] Epinephrine is the primary initial treatment of anaphylaxis.[1–3] This clinical report from the American Academy of Pediatrics (AAP) updates and amplifies the previous report on this topic.[4]

CLINICAL FEATURES OF ANAPHYLAXIS

Clinical criteria for anaphylaxis have been proposed and validated.[3,5] Anaphylaxis is highly likely when any 1 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 urticaria, itching or flushing, swollen lips/tongue/uvula), and at least 1 of the following: (1) respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, hypoxemia) or (2) reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence); OR
2. Two or more of the following that occur suddenly after exposure to a likely allergen for that patient (minutes to several hours): (1) involvement of the skin/mucosal tissue (eg, generalized urticaria, itch/flush, swollen lips/tongue/uvula), (2) respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, hypoxemia), (3) reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence), or (4) persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting); OR
3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours): (1) for infants and children, low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure, and (2) for teenagers and adults, systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline.[3]

These clinical criteria for the diagnosis of anaphylaxis have been validated in emergency department studies in children, teenagers, and adults. They have high sensitivity (96.7%), reasonable specificity (82.4%), and a high negative predictive value (98%).[3,5] Disorders such as acute asthma, acute generalized urticaria, aspiration of a foreign body such as a peanut, vasovagal episode, and anxiety or panic attacks can present with some similar symptoms.[1] There are age-related differences in the clinical presentation and differential diagnosis of anaphylaxis.[6,7] The clinical criteria have not yet been validated in infants.

Foods, especially peanut, tree nuts, milk, eggs, crustacean shellfish, and finned fish, are by far the most common triggers of anaphylaxis in the pediatric population.[8,9] Insect stings, drugs such as antibiotics, and various other allergens can also trigger anaphylaxis[1,2,10,11]; however, vaccinations to prevent infectious diseases seldom trigger it.[12]

Cofactors that lower the threshold at which triggers can cause anaphylaxis include exercise, upper respiratory tract infections, fever, ingestion of nonsteroidal antiinflammatory drugs or ethanol, emotional stress, and perimenstrual status.[13–15] Fatal anaphylaxis is often associated with adolescence, concomitant asthma (especially if severe or poorly controlled), and failure to inject epinephrine promptly.[16–18]

PRIMARY ROLE OF EPINEPHRINE

Epinephrine is the medication of choice for the first-aid treatment of anaphylaxis. Through vasoconstrictor effects, it prevents or decreases upper airway mucosal edema (laryngeal edema), hypotension, and shock. In addition, it has important bronchodilator effects and cardiac inotropic and chronotropic effects.[1–4,19–24]

Delayed epinephrine administration in anaphylaxis is associated with an increased risk of hospitalization[22] and poor outcomes, including hypoxic-ischemic encephalopathy and death.[16–18] Conversely, prompt prehospital epinephrine injection is associated with a lower risk of hospitalization[22] and fatality.[1,2,16–18] H_1-antihistamines prevent and relieve itching and hives but do not relieve life-threatening respiratory symptoms, hypotension, or shock[1,2,4,8,25,26]; therefore, like H_2-antihistamines and glucocorticoids, they are adjunctive treatments and are not appropriate for use as the initial treatment or the only treatment.[1,2,8,25,27,28] For children with concomitant asthma, inhaled β2-adrenergic agonists (eg, albuterol) can provide additional relief of lower respiratory tract symptoms but, like antihistamines and glucocorticoids, are not appropriate for use as the initial or only treatment in anaphylaxis.[1,2,8]

EPINEPHRINE ADMINISTRATION AND DOSING

Epinephrine can be life-saving when injected promptly by the intramuscular (IM) route in the mid-outer thigh (vastus lateralis muscle) as soon as anaphylaxis is recognized (Table 1).[1,2,4,6,8–10,23,24] For first-aid management of anaphylaxis in health care settings, traditionally an epinephrine dose of 0.01 mg/kg is injected IM, to a maximum of 0.3 mg in a prepubertal child and up to 0.5 mg in a teenager. Epinephrine

