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Abstract

Anaphylaxis is common in children and has many differences across age groups. A systematic review of the literature from the past 5 years was conducted with the goal of updating the pediatrician. Food is the most common trigger in children, but insect venom and drugs are other typical causes. Clinical diagnostic criteria include dermatological, respiratory, cardiovascular, and gastrointestinal manifestations. A biphasic reaction is seen in some, with recurrence usually within 8 hours of the initial episode. Epinephrine is the drug of choice for acute reactions and the only medication shown to be lifesaving when administered promptly, but it is underutilized. Patients should have ready access to ≥ 2 doses of an epinephrine autoinjector, with thorough training regarding correct use of a given device and an emergency action plan. Management of anaphylaxis in schools presents distinct challenges. Pediatricians are in a unique position to assess and treat these patients chronically.

Keywords

anaphylaxis, hypersensitivity, epinephrine, schools

Introduction

As defined by the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy & Anaphylaxis Network (FAAN)^{*}, anaphylaxis is “a serious allergic reaction that is rapid in onset and may cause death” and typically involves ≥ 2 organ systems.¹ It has been estimated that food allergy (FA) causes an emergency department (ED) visit every 3 minutes on average in the United States, with a food-induced anaphylaxis visit every 6 minutes.²

In addition to differences in comorbid conditions, risk factors, clinical manifestations, and so on compared with adults, there are differences within the pediatric age range itself. For example, preverbal infants may have difficulty expressing symptoms. The growing independence of teens results in more meals being taken outside the home. Peer pressure for adolescents may cause increased risk-taking behavior and reluctance to carry an epinephrine autoinjector (EAI). Other issues are related to the EAI, including whether the device is carried and/or administered by a caregiver or the patient and use in the school or day care setting. Finally, there are often questions regarding the safety of childhood vaccines, particularly in patients allergic to eggs.

In recent years, guidelines regarding the diagnosis and management of FA in particular have been published,

including those of the NIAID and World Allergy Organization (WAO),^{3,4} which were updated recently with additional supporting data.⁵ However, these guidelines are age independent and do not specifically address all issues related to children and adolescents. Pediatricians must be aware of current guidelines regarding anaphylaxis and how the presentation and management may differ from adults. This review is intended to update the pediatrician on the importance of this topic and literature published in the past 5 years.

Systematic Review Methods

To define the scope of this broad topic, a systematic review was conducted. MEDLINE and Embase were searched from June 2007 through May 2012 using the following search parameters: (anaphylaxis OR anaphylactic) AND (pediatric OR adolescent OR youth OR child). The results were limited to articles discussing humans and published in English. To make the search manageable, allergy not including anaphylaxis was

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excluded. Immunotherapy and food desensitization are not discussed at length in this review and, therefore, were also excluded. Finally, congress abstracts specifically were excluded. From the original literature search, articles were excluded manually if they were duplicates, not relevant to the topic, or focused on a situation primarily applicable to an audience outside of the United States. The original search resulted in 248 articles meeting criteria, with manual elimination of 103 and 145 articles remaining. Articles were later added if they were known to the author or in bibliographies of articles that were already found, even if they did not meet the search criteria themselves.

Epidemiology

The incidence of allergy and anaphylaxis is rising in developed countries, particularly in the youngest children.⁶⁻⁸ The precise incidence and prevalence is extremely variable as a result of differing definitions of anaphylaxis, underdiagnosis, underreporting, and other factors. In addition to changing frequency, symptom severity also may be increasing.⁸

A number of risk factors have been associated with anaphylaxis. The most commonly cited is asthma, with rising severity of pulmonary disease associated with increased risk.⁶ Asthma has been shown to be associated with a 4.0-fold risk of FA in children.⁹ Atopic dermatitis (2.4-fold increase) and respiratory allergies (3.6-fold increase) also have been linked to risk of anaphylaxis. The severity of an anaphylactic reaction cannot be predicted based on past reactions or diagnostic/laboratory tests, but comorbid asthma is the factor most often linked to severe reactions.⁹

Latitudes with reduced sunlight (eg, northern regions of the United States) have been associated with increased risk for anaphylaxis, perhaps positing a role for vitamin D insufficiency.⁶ In support, the prescribing of EpiPen in the United States was reported to be higher in the northern states and regions compared with the southern regions.¹⁰

Triggers

Foods

Outside of the hospital, foods are the most common triggers for anaphylactic reactions in children and adolescents.⁷ The prevalence of FA in this group in the United States is approximately 5% to 6%, with an 18% increase over the first decade of the 2000s. Up to half of the ED visits in the United States resulting from FAs are attributed to anaphylaxis, with about 150 to 200 deaths per year.

