



Contemporary issues in anaphylaxis and the evolution of epinephrine autoinjectors

What will the future bring?



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ARTICLE INFO

Article history:

Received for publication June 21, 2017.

Received in revised form July 17, 2017.

Accepted for publication July 24, 2017.

ABSTRACT

Background: Food allergy and anaphylaxis appear to be increasing in the United States, especially in young children, and preparedness is paramount to successful emergency management in the community. Although the treatment of choice for anaphylaxis is epinephrine delivered by autoinjection, some devices are challenged by less user-friendly designs or pose the risk of injury, especially in young patients. Human factors engineering has played a larger role in the development of more recent epinephrine autoinjector technologies and will continue to play a role in the evolution and future design of epinephrine autoinjectors.

Objective: To discuss contemporary issues related to the identification and management of anaphylaxis, current and future epinephrine autoinjector design, and unmet needs for the treatment of special populations, namely, young children weighing less than 15 kg.

Methods: The literature was reviewed and select articles retrieved to support expert clinical opinions on the need for improved recognition of anaphylaxis, epinephrine autoinjector design, and unmet needs in special populations.

Results: Anaphylaxis may be underrecognized and poorly defined in infant- and toddler-aged children, current devices may not be adequate to safely treat these patients (ie, inappropriate needle length), and health care professionals may not be aware of these issues.

Conclusion: As epinephrine autoinjector technology continues to evolve, device characteristics that promote safe, user-friendly experiences and give clinicians and their patients confidence to successfully treat anaphylaxis during an emergency, without injury, will be favored.

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Introduction

Food-related anaphylaxis is increasing, particularly in young children. From 1997 to 2007, the prevalence of food allergy in children increased by 18% in the United States,¹ and by 2010 its

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Disclosures: Dr Greenberger reported receiving consulting fees from Allergy Therapeutics and the US Food and Drug Administration Pulmonary and Allergy Drugs Advisory Committee and receiving royalties from UptoDate, Wolters Kluwer, and Lippincott, Williams and Wilkins. Dr Wallace reported receiving consulting fees from Kaléo, Mylan, DVB, Sanofi, Medical Marketing Solutions, and Allergan. Dr Lieberman reported receiving consulting fees from Kaléo and serving as a speaker for Mylan. No other disclosures were reported.

Funding Sources: Funding for medical writing and editorial assistance was provided by Kaléo Pharmaceuticals Inc. The funding source had no role in the development of this publication or its approval.

prevalence was as high as 8% in children younger than 18 years.² A more recent study of children from 6 months to 18 years of age (N = 3,652 from 37 children's hospitals between 2007 and 2012) suggests that emergency department (ED) visits for food-related anaphylaxis continue to increase.³ A retrospective claims study (2005–2014) using commercially insured and Medicare patients supported this trend by showing that the greatest increase in ED visits for anaphylaxis has been observed in children aged 0 to 5 years old (129% increase) and 5 to 17 year old (196% increase).⁴ In Illinois alone, there was an annual increase in ED visits and hospitalizations for food-induced anaphylaxis of 27.3% in children 0 to 4 years of age (n = 840) between 2008 and 2012.⁵

In a population-wide study using 3 national databases, the Nationwide Inpatient Sample (1999–2009), the Nationwide Emergency Department Sample (2006–2009), and Multiple Cause of Death Data (1999–2009), anaphylaxis-related mortality rates were between 0.25% and 0.33% among hospitalizations and ED