TABLE 1 Anaphylaxis: Recognition and First-aid Treatment

How to recognize anaphylaxis[a]
Anaphylaxis has a sudden onset (minutes to a few hours) after exposure to a food, drug, insect sting, or other trigger. It potentially involves some of the following symptoms and signs:
• skin: itching, redness, hives, or swelling; oral and nasal mucosa: itching, swelling; conjunctivae: itching, swelling, redness;
• respiratory tract: hoarseness, throat itching, throat tightness, stridor, cough, difficulty breathing, chest tightness, wheeze, cyanosis;
• cardiovascular symptoms: tachycardia, chest pain, hypotension, weak pulse, dizziness, collapse, incontinence, shock;
• gastrointestinal tract symptoms: nausea, crampy abdominal pain, persistent vomiting, diarrhea; and
• central nervous system: behavioral changes (infants), sense of doom, headache, altered mental status, confusion, tunnel vision.
How to treat anaphylaxis
Be prepared! Have a written anaphylaxis emergency action plan.
When anaphylaxis occurs, promptly assess the patient's airway, breathing, circulation, and skin and call for help: 911 or EMS in community settings, a resuscitation team in health care settings.
Inject epinephrine (adrenaline) IM in the mid-outer aspect of the thigh by using an EA. If needed, give a second injection 5 to 15 minutes after the first.
Place the patient on his or her back or in a position of comfort if there is respiratory distress and/or vomiting. Elevate the lower extremities. Do not allow standing, walking, or running.
Transport the patient to an emergency department, preferably by an EMS vehicle, for further assessment and monitoring. Additional treatment, including supplemental oxygen, intravenous fluids, and other interventions may be needed.

Adapted from refs [1–3,6].

[a] Note that only a few anaphylaxis symptoms may be present during an episode. Also, symptoms can differ among patients, and even in the same patient from 1 episode to the next. Typically, more than 1 body organ system is involved.

autoinjectors (EAs) can be used in health care settings to deliver a 0.15-mg dose in a young child and a 0.3-mg dose in a child or teenager.

If the response to the first epinephrine injection is inadequate, it can be repeated once or twice at 5- to 15-minute intervals.[1,2,8] From 6% to 19% of pediatric patients treated with a first epinephrine injection in anaphylaxis require a second dose.[29–31] A third dose is needed infrequently. Subsequent doses are typically given by a health care professional along with other interventions.[1,2,4,8] In a retrospective chart review study in emergency department patients with anaphylaxis, most of whom were children, 17% of those who received 1 epinephrine injection required 1 or more additional doses. The need for subsequent injections did not correlate with obesity or overweight status.[31]

Subsequent epinephrine doses are needed for severe or rapidly progressive anaphylaxis and for failure to respond to the initial injection because of delayed injection of the initial dose, inadequate initial dose, or administration through a suboptimal route.[23] Subsequent doses also might be needed in biphasic anaphylaxis, defined as recurrence of symptoms hours after resolution of initial symptoms despite no further exposure to the trigger, which is reported in up to 11% of pediatric patients. Food-induced anaphylaxis is associated with biphasic anaphylaxis less often than is venom- or drug-induced anaphylaxis.[32,33]

Reluctance to inject epinephrine promptly at the onset of anaphylaxis symptoms is best overcome by awareness that the severity of an anaphylactic episode can differ from 1 patient to another and in the same patient from 1 episode to another.[21] At the onset, it is impossible to predict whether the patient will respond promptly to treatment, die within minutes, or recover spontaneously because of secretion of endogenous epinephrine.

SAFETY OF EPINEPHRINE

Pharmacologic effects of epinephrine include transient pallor, tremor, anxiety, and palpitations, which, although perceived as adverse effects, are similar to the symptoms caused by increased endogenous epinephrine levels produced in the "fight or flight" response. These effects cannot be dissociated from the beneficial effects of epinephrine.[23]

Epinephrine given by IM injection achieves peak concentrations faster than that given by subcutaneous injection.[20] Epinephrine, 0.3 mg IM, is 10 times safer than epinephrine given as an intravenous bolus.[34] Serious adverse effects of IM epinephrine are rare in children. There is no absolute contraindication to epinephrine treatment in anaphylaxis.[1,2,8,23]

DILEMMAS IN EPINEPHRINE DOSING

Only 2 premeasured, fixed doses of epinephrine, 0.15 mg and 0.3 mg, are currently available in EA formulations in the United States and Canada.[35] EA manufacturers advise prescribing the 0.15-mg dose for patients weighing 15 to 30 kg and the 0.3-mg dose for those weighing 30 kg and over. These doses are optimal for many children but not necessarily for all children.