Because the main preventive approach for anaphylaxis is to avoid allergens entirely, FA presents a significant burden for caregivers and patients when shopping for groceries and eating meals. Resulting anxiety and other stressors may affect quality of life in caregivers and patients. The economic costs are not limited merely to persons affected directly but also to the health care system and society as a whole. One study has estimated that the US costs in 2007 for FA and associated anaphylaxis were \$307 million in direct costs and \$203 million in indirect costs, for a total exceeding \$500 million.⁷ Mean costs per ED visit of \$553 and per hospitalization of \$4719 were higher than previous cost estimates for asthma of \$345 and \$4570 per ED visit and hospitalization, respectively. Intangible costs, such as quality of life, EAs dispensed but not used, and self-treatment, were not included, so true costs are likely substantially higher.

The spectrum of foods causing allergy is wide and varies among countries, although peanuts, tree nuts, and seafood are common causes.⁶ In a study of 605 children presenting to an ED with FA, food triggers also varied across age groups (Table 1).¹¹ At the time of ED presentation, infants (age <2 years) were less likely to have prior diagnoses of FA or another allergic disorder (27% and 63%, respectively). However, older age groups (ages 2-18 years) still only had a prior diagnosis of FA in 48% to 57% ($P = .004$ across groups) or another allergic disorder in 80% to 86% ($P = .001$ across groups) of patients, respectively. Thus, anaphylaxis should be considered even in the absence of a history of allergic disorders.

When evaluating the presence of food triggers, consider foods given outside the home or caregiver's control (eg, in school or at a friend's). For infants, also consider indirect exposure to allergens through breastfeeding.⁹ For example, in a study of children allergic to peanuts, the annual rate of accidental exposure was 12.5%.¹² Most accidental exposures occurred at home (39.5%), but 16.5% occurred in another home and 10.9% occurred in restaurants. Most children in this study attended schools that prohibited peanuts, so the incidence at school was low. Consistent with increased independence, patients aged ≥ 13 years had increased risk (odds ratio [OR] = 2.33; 95% confidence interval [CI] = 1.20-4.53).

In addition to accidental exposures, the rising use of oral immunotherapy may increase the risk of iatrogenic anaphylaxis.⁶ Some studies of this treatment approach have shown that biphasic reactions may be more frequent, so health care professionals (HCPs), caregivers, and patients must be alert for anaphylaxis in and after leaving the office. Some patients may have exercise-induced anaphylaxis after ingestion of certain foods, typically within 2 hours.^{3,6,13}

Table 1. Food Triggers Among Children Presenting to the Emergency Department, Percentage (95% CI)^a

	Infants (<2 years), n = 191	Preschool Aged (2-5 years), n = 171	School Aged (6-11 years), n = 150	Adolescents (12-18 years), n = 145
Peanuts ^b	31 (20-43)	26 (17-36)	22 (13-32)	10 (7-13)
Tree nuts ^b	9 (4-14)	28 (18-38)	21 (9-33)	20 (12-28)
Seeds	0	— ^c	— ^c	— ^c
Fruits/Vegetables ^b	4 (0-9)	7 (0-13)	6 (0-11)	19 (7-32)
Shellfish	— ^c	— ^c	— ^c	22 (10-35)
Fish	— ^c	— ^c	— ^c	— ^c
Food additives	— ^c	0	0	— ^c
Milk products ^b	40 (28-51)	16 (7-26)	13 (4-21)	— ^c
Eggs	9 (3-16)	— ^c	— ^c	— ^c
Wheat	— ^c	— ^c	0	0
Other	13 (5-22)	22 (11-24)	28 (14-42)	20 (10-31)

Abbreviation: CI, confidence interval.

