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CLINICAL REPORT

Self-injectable Epinephrine for First-Aid Management of Anaphylaxis

Guidance for the Clinician in Rendering Pediatric Care

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ABSTRACT

Anaphylaxis is a severe, potentially fatal systemic allergic reaction that is rapid in onset and may cause death. Epinephrine is the primary medical therapy, and it must be administered promptly. This clinical report focuses on practical issues concerning the administration of self-injectable epinephrine for first-aid treatment of anaphylaxis in the community. The recommended epinephrine dose for anaphylaxis in children, based primarily on anecdotal evidence, is 0.01 mg/kg, up to 0.30 mg. Intramuscular injection of epinephrine into the lateral thigh (vastus lateralis) is the preferred route for therapy in first-aid treatment. Epinephrine autoinjectors are currently available in only 2 fixed doses: 0.15 and 0.30 mg. On the basis of current, albeit limited, data, it seems reasonable to recommend autoinjectors with 0.15 mg of epinephrine for otherwise healthy young children who weigh 10 to 25 kg (22–55 lb) and autoinjectors with 0.30 mg of epinephrine for those who weigh approximately 25 kg (55 lb) or more; however, specific clinical circumstances must be considered in these decisions. This report also describes several quandaries in regard to management, including the selection of dose, indications for prescribing an autoinjector, and decisions regarding when to inject epinephrine. Effective care for individuals at risk of anaphylaxis requires a comprehensive management approach involving families, allergic children, schools, camps, and other youth organizations. Risk reduction entails confirmation of the trigger, discussion of avoidance of the relevant allergen, a written individualized emergency anaphylaxis action plan, and education of supervising adults with regard to recognition and treatment of anaphylaxis.

INTRODUCTION

Anaphylaxis is an acute, life-threatening reaction, usually mediated by an immunologic mechanism involving immunoglobulin E, that results in sudden systemic release of mast-cell and basophil mediators such as histamine and tryptase.[1] Anaphylaxis has many clinical presentations, but respiratory compromise and cardiovascular collapse cause the greatest concern, because they can potentially lead to fatalities. Although a variety of different triggers for anaphylaxis episodes have been identified, food and insect stings are the most common identifiable triggers reported in the community setting.[2–4] Food allergies[5] and other allergies have increased in the past several years, and pediatricians increasingly need to prescribe emergency care plans for patients in the event of anaphylaxis outside the hospital/medical setting. Epinephrine is the primary medical therapy for a life-threatening allergic reaction.[1] This clinical report focuses on practical issues concerning the administration of self-injectable epinephrine for first-aid treatment of

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

Key Words
anaphylaxis, epinephrine, self-injectable epinephrine, food allergy, insect-sting allergy

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anaphylaxis in the community. In addition, several quandaries in management will be identified and possible solutions described.

DEFINITION AND FEATURES OF ANAPHYLAXIS

There is no current, universally accepted definition of anaphylaxis; however, at a recent symposium cosponsored by the National Institutes of Health and the Food Allergy & Anaphylaxis Network, the following definition was proposed: "Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."[6,7] Three clinical criteria for anaphylaxis based on symptoms and history were also proposed at the symposium. These criteria, as well as various signs and symptoms that may occur during anaphylaxis, are listed in Table 1. The clinician must also appreciate that certain disorders may appear to be anaphylaxis but are not (eg, vasovagal syncope or panic attack). Fatal anaphylaxis in the pediatric population has particularly been associated with known preexisting asthma, failure to administer epinephrine promptly, and the adolescent age group.[8,9]

TABLE 1 Clinical Criteria for Diagnosing Anaphylaxis (Fulfilling Any 1 Criterion Indicates That Anaphylaxis Is Highly Likely)[7]

Criterion 1	Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (eg, generalized hives, pruritus, or flushing, swollen lips/tongue/uvula) and at least 1 of the following: a. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
Criterion 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 peak expiratory flow, hypoxemia) c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
Criterion 3	Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)

Less common presentations also occur (eg, sudden isolated hypotension without a known allergen exposure). Additional symptoms and signs that may occur during anaphylaxis include morbilliform rash, conjunctival erythema, pruritus and tightness in the throat, dysphagia, dysphonia, hoarseness, dry staccato cough, sensation of pruritus in the external auditory canals, nasal pruritus, nasal congestion, rhinorrhea, sneezing, chest pain, dysrhythmia, feeling of faintness/dizziness (near-syncope), paleness, cyanosis, confusion/altered mental status, an aura of doom, and uterine contractions. Skin signs aid in recognition but may be absent or not observed in 10% of children with anaphylaxis; moreover, they may not be observed in reactions that end in fatality.