The 0.15-mg dose is high for infants (a twofold dose for those weighing ≤7.5 kg) and for some young children.[6,21] Some EA manufacturers have suggested that an alternative approach for infants is to have caregivers draw up the dose from

a 1-mL ampule by using a 1-mL syringe. However, dose preparation can take laypersons as long as 3 to 4 minutes; moreover, doses typically are inaccurate and can sometimes contain no epinephrine at all when the solution is ejected from the syringe along with the air.[36] Although unsealed 1-mL syringes prefilled by a health care professional with infant epinephrine doses also have been recommended, the doses can be lost, and the epinephrine solution typically degrades within a few months as a result of air exposure.[37]

After consideration of the aforementioned alternatives that potentially lead to delay in dosing, incorrect dosing, or no dose at all and consideration of the favorable benefit-to-risk ratio of epinephrine in young patients with anaphylaxis, many physicians recommend the use of the 0.15-mg EA in infants.[6] Most pediatricians (80%) report that they would prescribe the 0.15-mg EA for an infant or a child weighing 10 kg (22 lb).[38] International guidelines suggest that, when using EAs, patients weighing 7.5 to 25 kg should receive the 0.15-mg dose.[39] Physicians can discuss the benefits and risks of these options with families and prescribe on a case-by-case basis.[21]

On the basis of a pharmacokinetic study[40] and expert consensus, it is appropriate to switch most children from the 0.15-mg dose to the 0.3-mg dose when they reach a body weight of 25 to 30 kg (55–66 lb).[4,8,35]

PRESCRIBING EAS

Most anaphylaxis deaths occur in community settings rather than in health care settings[1,16–18]; yet, some physicians fail to prescribe EAs for their patients at risk of anaphylaxis in the community.[41] These patients include those with a history of anaphylaxis who can re-encounter their triggers, such as foods or stinging insects, those with idiopathic anaphylaxis, and those at increased risk of anaphylaxis who might not yet have experienced it (see next paragraph),[1,2,8–10] including patients living in remote areas with minimal or no access to emergency medical services (EMS).[1,2,4,35,39]

EA prescriptions also can be considered for patients with known sensitization to peanut, tree nuts, cow's milk, crustacean shellfish, and fish, which potentially are associated with severe and fatal anaphylaxis and can be difficult to avoid (eg, when peanut or milk are hidden ingredients in manufactured foods).[8,9] Consideration of prescribing an EA is especially important if the patient has had a previous food-induced allergic reaction, such as generalized acute urticaria, has reacted to trace amounts of a food, or has food allergy and concomitant asthma, which increases the risk of fatality from anaphylaxis. In fact, some experts have suggested that consideration be given to prescribing EAs for all patients with immunoglobulin E–mediated food allergy, because it is difficult or impossible to predict the occurrence or severity of future reactions.[8,9] It can be beneficial to prescribe EAs for children with a history of acute generalized urticaria after an insect sting, because if re-stung, the risk of a more severe systemic reaction is approximately 5% in this population.[10,35]

Definitive evaluation by an allergy/immunology specialist can provide confirmation of the diagnosis of anaphylaxis and the trigger and, for patients with idiopathic anaphylaxis, can clarify the diagnosis by performing additional investigations that reveal a trigger or identify comorbidities, such as systemic mastocytosis.[1,2,42] Allergy/immunology specialists also initiate comprehensive preventive care: prescription of EAs in the context of written, personalized anaphylaxis emergency action plans; education about anaphylaxis recognition and EA use; detailed information about how to avoid specific allergens; and allergen immunotherapy (eg, venom immunotherapy, if relevant) to prevent the recurrence of insect sting anaphylaxis.[1,2,10,43,44]

USING EAS

Guidelines recommend prompt epinephrine injection for the sudden onset of any anaphylaxis symptoms after exposure to an allergen that previously caused anaphylaxis in that patient.[1,2,8–10] Systemic allergic reactions can rapidly progress from mild to life-threatening symptoms, and early treatment before, or at the first sign of, symptoms can sometimes prevent escalation of symptoms.[35] As an example, generalized acute urticaria is not life-threatening; yet, in a community setting, in the context of a known exposure to an allergen (eg, peanut or milk) that previously triggered anaphylaxis, it could be beneficial to inject epinephrine to prevent additional symptoms.[8,35] It can sometimes be difficult to distinguish anaphylaxis from other diagnostic entities such as acute asthma, acute generalized urticaria, aspiration of a foreign body such as a peanut, a vasovagal episode, or an anxiety or panic attack.[35] In such situations, if unsure, erring on the side of caution and injecting epinephrine, then observing the patient closely, is advised.