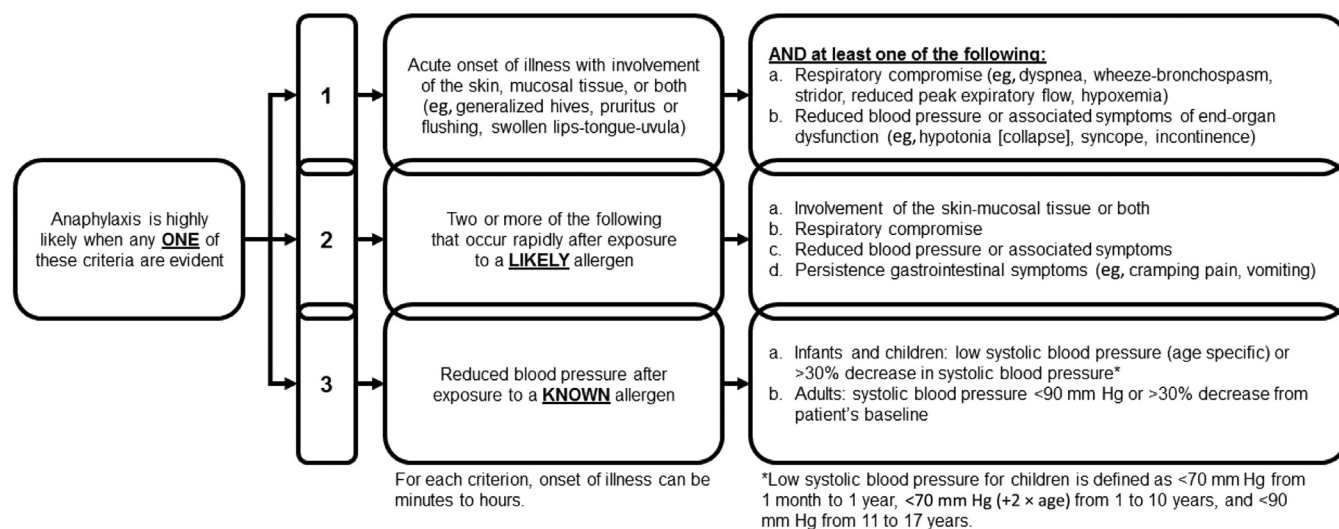


Figure 1. National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network Clinical Criteria for Anaphylaxis. Adapted from *J Allergy Clin Immunol* 117(2), Sampson HA et al, Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, Pages 391–397, Copyright 2006⁷, with permission from Elsevier.

presentations, respectively, and were stable during the analysis period.⁶ These rates represent 63 to 99 deaths per year in the United States. In the study by Ma et al,⁶ there were 84 deaths observed in children 17 years or younger. These data suggest that food allergies and food-related anaphylaxis are increasing, especially in young children, and deaths from anaphylaxis continue to be a problem in the United States.

Methods

A literature search was conducted using the keywords *anaphylaxis AND epidemiology OR hospitalizations OR emergency department visits OR fatalities OR infants OR children OR treatment OR epinephrine auto-injector OR needle length OR epinephrine auto-injector safety*. Secondary keywords used to narrow individual searches included *device usability OR device preference OR epinephrine auto-injector injuries OR novel delivery methods for epinephrine*. Select literature was reviewed on recent epidemiologic trends in anaphylaxis, symptoms of anaphylaxis in infants and young children, the history and design of epinephrine autoinjectors (EAI), safety of EAI, adequacy of needle length in available pediatric EAI, and future of EAI design. Expert clinical opinions were incorporated to support the need for improved recognition of anaphylaxis, novel EAI design, and unmet needs in special populations.

Results

Understanding Anaphylaxis Symptoms in the Young

Although criteria for the diagnosis of anaphylaxis in older children and adults are widely accepted (Fig 1),⁷ the precise symptoms for infant or toddler-aged children are less well understood, as discussed by Simons and Sampson.⁸ Food-related anaphylaxis can occur with direct consumption or indirectly through breast milk,⁹ and typical triggers are cow's milk, egg, and peanut.⁸ However, what may be less known are the symptoms that accompany an exposure in an infant, which may appear different than in older children or adults. Anaphylaxis may be characterized by generalized urticaria, cough, wheeze, stridor, and/or persistent vomiting (sometimes this may be the only symptom). Shock may more likely manifest initially as tachycardia vs hypotension. Behaviors that one might witness in a healthy infant may also be demonstrated during a reaction (eg, irritability, inconsolable crying, dysphonia, drooling,

regurgitation, and urine and stool incontinence). Infants cannot verbalize symptoms such as throat tightness, so awareness is critical to identifying a reaction. Factors that may amplify anaphylaxis symptoms in infants include upper respiratory tract infection, fever, exertion, or emotional stress.⁸ Comorbid conditions that put infants at risk for severe anaphylaxis may be recurrent wheezing or asthma, eczema or atopic dermatitis, and mastocytosis, but these conditions also need to be more clearly defined.⁸ One study found that only 6% of infants who met the clinical criteria for anaphylaxis during an ED visit were recorded on discharge as having anaphylaxis.¹⁰ More work is needed to qualify and validate the criteria for anaphylaxis in the infant and toddler population for practicing clinicians.