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^b $P \leq .02$ across age groups. mm Hg + [2 × age] from 1 to 10 years, and <90 mm Hg from 11 to 17 years

^cNot calculated because of an insufficient number of observations.

As children age, a natural tolerance develops to many food allergens.⁹ Tolerance usually evolves by the teen years to cow's milk, eggs, soy, and wheat, with tolerance to peanuts, tree nuts, fish, and shellfish occurring less often. Risk factors for persistence of FA include baseline high levels of allergen-specific IgE, other atopic disorders, and multiple-food allergy.

Insect Venom

Allergy to stinging insects (order Hymenoptera) is most common in the United States, but specific insects vary across regions/countries. Patients with allergy to insect venom may be at special risk of a biphasic reaction, with 16% requiring a second epinephrine injection among 153 patients in Boston (age interquartile range, 14-51 years), thus potentially affecting need for prescription of a second EAI.¹⁴ This study was a chart review of all admissions to the pediatric EDs of 3 major academic medical centers for stinging insect hypersensitivity reactions from 2001 through 2006.

Medications, Recreational Drugs, and Latex

Anaphylactic reactions to medications may be either IgE mediated (eg, penicillins and anesthetics) or non-IgE mediated (eg, nonsteroidal anti-inflammatory drugs and radiocontrast dye).⁶ Adolescents in particular may experiment with recreational drugs, exposing themselves to other potential allergens. Reactions also may be caused by allergen skin tests, food/medication

challenges, immunotherapy, and medication desensitization.⁴ Latex is prevalent in both the hospital and community settings (eg, pacifiers, toys, and sports equipment) and is a common allergen.

Vaccines may contain allergens (eg, egg protein and gelatin) or be packaged in vials with latex stoppers, but anaphylactic reactions occur with only about 1 per million doses, with probable anaphylaxis defined as a reaction occurring within 4 hours of vaccine administration and involving at least 1 of the following systems: dermatological, respiratory, cardiovascular, or gastrointestinal (GI).¹⁵ Patients with suspected delayed or immediate hypersensitivity reactions should be evaluated by an allergist. If subsequent evaluation by an allergist demonstrates or raises suspicion that the reaction was IgE mediated, further doses should be administered with epinephrine available and/or using graded doses. However, the risk of subsequent reaction is almost always less than the benefits of full vaccination. For further recommendations, see the complete guidelines from the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma and Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology.

Clinical Features of Anaphylaxis

In 2005, the NIAID and FAAN updated their criteria for the clinical diagnosis of anaphylaxis (Table 2).¹ These criteria have been adopted widely. In this statement, anaphylaxis was defined as "a serious allergic reaction that is rapid in onset and may cause death." Participants

Table 2. Clinical Criteria for Diagnosing Anaphylaxis^a

Anaphylaxis is highly likely when any of the following 3 criteria are met:

1. Acute onset (minutes to several hours) of an illness with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritis or flushing, swollen lips/tongue/uvula)

AND AT LEAST 1 OF THE FOLLOWING:

- a. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
- b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly (minutes to several hours) after exposure to a likely allergen for that patient:
 - 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 PEF, hypoxemia)
 - c. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Rapid (minutes to several hours) reduction in BP after exposure to known allergen for that patient:
 - a. Infants and children: low systolic BP (age specific)^b or >30% decrease in systolic BP
 - b. Adults: systolic BP <90 mm Hg or >30% decrease from that person's baseline

Abbreviation: BP, blood pressure; PEF, peak expiratory flow.

^aReprinted from Sampson et al.¹ Copyright 2006, with permission from Elsevier.