Even physicians with years of experience in diagnosing and treating anaphylaxis cannot determine, at the onset of an episode, whether that episode will remain mild or escalate over minutes to become life-threatening. In this situation, although some oral H_1-antihistamines relieve itching and hives within 30 or 40 minutes,[25,26] severe, life-threatening respiratory and/or cardiovascular symptoms can appear suddenly after the hives have disappeared.[1,8,24] In community

settings, patients experiencing anaphylaxis or caregivers without medical training may be so anxious that they cannot assess the situation accurately and remember what to do. It is therefore important that physicians instruct patients and caregivers to err on the side of prompt epinephrine injection.[1,3,8,35]

Many patients and caregivers fail to carry EAs consistently or to use them when anaphylaxis occurs, even for severe symptoms, including throat tightness, difficulty breathing, wheezing, and loss of consciousness.[41,45,46] People may have different reasons for not using EAs, including failure to recognize anaphylaxis symptoms, spontaneous recovery from a previous anaphylactic episode and the assumption that this will happen in every episode, reliance on oral H_1-antihistamines and/or inhaled bronchodilators, no EA available, fear of needles, and concerns about epinephrine adverse effects.[41,45–48]

Many parents fear using an EA because they worry about hurting or injuring their child or a bad outcome.[46,47] Unintentional injections into digits and other body parts, with or without injuries,[48] and lacerations incurred when an inadequately restrained child moves during the injection are reported from pen-type EAs.[49]

Teenagers are at increased risk of death in anaphylaxis[16–18] because of high-risk behaviors, including ethanol and/or recreational drug use, failure to recognize triggers, denial of symptoms, and failure to carry their EAs and inject epinephrine promptly when anaphylaxis occurs.[16–18] Additional efforts to provide anaphylaxis education for adolescents, their peers, and their communities are needed.[50]

Patients and caregivers need training in how to recognize anaphylaxis and use an EA. Epinephrine injections can be given through clothing, although care must be taken to avoid obstructing seams or items in pockets. Regular review (eg, annually) of anaphylaxis recognition and injection technique is advisable, because errors are common and acquired skills may not be retained permanently.[51,52] Technique can be practiced at home by using a "trainer." Various EAs may come to market having different mechanisms of activation and variations in ease of use.[53,54] Education about anaphylaxis recognition and injection technique is advised to ensure familiarity with the specific device prescribed.

After treatment with epinephrine for anaphylaxis in community settings, it is important for patients to be assessed in an emergency department to determine whether additional interventions are needed.[1,2,8] It may be helpful for families to know they are seeking additional medical care not because of the use of the EA, a safe treatment, but rather to assess and monitor the anaphylactic episode.

Pediatric allergists who are members of the AAP Section on Allergy and Immunology were surveyed about when they typically begin to transfer responsibilities for anaphylaxis recognition and EA use from adult caregivers to children and teenagers at risk of anaphylaxis in community settings. They expected that by age 12 to 14 years, their patients should begin to share these responsibilities. They started to train early and individualized the time of transfer on the basis of patient factors, such as the presence of asthma and absence of cognitive dysfunction.[55] In contrast, caregivers of at-risk children and teenagers who were surveyed expected to begin transfer of responsibilities considerably earlier, by 6 to 11 years of age.[56] In both of these studies, the investigators commented that adults (parents, teachers, coaches, and others) have the ultimate responsibility for children and teenagers under their supervision who experience anaphylaxis.[55,56]

It is advised not to store EAs under conditions of excessive heat or cold (eg, in a car or beach bag on a hot day). Manufacturers recommend keeping them at 20° to 25°C (68°–77°F), with excursions permitted to 15° to 30°C (59°–86°F). Degradation of the epinephrine solution in EAs can occur without visible discoloration or precipitates. It is beneficial to check EA expiration dates and renew prescriptions in a timely manner. However, if the only EA available during an episode of anaphylaxis is past the expiration date, it can be used in preference to no epinephrine injection at all.[57–59]