Current Medications Used to Treat Anaphylaxis

Intramuscular epinephrine is recommended as the therapy of choice for anaphylaxis.¹¹ In the event of an allergic emergency, treatment with epinephrine by autoinjector into the anterolateral aspect of the vastus lateralis should be given quickly. Clinical practice guidelines recommend that corticosteroids and antihistamines should only be used as supportive therapies and neither should be used in place of epinephrine.¹¹ For example, the time to 50% reduction in histamine-induced flares was 52 minutes for intramuscular diphenhydramine and 80 minutes for oral diphenhydramine,¹² which makes their use incompatible with the onset of severe anaphylaxis and death in some cases (within 30 minutes).^{13,14} The inappropriate use of supportive therapies for anaphylaxis has been previously demonstrated. In a study of pediatric patients treated in the ED for anaphylaxis (defined by ≥ 2 organ systems or hypotension), high proportions were inappropriately treated with corticosteroids (78%), histamine₁ (H₁)– or histamine₂ (H₂)–blockers (92%), or albuterol by nebulization (30%).¹⁵ Only 54% of patients in this study received epinephrine initially for anaphylaxis. Antihistamines can be given after epinephrine is administered to help control cutaneous symptoms, such as itching, flushing, urticaria, and nasal and eye symptoms, and corticosteroids can be administered to potentially prevent protracted or recurrent reactions. Lastly, oxygen and short-acting bronchodilators can be given if necessary, and intravenous fluids should be used to achieve optimal hemodynamic response in cases of profound hypotension.

Underuse or Delays in Treatment With Epinephrine for Anaphylaxis

Despite the knowledge that epinephrine can save lives, it may be underused by physicians, health care professionals, emergency medical services, and patients. Rates of epinephrine use in the ED as first-line treatment of anaphylaxis are generally low, even in patients who have been clearly diagnosed with anaphylaxis.¹⁶ In a small 2013 cross-sectional survey of emergency medical health professionals (N = 207) in US EDs, only 42% of health care professionals reported using epinephrine in the ED for most anaphylactic episodes and less than 50% provided patients with a prescription for an EAI and/or a referral to an allergist at discharge.¹⁶ In a retrospective study analyzing anaphylaxis-related *International Classification of Diseases, Ninth Revision* codes in a large health maintenance organization from 2008 to 2012 (N > 150,000), epinephrine was only prescribed in 16.2% of total anaphylaxis cases.¹⁷ In a survey of patients with anaphylaxis, 52% had never received an EAI prescription despite reporting 2 or more prior episodes, and 60% of patients with a prescription did not currently have their EAI available.¹⁸ In one study of children with anaphylaxis (n = 292) identified from 3 EDs and an emergency medical response service, epinephrine was used outside a healthcare facility only 51% of the time.¹⁹ Patients and caregivers underuse epinephrine with some of the more common reasons reported as follows²⁰: patient was unsure if they needed to inject, patient was afraid to inject, EAI was difficult to use, EAI was not accessible when anaphylaxis occurred, and patient used another medication (eg, H₁-antihistamine or asthma inhaler).

There have also been reported cases of unintentional injection in a finger, thumb, or hand.²⁰ This is a cause of injury and a wasted and lost dose during an emergency. Furthermore, some patients at risk for anaphylaxis do not always carry their prescribed EAI. Education by the allergy community is needed to address these issues.

Does Time to Epinephrine Matter?

It is important to recognize that, although rare, deaths continue to occur from anaphylaxis. Among postmortem anaphylaxis case reviews,^{13,14} the time to cardiac arrest or death can be measured in minutes. For example, the median time to respiratory or cardiac arrest reported by Pumphrey et al¹⁴ was 30 minutes for foods, 15 minutes for venom, and 5 minutes for iatrogenic reactions. Greenberger et al¹³ observed from fatal cases of anaphylaxis that severe reactions occurred in less than 30 minutes from exposure in nearly every case and that death began within 60 minutes in approximately half of all cases. Respiratory compromise and cardiovascular collapse are the most frequent causes of fatalities.^{13,14} Given the fact that most episodes of nonparental medication-induced anaphylaxis starts outside a medical setting and given the timeline that is described above, it will almost always be the non-health care professional who must recognize anaphylaxis, initiate treatment, prevent the progression of symptoms, and reduce the risk of death. One could argue that it is less crucial which treatment is provided in the ED vs the outpatient setting because, as the timeline above suggests, the window of time for treatment to prevent fatalities may have already passed in some cases. Furthermore, emergency medical services often work with protocols that delay the administration of epinephrine until symptoms have reached a severe, potentially irreversible state. It is the patient, caregiver, teacher or school nurse, or community member who must recognize and initiate treatment for anaphylaxis. Common features of fatal food anaphylaxis, which occur in 30% of fatal cases, include the following¹³: reactions to tree nut and peanuts, a history of food allergy and asthma, and failure to administer epinephrine promptly. Furthermore, a mild reaction does not always guarantee that future reactions will also be mild. Many fatal food-related reactions have occurred in people with a previous mild reaction.²¹