The clinical criteria were adapted from Sampson HA, Muñoz-Furlong A, Campbell RL, et al. *J Allergy Clin Immunol*. 2006;117:391–397.

ROLE OF EPINEPHRINE

Epinephrine, the medication of choice for first-aid treatment of an episode of anaphylaxis, is a direct-acting sympathomimetic agent with effects on many target organs, including increased vasoconstriction, decreased mucosal edema, increased inotropy/chronotropy, and bronchodilation. In addition, epinephrine downregulates further mast-cell release of histamine, tryptase, and other mediators of inflammation. Delayed administration of epinephrine in anaphylaxis is associated with poor outcomes including fatality.[8–11] Oral H_1 antihistamines are not an optimal first-line therapy for anaphylaxis, because they have a slow onset of action (1 or more hours), primarily relieve cutaneous symptoms, and do not relieve respiratory symptoms or shock.[12] For children with known preexisting asthma who experience anaphylaxis, administration of an asthma-reliever medication (such as the inhaled selective β_2-adrenergic agonist albuterol) may provide adjunctive therapy for wheezing, coughing, and shortness of breath but does not relieve upper airway edema or shock, and therefore does not replace injected epinephrine in anaphylaxis management.

ROUTE OF ADMINISTRATION OF EPINEPHRINE

For first-aid treatment of anaphylaxis, administration of epinephrine by either the subcutaneous or intramuscular route has been recommended traditionally. However, studies on the rate of absorption of epinephrine injected by different routes and in different locations (eg, arm or thigh) have shown significant differences in time to peak concentrations, favoring intramuscular injection in the lateral thigh (vastus lateralis muscle), which leads promptly to peak plasma epinephrine concentrations. In a prospective, randomized, blinded study of children at risk of anaphylaxis,[13] the time to maximum epinephrine concentrations was 8 ± 2 minutes after injection of 0.30 mg of epinephrine from an EpiPen (Dey LP, Napa, CA) intramuscularly in the vastus lateralis. In contrast, the time to maximum plasma epinephrine concentration was 34 ± 14 minutes (range: 5–120 minutes) after injection of 0.01 mg/kg of epinephrine subcutaneously in the deltoid region.[13] These findings have been confirmed and extended in a randomized, double-blind, placebo-controlled crossover study in adults.[14] On the basis of studies in an animal model of anaphylaxis, achieving high plasma and tissue concentrations of epinephrine may be critical for reversal of hypotension.[15] The ½-inch (14.29-mm) needle on autoinjectors likely provides an intramuscular dose in most children, although it may not do so in obese adolescents, especially girls.[16]

It is not ethical to perform randomized, double-blind, placebo-controlled comparative studies on route of administration of epinephrine in children who are experiencing anaphylaxis, so definitive evidence-based recommendations on route of dosing cannot be made. On the

basis of the aforementioned available data at this time, intramuscular injection of epinephrine into the lateral thigh seems to be the preferred route for therapy in first-aid treatment. Intravenous administration carries risks of dilution errors and dosing errors, and many of the serious adverse effects attributed to epinephrine have followed large overdoses given intravenously. This route of administration should be reserved for those with severe anaphylaxis that does not respond to intramuscular epinephrine and/or individuals with anaphylaxis who are being treated in hospital settings.

EPINEPHRINE DOSING FOR FIRST-AID TREATMENT IN THE COMMUNITY

The recommendation for epinephrine dosing in children with anaphylaxis, based primarily on anecdotal evidence, is to inject 0.01 mg/kg, up to 0.30 mg.[17–19] Epinephrine autoinjectors are currently available in 2 fixed doses: 0.15 and 0.30 mg. Physicians, therefore, face a quandary with regard to dosing children who do not weigh approximately 15 kg (33 lbs [for whom the 0.15-mg dose is ideal]) or 30 kg (66 pounds or more [for whom the 0.30-mg dose is recommended]). The *Physician's Desk Reference*[20] and product inserts provide ambiguous advice and place the responsibility of dose selection entirely on the prescribing physician. Not surprisingly, therefore, both autoinjector doses are dispensed across almost the entire pediatric age range, indicating the potential for overdosing with the 0.15-mg dose in many infants, overdosing with the 0.30-mg dose in some young children, and underdosing with the 0.15-mg dose in many adolescents.[21] In a prospective, randomized, double-blind, parallel-group study of children at risk of anaphylaxis who self-injected either EpiPen 0.30 mg or EpiPen Jr 0.15 mg, pharmacologic effects such as pallor, tremor, and anxiety were observed transiently after injection of both doses, and additional effects including palpitations, headache, and nausea were observed in those who received the higher dose.[22] This study showed that the therapeutic effects of epinephrine could not be dissociated from the nontherapeutic effects. In the absence of availability of additional fixed doses (eg, 0.05, 0.10, 0.20, and 0.25 mg) in autoinjectors, the manufacturers' advice should be taken in the context of these benefits and risks.