^bLow systolic BP for children is defined as <70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and <90 mm Hg from 11 to 17 years.

in the development of these consensus criteria believe that they will diagnose 95% of cases of anaphylaxis. It is important to note that up to 20% of patients have no dermatological findings, and GI symptoms, which often may not be associated with anaphylaxis, are included in the diagnostic criteria because they have been linked to poor outcomes in anaphylactic reactions. These criteria recently have been validated in ED patients, with 97% sensitivity and 82% specificity.⁵

Manifestations varied among age groups in 605 pediatric patients presenting to an ED over a 6-month period (Table 3).¹¹ As expected, dermatological signs and symptoms were prominent, with cutaneous involvement in >85% of all age groups. Respiratory manifestations were noted in 59% to 81% of the youngest groups, and the GI system was involved in ≥50% of all ages. Cardiovascular signs and symptoms were rarely observed, mostly in adolescents; however, a previous study has shown that hypotension may go unnoticed in infants.¹⁶ Anaphylaxis was underdiagnosed, with only 14% of children who met the criteria for anaphylaxis discharged from the ED with a code that included this term; this was reduced further to 6% among infants.

Additional signs and symptoms of anaphylaxis include tachycardia; conjunctival erythema and tearing; nasal congestion, rhinorrhea, and sneezing; and irritability, altered mental state, and loss of consciousness.^{3,4} It is particularly important to remember that infants and young children may have difficulty expressing symptoms compared with adolescents or adults. At onset, it may be difficult to predict the rate of progression of a reaction (eg, mild symptoms may progress rapidly to severe or life-threatening ones).⁴

A biphasic reaction is defined as the recurrence of symptoms after resolution of the initial manifestations.^{9,17} Such reactions occur in about 6% to 11% of children.^{3,4,17} Biphasic reactions generally occur within 8 hours of the first episode, but they may manifest up to 72 hours later.^{9,17,18} Awareness of this issue is critical for management of anaphylaxis. Biphasic reactions emphasize the importance of the availability of a second EAI and may necessitate retreatment after discharge from an ED.

Diagnosis and Testing

The cornerstone of diagnosis is a thorough medical history and physical examination, with a classic presentation of sudden onset of signs and symptoms after exposure to a known trigger. However, HCPs must be alert because some patients may be experiencing an allergic reaction for the first time or have no obvious triggers. In addition, atypical signs and symptoms may predominate.

In the acute setting, laboratory tests such as serum tryptase are of limited value.^{3,4} Optimally, tryptase should be drawn 15 minutes to 3 hours after clinical onset.⁴ Tryptase is not specific for anaphylaxis or available at all laboratories. When anaphylaxis is suspected, an elevated tryptase may support the diagnosis; however, normal levels do not exclude anaphylaxis, particularly in FA. A baseline level after resolution of a reaction and serial measurement during an anaphylactic episode may be more useful.

Other diagnostic tests include the skin prick test and total and allergen-specific IgE; however, these tests are

Table 3. Clinical Presentation Among Children Presenting to the ED Who Met the Clinical Diagnostic Criteria for Anaphylaxis, Percentage (95% CI)^a

	Infants (<2 years), n = 191	Preschool Aged (2-5 years), n = 171	School Aged (6-11 years), n = 150	Adolescents (12-18 years), n = 145
Organ system involvement				
Cutaneous	98 (94-100)	95 (90-99)	92 (87-99)	87 (78-96)
Respiratory	59 (47-71)	81 (72-89)	70 (56-83)	71 (58-83)
Gastrointestinal	56 (44-67)	50 (38-61)	59 (45-72)	59 (46-72)
Cardiovascular ^b	— ^c	— ^c	— ^c	12 (4-20)
Signs and symptoms				
Hives ^b	89 (79-97)	78 (69-88)	64 (51-77)	59 (46-72)
Swelling	53 (41-65)	56 (45-68)	44 (30-57)	36 (24-48)
Nausea/Vomiting ^b	53 (41-65)	34 (24-45)	29 (17-42)	17 (9-26)
Trouble breathing/ Shortness of breath	37 (26-48)	34 (23-45)	39 (27-52)	57 (44-70)
Wheezing ^b	29 (20-39)	55 (43-66)	42 (29-56)	23 (13-32)
Itching ^b	19 (10-29)	29 (18-40)	54 (40-67)	36 (24-48)
Stridor ^b	5 (3-7)	10 (2-18)	— ^c	— ^c
Dizziness/Fainting	0	0	— ^c	12 (4-20)
Abdominal pain/Cramps	0	— ^c	12 (3-21)	— ^c
Trouble swallowing ^b	— ^c	18 (8-29)	41 (27-55)	48 (35-61)
Hoarse voice	— ^c	12 (4-19)	— ^c	13 (3-22)
Diarrhea	— ^c	0	0	— ^c
Altered mental state	— ^c	— ^c	— ^c	0
Angioedema	— ^c	— ^c	— ^c	— ^c
ED discharge diagnosis included the term <i>anaphylaxis</i> ^b	6 (3-9)	25 (14-37)	13 (7-19)	13 (1-24)