ANAPHYLAXIS EMERGENCY ACTION PLANS AND MEDICAL IDENTIFICATION

EAs are best prescribed in the context of written, personalized anaphylaxis emergency action plans. Such plans typically list common symptoms and signs of anaphylaxis and outline initial anaphylaxis treatment (Table 1): specifically, prioritize calling for help (911 or EMS), injecting epinephrine from an EA, and positioning the patient supine or in a position of comfort.[1–3,6,8] Action plans can also provide information such as the individual's anaphylaxis triggers and, if relevant, any history of severe anaphylaxis and/or comorbid conditions such as asthma. In addition, they can remind readers that H_1-antihistamines and asthma inhalers should not be used as the initial treatment or only treatment of anaphylaxis.

Patients at risk of anaphylaxis recurrences can wear medical identification jewelry and/or carry a wallet card that states "anaphylaxis" and lists their

confirmed triggers and relevant comorbidities such as asthma. Knowledge about the recognition and treatment of anaphylaxis increased significantly after brief study of an anaphylaxis wallet card.[60] Plans and medical IDs are best reviewed and updated regularly, such as annually.[1,2,8]

SPECIAL ISSUES FOR SCHOOLS AND OTHER PUBLIC VENUES

Prevention and treatment of anaphylaxis in schools, child care settings, camps, and other venues for young people are multifaceted and require a comprehensive approach, including awareness training and practical preparation.[61] Approaches are outlined in an AAP clinical report[61] and in guidelines from the Centers for Disease Control and Prevention (http://www.cdc.gov/healthyyouth/foodallergies). In many US schools, unassigned EAs are available for use when anaphylaxis occurs in a student who does not have a personal EA available[62]; clinicians can check with their state legislature regarding such regulations.

SUMMARY

1. Epinephrine is the medication of choice for the initial treatment of anaphylaxis. If injected promptly, it is nearly always effective. Delayed injection can be associated with poor outcomes, including fatality. All other medications, including H_1-antihistamines and bronchodilators such as albuterol, provide adjunctive treatment but do not replace epinephrine. After treatment with epinephrine for anaphylaxis in community settings, it is important for patients to be assessed in an emergency department to determine whether additional interventions, including oxygen, intravenous fluids, and adjunctive medications, are needed.
2. When anaphylaxis occurs in health care settings, epinephrine (0.01 mg/kg [maximum dose: 0.3 mg in a prepubertal child and up to 0.5 mg in a teenager]) by IM injection in the mid-outer thigh (vastus lateralis muscle) is recommended. IM epinephrine achieves peak epinephrine concentrations promptly and is safer than an intravenous bolus injection.
3. When anaphylaxis occurs in community settings, EAs are preferred because of their ease of use and accuracy of dosing as compared with the use of an ampule, syringe, and needle by laypersons or the use of an unsealed syringe prefilled with epinephrine. In the United States and Canada, EAs are currently available in only 2 fixed doses: 0.15 mg and 0.3 mg. International guidelines suggest that when using EAs, patients weighing 7.5 kg (16.5 lb) to 25 kg (55 lb) should receive the 0.15-mg dose; although this dose is not ideal for those who weigh less than 15 kg (33 lb), the alternatives are associated with delay in dosing, inaccurate dosing, and potential loss of the dose. It is reasonable to recommend EAs containing a 0.3-mg epinephrine dose for those weighing 25 kg (55 lb) or more.
4. It is beneficial to prescribe EAs for all patients who have experienced anaphylaxis and who may re-encounter their trigger in a community setting. If specific circumstances warrant, EAs may also be prescribed for some high-risk patients without a history of anaphylaxis.
5. Epinephrine is best prescribed in the context of a written, personalized anaphylaxis emergency action plan, developed by the medical home with input from the family. A relevant AAP clinical report provides an example of such a written plan with instructions on completing it.[63] Protocols for the use of unassigned EAs may also be beneficial. Children at risk of anaphylaxis require a comprehensive approach to management. It is important to teach patients and caregivers how to recognize anaphylaxis symptoms; when, why, and how to use an EA; and the rationale for calling 911 or EMS.
6. Children who have experienced anaphylaxis benefit from evaluation by an allergy/immunology specialist for confirmation of the diagnosis, confirmation of specific triggers, and preventive care.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
EA: epinephrine autoinjector
EMS: emergency medical services
IM: intramuscular(ly)

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