The Risks of Prescribing an Epinephrine Ampule, Syringe, and Needle

Physicians face a particularly difficult dilemma in prescribing epinephrine doses for infants and children who weigh less than 15 kg (33 lb). One option may be to prescribe an epinephrine ampule/syringe/needle and instruct caregivers on how to draw up and inject epinephrine using these supplies. This approach was studied in 18 parents who were trained in the technique and whose speed and accuracy of drawing up an infant epinephrine dose (0.09 mL) was compared with that of 54 physicians and nurses (controls).[23] The parents took significantly ($P < .05$) longer than the controls to draw up the dose. The mean ± SEM times for drawing up doses were 142 ± 13 seconds (range: 83–248 seconds) for parents, 52 ± 3 seconds (range: 30–83 seconds) for physicians, 40 ± 2 seconds (range: 26–71 seconds) for general duty nurses, and 29 ± 0.09 seconds (range: 27–33 seconds) for emergency department nurses. The epinephrine content of the doses drawn up by parents, who were asked to draw up 0.09 mL, ranged from 0.004 to 0.151 mL (ie, nearly 40-fold). There was no correlation between speed of drawing up the epinephrine and accuracy of dosing. Parents had many concerns about successfully preparing and administering a dose by this method and about teaching other caregivers to use the method. The study was undertaken in a relaxed atmosphere, and one might expect more difficulties if the dosing were undertaken by laypersons while a child was experiencing anaphylaxis.[24]

Unfortunately, the current lack of autoinjectors with a low or adjustable dose and the problems involved with prescribing an epinephrine ampule along with a syringe/needle require that the physician and family arrive at a reasonable compromise for safe and effective administration of epinephrine in the event of anaphylaxis. In a survey of 29 pediatricians, 80% responded that they would prescribe the 0.15-mg autoinjector dose for a child who weighs 10 kg (22 lb); 100% responded that they would prescribe it for a child who weighs 15 kg (33 lb); and 70% responded that they would prescribe it for a child who weighs 20 kg (44 lb).[25] In a study of epinephrine-dispensing patterns,[21] 72% of prescriptions for infants younger than 6 months (weighing less than approximately 7 kg [15 lb]) were for a 0.15-mg autoinjector, and 20% were for ampule/syringe/needle; 95% of prescriptions for infants 6 to 12 months of age (likely weighing up to approximately 10 kg [22 lb]) were for a 0.15-mg autoinjector. Until a wider range of epinephrine autoinjector doses is available, pediatricians are forced to consider prescribing an autoinjector with a known, albeit not ideal, dose rather than risk likely overdosing or underdosing with ampule/syringe/needle.

Epinephrine Autoinjectors: 0.15 or 0.30 mg?

In the absence of a strong evidence base and a larger selection of premeasured autoinjector doses, and in light of studies showing elevated plasma concentrations and relatively modest adverse effects in children who weigh approximately 25 kg (55 lb) injected with approximately a 1.2-fold overdose of intramuscular epinephrine, it seems appropriate to switch most children from the 0.15-mg dose to the 0.30-mg dose at approximately 25 kg (55 lb)—that is, to provide a slightly higher dose (0.012 mg/kg) rather than an underdose (0.006 mg/kg) for a 25-kg (55-lb) child. For children who have asthma

