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Contemporary issues in anaphylaxis and the evolution of epinephrine autoinjectors

What will the future bring?

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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.

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 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

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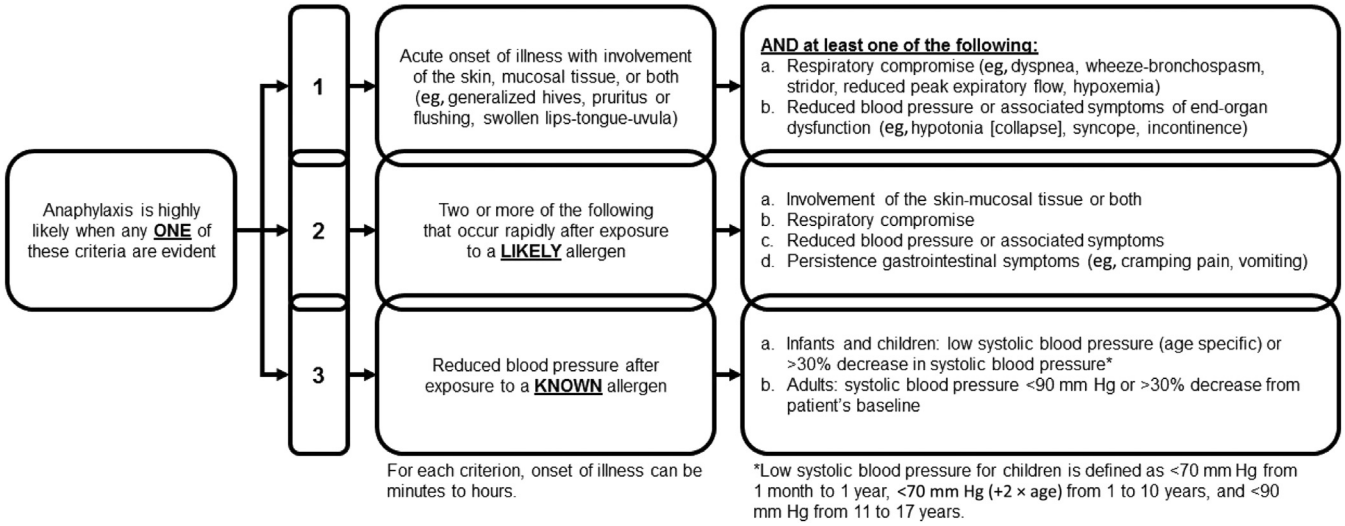

Figure 1. National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network Clinical Criteria for Anaphylaxis. Adapted from *J Allergy Clin Immunol* 117(2), Sampson HA et al, Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, Pages 391-397, Copyright 2006[7], 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 (EAIs), safety of EAIs, adequacy of needle length in available pediatric EAIs, 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 placed 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 $\geq$2 organ systems or hypotension), high proportions were inappropriately treated with corticosteroids (78%), histamine$_1$ (H_1)– or histamine$_2$ (H_2)–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.