Patients and Caregivers Should Carry 2 Doses of Epinephrine

Two doses of epinephrine may be required in approximately 20% to as high as 36% of cases of anaphylaxis.²² Risk factors for prescribing a second dose are lack of rapid access to medical assistance, a previous event requiring a second dose before reaching emergency medical care, a previous near-fatal anaphylactic episode, high body weight, and the presence of asthma.²³ There are 3 main reasons why patients should carry 2 doses of epinephrine at all times: (1) the reaction may be severe and not resolve with a single dose; (2) loss of the first dose because of an error in the administration of the injection (eg, unintentional self-injection by caregiver or patient to thumb or fingers)²⁴; and (3) a biphasic or protracted reaction (ie, second phase occurring an hour or more after the onset of the first phase or reactions lasting several hours, respectively). Biphasic anaphylaxis is believed to occur in up to at least 23% of reactions.²⁵ Risk factors for biphasic reactions include the following: initial phase severity, delayed or suboptimal doses of epinephrine given during initial treatment, laryngeal edema or hypotension during initial phase, delayed symptomatic onset after antigen exposure, and history of a previous biphasic event. Furthermore, mild symptoms presenting at the onset of anaphylaxis can progress to severe, life-threatening symptoms rapidly or after a delay of several minutes. When one dose is not effective, a patient carrying 2 EAI's can administer a second dose while waiting for emergency medical services. It is also for these reasons that observation periods and follow-up should be individualized.

Evolution and Attributes of EAI's

The history and development of EAI's in the United States continue to evolve (Table 1). Physicians and other health care professionals should be familiar with the history and evolution of available devices, including important engineered features, because current EAI's are not the same. Furthermore, anyone from a young child to an adult may have to use an EAI for anaphylaxis; therefore, it is important that practitioners are able to educate their patients on the appropriate use of each device during an allergic emergency. Practitioners should also be familiar with the attributes of each device (Table 2). Pen-style EAI's have similar attributes and functionality, and the major differences between EpiPen devices and Adrenaclick devices are the extra cap to remove before injection, a 10-second hold vs a 3-second hold, and the absence of a needle guard (ie, the needle remains exposed) after injection with the latter. Recently, the Auvi-Q was reintroduced by Kaléo and was engineered differently than pen-style EAI's. Auvi-Q, unlike other EAI's, has audio and visual cues to assist patients during an allergic emergency. It also was engineered with an autoretractable needle and to be pocket-sized, which may improve carry rates in populations such as teenagers.

EAI Safety

Injuries have occurred in children (N = 22) using EpiPen, primarily toddlers.²⁶ Lacerations to the leg (n = 17), embedded needles (n = 4), and 1-digit laceration in a nurse have been reported. Embedded needles were suspected to be possible unintentional bone injections after radiographic imaging. The package inserts of pen-style EAI's were updated in 2016 to include an additional warning that states, "Hold leg firmly during injection. Lacerations, bent needles, and embedded needles have been reported when [EpiPen, EpiPen Jr and Adrenaclick] have been injected into the thigh of young children who are uncooperative and kick or move during an injection." It might be expected that an immediately retractable needle, or needless delivery method, would prevent these types of adverse events.