or other additional risk factors for fatality from anaphylaxis, switching to the higher dose at a lower weight might be considered.[19] There are no data at this time to support specific recommendations for children who weigh less than 15 kg (33 lb). It is not known whether the adverse effects from a previously studied 1.2-fold overdose are similar in infants and very young, small children to those reported in children who weigh approximately 25 kg (55 lb). Considering the ease of use of self-injectable epinephrine compared with the ampule/syringe/needle technique and the preferences of pediatricians[21,25] and parents,[23] it seems reasonable to consider autoinjectors containing 0.15 mg of epinephrine for otherwise healthy infants/young children who weigh 10 to 25 kg (22–55 lb), although the physician is cautioned that manufacturers suggest alternative modalities for those who weigh less than 15 kg (33 lb). Clearly, specific clinical circumstances must be considered in this decision. For infants who weigh less than 10 kg (22 lb), dosing with 0.15-mg autoinjectors would exceed 1.5-fold overdosage, and although this situation is unacceptable from the standpoint of autoinjector availability, it is apparent that many pediatricians opt for the certainty of an autoinjector dose compared with the uncertainty of an ideal dose when the epinephrine ampule/syringe/needle technique is used.[21] Still, physicians and families should consider and discuss the benefits and risks of choosing between an autoinjector or epinephrine ampule/syringe/needle for this age group on a case-by-case basis. Current dilemmas in selecting a dose and factors that may sway a decision to switch to a particular dose unit are listed in Table 2. Lack of worldwide availability of autoinjectors[26] often requires prescription of the less costly epinephrine ampule/syringe/needle technique in developing countries despite the fact that it requires additional training, is error prone, and may lead to delay in injection.[23] Preloading the syringe with an appropriate dose of epinephrine is a possible partial solution, but contamination and degradation of the drug, particularly in hot climates, are serious concerns.[27]

Repeating the Epinephrine Dose

Anecdotal evidence generally suggests that in the absence of a response to epinephrine, the epinephrine injection may be repeated at 5- to 20-minute intervals.[1,28] Retrospective studies have suggested that a sec-

TABLE 2 **Epinephrine Autoinjectors for Infants and Children: Dilemmas in Dosing and Possible Solutions[19]**

Patient's Weight, kg (lb)	Optimal Dose (0.01 mg/kg), mg	Availability of Autoinjector[a]	Alternatives/Implications[b]	Comments/Recommendations[c]
≤10 (≤22)	≤0.10	No	Fixed-dose 0.15-mg autoinjector provides ≥1.5-fold overdose; ampule/syringe/needle technique may lead to delay in injection and inaccurate dosing	Evaluate degree of overdose vs ability to use ampule/syringe/needle; no specific evidence base for decision except that ampule/syringe/needle technique is delay and error prone, and autoinjector (0.15 mg) is more commonly prescribed for infants by physicians forced to choose
15 (33)	0.15	Yes	0.15-mg autoinjector provides optimum dose	Prescribe autoinjector (0.15 mg)
20 (44)	0.20	No	0.15-mg autoinjector provides 1.3-fold underdose; 0.30-mg autoinjector provides 1.5-fold overdose	Usually prescribe 0.15-mg autoinjector, but increasing weight of child over 20 kg and high risk on the basis of clinical history[d] may be considered an appropriate rationale for prescribing a 0.30-mg autoinjector
25 (55)	0.25	No	0.15-mg autoinjector provides 1.7-fold underdose; 0.30-mg autoinjector provides 1.2-fold overdose	Usually prescribe 0.30-mg autoinjector; a small overdose in a healthy child generally carries a low risk of adverse effects compared with the risk of an underdose during anaphylaxis
≥30 (≥66)	0.30	Yes	0.30-mg autoinjector provides optimum dose	Prescribe autoinjector (0.30 mg)

[a] For situations in which an autoinjector containing an appropriate dose is not available, the situation is never truly acceptable, because using an epinephrine ampule/syringe/needle (see text) is prone to delay in dosing or inaccurate dosing. However, until such autoinjectors are manufactured and fixed doses of 0.05, 0.10, 0.20, and 0.25 mg are available in addition to the 0.15- and 0.30-mg doses currently available, the physician has to determine the risk versus the benefit of selecting a fixed dose that is either too low or too high and the risk/benefit of an optimal technique of administration (autoinjector) versus a technique (ampule/syringe/needle) that may be prone to delay and error in the hands of non–health care professionals.

[b] There are no studies that have provided details about risks of overdose and underdose of epinephrine in the context of first-aid treatment of anaphylaxis at most dose ranges, particularly in children who weigh less than 15 kg (33 lb). It is presumed, on the basis of limited data, that otherwise healthy children (normal cardiac status, not taking other sympathomimetics, tricyclic antidepressants, or monoamine oxidase inhibitors, etc) would tolerate modest overdoses of epinephrine. In older children not experiencing anaphylaxis, a 1.2-fold overdose has been associated with adverse pharmacologic effects.

[c] Distributors' recommendations regarding autoinjector indications for weight/age differ from country to country, but an alternative form of epinephrine for self-injection, such as ampule/syringe/needle rather than an autoinjector, has been suggested for children who weigh less than 15 kg (33 lb). The perceived comfort and ability of families and caregivers to provide accurate doses of epinephrine for infants using an epinephrine ampule/syringe/needle should be considered in deciding the best modality and the potential degree of overdose or underdose if an autoinjector were prescribed. Although not per manufacturer's advice, it is suggested that the available evidence (error rates of ampule/syringe/needle of no dose to almost 40-fold overdose in the hands of non–health care professionals, adverse pharmacologic effects of a modest overdose in a healthy child, lack of additional fixed-dose autoinjectors) may warrant prescription of a 0.15-mg autoinjector for most healthy children who weigh 10 kg (22 lb) and more; however, individual circumstances may vary. Depending on the circumstances, provision of an autoinjector to those who weigh less than 10 kg (22 lb) may also be warranted.

[d] In addition to consideration of body weight, clinical issues that may add risk to underdosing and indicate a relative benefit for a higher dose may include 1 or more of the following: concurrent asthma; previous anaphylaxis to peanut, tree nut, milk, egg, seafood, and/or fin fish; poor access to emergency services; and/or lack of supervision.

ond dose may be required in 18% to 35% of cases, although data in this regard are limited.[29,30] As stated previously, some of the effects of epinephrine (pallor, tremor, anxiety, and palpitations) and even severe adverse effects (such as cough from pulmonary edema) can mimic some of the symptoms of anaphylaxis. Caregivers should be aware of these issues and avoid unnecessary repeat dosing.

In some adults experiencing anaphylaxis who were raised from the supine to the upright position during transport to a hospital, death occurred suddenly, presumably from an "empty-ventricle syndrome" caused by blood pooling in the legs during anaphylactic shock.[31] The implications of this observation for children, who more typically succumb to respiratory insufficiency during anaphylaxis and who often vomit during anaphylaxis, are not known. Nevertheless, caregivers should be advised that individuals with severe anaphylaxis who may benefit from being in a supine position with legs raised should remain in that position and be transported that way by emergency personnel until advanced care can be accessed (eg, additional medications and intravenous fluids).

PRESCRIPTION OF SELF-INJECTABLE EPINEPHRINE

The primary indication for prescription of self-injectable epinephrine is a history of anaphylaxis in an individual who may re-encounter the triggering agent outside of a medical setting or who has idiopathic anaphylaxis, which is uncommon in childhood. Identification of individuals who have experienced anaphylaxis is not necessarily easy. It is clear that persons with a previous episode of anaphylaxis that was characterized by respiratory or cardiovascular compromise to a trigger that may be encountered outside the hospital should carry self-injectable epinephrine, but only approximately 70% of individuals with anaphylaxis have respiratory symptoms, and even fewer (only approximately 10%) experience cardiovascular symptoms.[32] Skin manifestations such as urticaria, angioedema, flushing, or itching occur in more than 80% of children with anaphylaxis. When present, these symptoms are helpful in the recognition of anaphylaxis; when absent, they make the recognition of anaphylaxis more difficult.[32] Moreover, acute generalized urticaria and angioedema alone may not necessarily warrant a diagnosis of "anaphylaxis" (a point of controversy). However, on the basis of available evidence, self-injectable epinephrine should be prescribed for a child who has experienced generalized acute urticaria after an insect sting, because the risk of a more severe reaction from a future sting is approximately 10%.[33] Finally, physicians cannot assume that patients and caregivers necessarily recognize and report all symptoms, because even trained health care professionals underrecognize anaphylaxis.[2] For all of these reasons, a high index of suspicion is needed to identify those who have had anaphylaxis and require an epinephrine prescription.