Table 1
Anaphylaxis- and EAI-Related Milestones in the United States

Year	Milestones
1987	EpiPen is approved by FDA
2005	Twinject launched by Verus Pharmaceuticals
2008	Sciele Pharma acquires Twinject and was then bought by Shionogi
2009	FDA allows EpiPen to be marketed to anyone at risk for anaphylaxis Previously, the autoinjector could be marketed only to patients with a history of an anaphylactic reaction
2010	EpiPen redesigned with stronger spring and improved safety features Sciele/Shionogi face recalls of Twinject Branded and generic versions of Adrenaclick are launched in the United States by Shionogi and Greenstone, respectively NIAID guidelines for the diagnosis and management of food allergy published in the <i>Journal of Allergy and Clinical Immunology</i> Updated Joint Task (AAAAI/ACAAI/JCAAI) Force Practice Parameter on the management of anaphylaxis published the <i>Journal of Allergy and Clinical Immunology</i> . Guidelines recommend that patients be prescribed 2 doses of epinephrine instead of one
2012	Shionogi discontinued Twinject, Adrenaclick, and the authorized generic Mylan launches the EpiPen4Schools program, which offers free and discounted EpiPens to schools
2013	Auvi-Q launches in the United States after receiving FDA approval in late 2012 Branded and generic versions of Adrenaclick are relaunched into the US market by Amedra and Lineage Therapeutics, respectively Centers for Disease Control and Prevention releases voluntary guidelines recommending that schools keep multiple doses of epinephrine available on site The federal School Access to Emergency Epinephrine Act becomes law
2014	Updated Joint Task (AAAAI/ACAAI/JCAAI) Force Practice Parameter on food allergy published the <i>Journal of Allergy and Clinical Immunology</i>
2015	Impax Laboratories acquires Amedra and Lineage Therapeutics and the Adrenaclick and its authorized generic Sanofi voluntarily recalls the Auvi-Q Updated Joint Task (AAAAI/ACAAI/JCAAI) Force Practice Parameter on the management of anaphylaxis published the <i>Annals of Allergy, Asthma & Immunology</i>
2016	Prescribing information for pen-style EAI's updated with warnings on lacerations and embedded needles in children Mylan introduces a generic version of the EpiPen in the United States
2017	Authorized generic of the Adrenaclick offered at CVS pharmacies Kaléo relaunches Auvi-Q in the United States Mylan issues EpiPen recall for reported device activation failures

Abbreviations: AAAAI/ACAAI, American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma, and Immunology; EAI, epinephrine autoinjector; FDA, US Food and Drug Administration; NIAID, National Institute of Allergy and Infectious Diseases.

Is Needle Length an Issue of Safety, Efficacy, or Both?

Recently, the needle length of available EAI's has become a topic of controversy.^{27–29} This is based on a few lines of recent evidence.

Although epinephrine administered by an EpiPen is delivered at a depth over double the length of the needle (attributable to compression of tissue and propulsive forces), the propulsive force might not be sufficient to allow penetration of the fluid through the fascial plane and therefore result in subcutaneous rather than intramuscular deposition. This is especially true if the patient has a skin-to-muscle depth greater than the needle length of available EAI's (ie, depth of subcutaneous adiposity). This would in turn alter the pharmacokinetic profile of the injection, resulting in a delayed time to reach maximum serum concentration. Needle penetration of the fascial plane is not required to ensure intramuscular delivery. Needle-free injection technology (Bioject from Inovio Pharmaceuticals and Zeneo from Crossject) delivers intramuscular liquid preparations with consistency.^{30,31} Therefore, whether delivery to the muscle with a needle length unable to reach the muscle itself is dependent on the propulsive force of the device has not been thoroughly investigated. However, it may be that penetration of the needle may not be necessary if the propulsive force of a given device is enough to propel drug across the fascial plane and into the muscle. This information is currently unavailable. In response to this possibility, however, an EAI (Emerade, Namtall AB and Medeca Pharma AB) is available in Europe with a needle length of approximately 1.0 in for adults and approximately 0.63 in for children. The risk in using an EAI with a needle length of the latter in infants may be unintentional penetration of the bone.

It is possible that the needle in available pediatric EAI's (indicated for patients weighing 15–30 kg) could strike the bone in patients weighing less than 15 kg and is based on skin-to-bone depth.^{32,33} One study found that 29% of children weighing less than 15 kg (N = 100) had a skin-to-bone depth (with maximal pressure during a simulated injection) less than 12.7 mm (12.7 mm [0.5 in] is the needle length of available pediatric EAI's), which would put them at risk for an unintentional bone injection.³² In the subgroup of children weighing less than 10 kg in this study, 60% would be at risk for unintentional injection to the bone.³² A more recent study of children weighing between 7.5 and 15 kg (n = 51) found that applying 10 lb of pressure with a pediatric EAI (needle length of 12.7 mm) would put 43.1% of these patients at risk of an unintentional bone injection.³³ This study determined that the appropriate needle length for children weighing 7.5 to 15 kg would be 7 to 8 mm (0.28 to 0.31 in). In fact, it has been suggested that available pediatric EAI's may put some children who weigh 15 to 30 kg at risk for unintentional bone injections as well.³⁴ These data suggest that a new device, one with a shorter needle length, may be necessary to ensure safe injections in

Table 2
Attributes of Currently Available Epinephrine Autoinjectors in the United States^a