An additional point of judgment regarding prescription of self-injectable epinephrine is that a physician may identify a child who has not yet experienced anaphylaxis but may nevertheless be at increased risk of anaphylaxis and may warrant prescription of self-injectable epinephrine. Vander Leek et al[34] showed that among 24 young children with peanut allergy whose first reaction was isolated to the skin after ingestion or skin contact, 18 (75%) experienced symptoms beyond the skin in a subsequent reaction. Indeed, severity of a previous reaction is a poor guide to symptoms during a future reaction.[9,11,35] In young children with peanut- or tree nut–related anaphylaxis, episodes may worsen progressively with time, perhaps related to the fact that increased numbers of such children develop asthma as they get older.[36] Asthma, which is associated with severe and fatal anaphylaxis,[8,9,28] is an important comorbidity that should influence the decision to prescribe self-injectable epinephrine. Some "high-risk" circumstances that may justify prescription of self-injectable epinephrine in the absence of previous anaphylaxis are summarized in Table 3.[18,37,38] Definitive evaluations of such children by an allergy/immunology specialist with American Board of Allergy and Immunology certification or international equivalent should be encouraged.[39]

In summary, epinephrine should be prescribed for children who have experienced anaphylaxis and may re-encounter the trigger outside of a hospital setting. In some circumstances, epinephrine for self-injection should be prescribed for persons who have not experienced anaphylaxis but are at increased risk of anaphylaxis on the basis of their specific comorbid medical conditions and medical-social evaluation.

INSTRUCTIONS FOR WHEN TO USE EPINEPHRINE

Physicians should carefully instruct patients and families on the indications for, and the technique for using,

TABLE 3 Examples of Factors That May Indicate the Need to Prescribe Epinephrine for Persons "at Risk" of Anaphylaxis[18,37,38]

Reaction history
Reaction to trace allergen exposure
Repeat exposures likely
Specific food triggers known to be associated with severe/fatal reactions (eg, peanut, tree nut, seafood, milk)
Generalized urticaria from insect venom
Certain comorbidities
Asthma
Use of nonselective β-blockers
Additional factors
Initial reaction details unclear, possible anaphylaxis
Those living in a remote area away from medical care/access

An at-risk person can be, for example, one with a confirmed allergy to food or insect venom who has not experienced anaphylaxis. Note: a first episode of anaphylaxis can be fatal.[10,11]

self-injectable epinephrine. Prompt administration of epinephrine is clearly indicated for treatment of significant respiratory or cardiovascular symptoms of anaphylaxis, but considerable judgment is required in many actual or possible allergic reactions in which life-threatening symptoms have not yet developed but may develop. Previous guidelines have suggested that epinephrine should be administered promptly at the onset of symptoms after exposure to an allergen that had previously caused anaphylaxis and possibly even in the absence of symptoms if there was a known exposure to an allergen that previously caused anaphylaxis with cardiovascular collapse.[28] Generalized acute urticaria itself is not a life-threatening symptom, yet in the context of a known exposure to an allergen that previously triggered anaphylaxis, the recommendation for an exposure outside of a medical setting is to inject epinephrine.[28] Whether an individual with generalized acute urticaria has "anaphylaxis" and should be given epinephrine is controversial. In many circumstances, astute clinical judgment is required to differentiate symptoms that may mimic aspects of an episode of anaphylaxis (eg, viral syndrome with acute urticaria, asthma, choking, a panic episode) or represent a mild allergic reaction that does not require epinephrine. In the community setting, individuals who experience anaphylaxis, whose judgment may be clouded by anxiety or central nervous system symptoms, or caregivers without medical training, whose judgment may be clouded by anxiety, are required to evaluate symptoms.[39] Consequently, physicians should always instruct these individuals to err on the side of injecting epinephrine rather than waiting too long.[28]

Individuals and caregivers are often reluctant to use self-injectable epinephrine in anaphylaxis despite instruction to do so. This probably occurs for a variety of reasons, including failure to recognize anaphylaxis; spontaneous recovery from a previous episode; incorrectly thinking the episode is mild; reliance on oral H_1 antihistamines or asthma-relief inhalers such as albuterol; fear of needles and injections; epinephrine autoinjector not being available; and concern about adverse effects of epinephrine.[19] In contrast to transient pallor, tremor, anxiety, and palpitations, which are common and anticipated pharmacologic effects of epinephrine, serious adverse effects are generally not a concern for otherwise healthy children, although they have been reported when epinephrine was given in overdose, especially when it was administered intravenously in an overdose, given at an inappropriately high concentration, or infused too rapidly.[11,22,40]

It seems that adolescents are at particular risk of fatal anaphylaxis, possibly because they are more likely to engage in risky behaviors, fail to recognize triggers, deny symptoms, and not carry or use emergency medications.[8,9] Additional efforts to provide anaphylaxis education for adolescents and their friends and peers are needed.

Prompt administration of epinephrine for anaphylaxis is key. Sampson et al[9] described 6 children with fatal reactions to food, all of whom had asthma, previous reactions to foods, and delay in treatment with epinephrine. None of the children received epinephrine before onset of severe respiratory symptoms (obvious respiratory distress, retractions, wheezing, and, in some cases, cyanosis), and 7 children in the same study with near-fatal food anaphylaxis received epinephrine before or within 5 minutes of severe respiratory symptoms. Only 1 of the children with fatal reactions had cutaneous symptoms; in contrast, all of those with near-fatal reactions had cutaneous symptoms. This raises the concern that absence of, or failure to recognize, skin symptoms and other symptoms could result in a delay in treatment and a poor outcome. Among 32 food-anaphylaxis fatalities recorded in a registry maintained through the Food Allergy & Anaphylaxis Network,[8] all but 1 individual had a known allergy to the food, only 10% had self-injectable epinephrine available, peanut or tree nut caused 94% of the reactions (milk and fish caused the others), most of those who died were adolescents or young adults, and 96% had asthma.

Gold and Sainsbury[41] surveyed families of children for whom self-injectable epinephrine was prescribed for a previous reaction with respiratory or cardiovascular involvement. Although recurrences were common, epinephrine was injected in only 12% of subsequent reactions. When it was given, although it was seldom injected before onset of respiratory or cardiovascular symptoms, it resulted in a significantly lower hospitalization rate and reduced morbidity.

When developing an anaphylaxis emergency action plan for an individual to use in the community in the absence of a health care professional, presumably for a circumstance in which definitive diagnosis is unlikely, it seems advisable to instruct patients/caregivers to inject epinephrine promptly when symptoms occur after known exposure to a trigger that previously caused a significant reaction. For the occasional child or adolescent who has idiopathic anaphylaxis, where "exposure" is an irrelevant issue, a symptom-based approach is required.

Patients and caregivers must also be instructed in the techniques of autoinjector use or epinephrine ampule/syringe/needle use. Although the autoinjector devices are not particularly difficult to use, errors are common.[25] The injection may be given through clothing, although care must be taken to avoid obstructions such as seams or items in pockets. Accidental injection of epinephrine into a digit can cause vasoconstriction and necrosis and should be promptly evaluated and treated, if necessary, with warming, topical nitroglycerin cream, or locally injected phentolamine or other vasodilator.[42] Review

and practice of injection technique using "trainers" and review of manufacturer's educational materials (eg, DVDs) are strongly recommended. Proper storage of the epinephrine, away from extremes of temperature and direct sunlight to protect the drug from degradation, is also important. Degradation may occur without discoloration or precipitation.[43] It is important to remind patients and families to check autoinjector expiration dates and renew prescriptions promptly.

Preparation for first-aid treatment of anaphylaxis additionally requires medical home development and review of a personalized anaphylaxis emergency action plan that lists potential anaphylaxis symptoms and gives instructions for the indications for self-injectable epinephrine, the technique for using epinephrine autoinjectors, and the necessity of taking the patient to an emergency department after an epinephrine injection. Downloadable examples of written plans that can be personalized are available through the Food Allergy & Anaphylaxis Network Web site (www.foodallergy.org/actionplan.pdf [in English] or www.foodallergy.org/spanishaction.pdf [in Spanish]) and from the American Academy of Allergy, Asthma and Immunology Web site (www.aaaai.org/members/resources/anaphylaxis_toolkit/action_plan.pdf).[39] The emergency action plan and coaching with regard to use of self-injectable epinephrine should be reviewed with the patient on a regular basis. Additional important considerations include diagnostic confirmation/reconfirmation of the triggering allergen, instructions with regard to trigger avoidance (for foods, insect stings, etc), and medical identification (eg, bracelet, wallet card[39]). When relevant, specific preventive measures should be recommended (eg, for venom anaphylaxis, allergen-specific immunotherapy should be instituted to provide long-lasting protection).[44] For exercise-induced anaphylaxis, physicians should recommend appropriate avoidance of food or medication co-triggers, and if no co-trigger has been identified, they should advise individuals to avoid ingestion of anything within 3 to 4 hours of strenuous exercise. Evaluation by an allergy/immunology specialist (with American Board of Allergy and Immunology or international equivalent certification) is typically required to address these issues. Lay organizations such as the Food Allergy & Anaphylaxis Network (www.foodallergy.org) are an important resource for educational materials and support. Omission of these preventive strategies may contribute to poor outcomes.[9,11]