Attribute	Auvi-Q	EpiPen ^b	Adrenaclick ^b
Manufacturer	Kaléo	Mylan	Amedra
Dosages, mg	0.15, 0.3	0.15, 0.3	0.15, 0.3
Trainer	Yes	Yes	No
Supplied	2-pack	2-pack	2-pack
Needle gauge	23 ^c	22 ^d	25 ^d
Exposed needle length	0.62 in for 0.3 mg ^c 0.5 in for 0.15 mg ^c	0.58 in for 0.3 mg ^d 0.51 in for 0.15 mg ^d	0.52 in for 0.3 mg ^d 0.51 in for 0.15 mg ^d
Injection hold time	5 seconds, no massage	3 seconds, 10-second massage	10 seconds, 10-second massage
Directions for injection technique	"Place end against thigh, press and hold"	"Swing and push until click"	"Put tip against thigh, press down and hold"
Needle guard	Yes	Yes	Blue cap needle guard before device is used, but no sharps injury protection after injection
Autoretractable Needle	Yes	No	No
Talking feature	Yes	No	No

^aAttributes excerpted from the prescribing information for each respective autoinjector except where noted.

^bGeneric alternatives for the EpiPen and Adrenaclick are available in the United States.

^cKaléo medical information query, oral communication, 2017.

^dData taken from Simons and Simons.²⁰

children weighing less than 15 kg. There are no formal guidelines or recommendations supporting what the appropriate needle length is for children weighing less than 15 kg, and this continues to be an unmet need. However, a device with shorter, autoretractable needles may prevent unintended injuries in our youngest patients.

Using an EAI: Does the Device Matter?

In some studies, patients have demonstrated greater success with the administration of and preference for a specific EAI vs another. In one study, patients correctly followed instructions for and preferred Auvi-Q vs EpiPen in areas of safety, clarity of instructions, ease of use, ease of carrying, shape, and size.³⁵ In a large simulated-use study, patients preferred Auvi-Q over EpiPen on all primary study end points ($P < .001$), which included preference for device size, device shape, method of instruction, and whether it was easy to carry.³⁶ In a more recent study of mothers of children with anaphylaxis ($N = 158$), participants were randomized to EpiPen or Anapen for 1 year and then switched to a new device without specific training.³⁷ Importantly, after the switch from EpiPen or Anapen to another device, successful administration rates were higher with Auvi-Q than with other devices (93% vs 49%; $P < .001$). Regardless of which device is prescribed, it is important that the patient be trained on the device. Instructions are unique for each device, and they are not interchangeable. Therefore, generic substitution at the pharmacy should not occur.

Future of Epinephrine Delivery and Device Development for Anaphylaxis

As EAI continue to develop, it may be worth looking at how the delivery of epinephrine may change in the future. The following is list of a few products on the horizon in the United States and the features that may help improve future EAI.

- Device that is smaller, is more portable, and may have a more innovative design (eg, AdrenaCard, Abiliject, Epi-Bracelet—concept products on the horizon in the United States)
- Different delivery options for epinephrine (eg, needleless injection,^{30,31} sublingual³⁸)
- EAI with needle lengths appropriate for individual patient needs (ie, accounting for age and skin-to-muscle depth^{29,32–34})
- EAI with 2 autoinjectable doses in 1 device
- EAI made with a 0.1-mg dose of epinephrine for infants
- EAI made with a 0.5- or 0.75-mg dose of epinephrine for larger adults
- Better temperature stability and longer shelf life for epinephrine (eg, epinephrine stored as dry powder and then reconstituted when needed, epinephrine vs epinephrine tartrate or bitartrate)
- Impact and weather-resistant casing
- More intuitive and easier to use
 - Indicators that let the patient know that the dose was successfully delivered
 - One-touch device activation before injection
- Less expensive

Discussion

Anaphylaxis is increasing, particularly in younger children, and timely and correct use of EAI can prevent fatalities. Every effort should be made to identify triggers and accurately diagnose patients with suspected or proven anaphylaxis. More intuitive EAI design and features that promote safe and efficient EAI use in patients under stress during a reaction are favorable in current and future autoinjector designs. For example, having an EAI for

infants and toddlers with a needle length that accounts for their skin-to-bone depth will be important for preventing potential EAI-related injuries to the bone, which remains an area of unmet need. Ensuring patients have 2 EAI, regular device training, and referral to an allergy specialist after, or preferably before, an ED visit can help patients successfully manage a future life-threatening allergic reaction. Increased vigilance for anaphylaxis in younger age groups and public education by the allergist community is necessary to combat this increasing health care issue.

Acknowledgment

We thank Sandi Ward, MA, for editorial assistance on the manuscript.

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