In summary, epinephrine is the drug of choice for first-aid treatment of anaphylaxis and should be injected promptly in the event of an anaphylactic reaction or when progression to anaphylaxis is likely and advanced care is not promptly available. Asthma puffers and/or antihistamines cannot be depended on in anaphylaxis.[39]

SPECIAL ISSUES FOR SCHOOLS

Protection of children at risk of anaphylaxis while in school, child care, or camp requires a concerted effort.[28] Several organizations have developed thoughtful summaries of shared responsibilities concerning food allergies for use by schools, children, adolescents, and parents (a list is available online at www.foodallergy.org/school/SchoolGuidelines.pdf). The physician should work with school administrators, teachers, school nurses, and others to ensure that an appropriate diagnosis has been obtained and that an appropriate anaphylaxis emergency action plan is prescribed.

SUMMARY

1. Epinephrine is the medication of choice for first-aid treatment of an episode of anaphylaxis. Prompt injection of epinephrine is nearly always effective in the treatment of anaphylaxis, and delayed injection of epinephrine is associated with poor outcomes including fatality. Antihistamines and, for those with asthma, inhaled selective β_2-adrenergic agonists such as albuterol provide adjunctive therapy but cannot replace epinephrine. Advanced care for anaphylaxis should be sought promptly (call 911 or equivalent for additional care and emergency transport to a hospital/emergency department) after epinephrine injection for first-aid treatment of anaphylaxis.
2. The recommended epinephrine dose for anaphylaxis in children, based primarily on anecdotal evidence, is 0.01 mg/kg, up to 0.30 mg.
3. On the basis of the available data at this time, intramuscular injection of epinephrine into the lateral thigh (vastus lateralis) seems to be the preferred route for therapy in first-aid treatment, assuming that an early peak epinephrine concentration is important to effective management. Intravenous administration of epinephrine carries increased risks of dilution errors and dosing errors, with consequent increased risk of overdose and adverse effects such as cardiac dysrhythmias.
4. Epinephrine autoinjectors, preferred for ease of use compared with an ampule, syringe, and needle, are currently available in only 2 fixed doses: 0.15 and 0.30 mg. The lack of additional autoinjector doses is a serious concern. Nevertheless, pediatricians are advised to prescribe the optimal dose from an autoinjector for each child, even when that dose cannot possibly be precisely 0.01 mg/kg. On the basis of current, albeit limited, data, it seems reasonable to recommend autoinjectors with 0.15 mg of epinephrine for otherwise healthy young children who weigh 10 to 25 kg (22–55 lb) and autoinjectors with 0.30 mg of epinephrine for those who weigh approximately 25 kg (55 lb) and more. However, specific clinical

circumstances must be considered when making these decisions. For children who weigh less than 10 kg (22 lb), the physician and family should weigh the risks of delay in dosing and dosing errors when an ampule/syringe/needle is used against accepting non-ideal autoinjector doses, taking into consideration the specific health needs of the individual child and abilities of the caregivers.

5. Epinephrine should be prescribed for children who have experienced anaphylaxis who may re-encounter the trigger outside of a health care setting. In some circumstances, epinephrine for self-injection should be prescribed for persons who have not yet experienced anaphylaxis but are at increased risk of anaphylaxis on the basis of their specific trigger for anaphylaxis, comorbid medical conditions such as asthma, and/or limited ability to recognize anaphylaxis.
6. Epinephrine should always be prescribed in the context of an anaphylaxis emergency action plan developed by the medical home with the families. Effective care for individuals at risk of anaphylaxis requires a comprehensive management approach. Patients and caregivers must be carefully instructed on the technique for use of, and indications for, self-injectable epinephrine, how to recognize the symptoms of anaphylaxis, and the need to activate emergency services (call 911 or equivalent) in the event of anaphylaxis. Instructions on allergen avoidance are key. Optimally, evaluation by an allergy/immunology specialist with American Board of Allergy and Immunology or international equivalent certification should be obtained to confirm allergic triggers, to provide education on trigger avoidance, and to initiate specific preventivetreatment (eg, venom-injection immunotherapy for insect-sting anaphylaxis). Written emergency action plans and review of care plans in the child's medical home with specific responsibilities for school, child care, or camp personnel; families; and children are needed to ensure a safe environment for those at risk.

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