Abbreviation: ED, emergency department.

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not diagnostic when performed in isolation.³ The gold standard for diagnosis of FA is the double-blind, placebo-controlled food challenge.³ See guidelines for further discussion regarding testing and differential diagnosis.^{3-5,19}

Management of an Acute Reaction

Epinephrine and many antihistamines and corticosteroids were used for anaphylaxis before the prevalence of randomized controlled trials; thus, uncontrolled trials, case reports, and expert opinion are often used to support recommendations.⁴ However, even given the dearth of randomized controlled trials, epinephrine has emerged as the consensus drug of choice for treatment of acute reactions.^{3,4}

To expedite delivery of appropriate care, an institution should have a protocol for management, including ready access to necessary supplies and equipment. Examples of protocols and supply lists are shown in the WAO guidelines.⁴ Acute care of anaphylaxis should be

rehearsed periodically. In a before-after study of a pediatric ED, implementation of a protocol for anaphylaxis management significantly improved treatment.²⁰ Over 4 years, 1673 discharge summaries were reviewed for visits relating to suspected allergy or anaphylaxis, with 64 cases of anaphylaxis identified. After introduction of the protocol, significant improvements were seen for epinephrine administration (27% vs 57.6% [$P = .012$]); prescription of an EAI (6.7% vs 54.5% [$P = .005$]); admission to an emergency observation area (49.0% vs 84.8% [$P = .003$]); time in the emergency observation area (2.5 hours vs 9 hours [$P = .003$]); use of corticosteroid monotherapy (29% vs 3% [$P = .005$]); and discharge without follow-up instructions (69% vs 22% [$P = .001$]).

Epinephrine

Prompt administration of epinephrine is first-line therapy during acute anaphylaxis.^{3,4,18} Epinephrine is the only medication that has exhibited lifesaving properties,⁴ and delays in administration have been associated

with increased morbidity, mortality, and the incidence of biphasic reactions.^{3,4,18} A pharmacokinetic study of the recently approved EAI Auvi-Q reports slower absorption of epinephrine compared with EpiPen (median $T_{\max}$ of 20 minutes with Auvi-Q [$n=67$] versus 10 minutes with EpiPen [$n=135$]).²¹ The clinical significance of the delayed absorption of Auvi-Q has not been established. All other treatments have a delayed onset of action.³ Even in the event of failure of an initial dose of epinephrine to resolve symptoms, repeat dosing is preferred over other therapies.³

Concurrently with administration of epinephrine, further exposure to the allergen should be eliminated.^{3,4} The caregiver or the patient should immediately call for help (eg, 911), although this should not delay use of epinephrine. In part to avoid the empty ventricle syndrome, in which severe hypotension leads to inadequate filling of the heart, the patient should be placed in a recumbent position (if tolerated) with the lower extremities elevated; patients developing this syndrome may not respond to epinephrine because of poor circulation. Cardiopulmonary resuscitation should be implemented as needed, quickly followed by supplemental oxygen and volume resuscitation with intravenous (IV) fluids.

The recommended dose of epinephrine is 0.01 mg/kg of the 1:1000 solution, up to a maximum of 0.3 mg in children (0.5 mg in adults).^{3,4} With the current EAIs, the 0.15-mg dose can be used for patients weighing <25 kg and 0.3 mg for those weighing >25 kg³; however, an exact dose (eg, 0.05 mg for a 5-kg child) is preferable in small infants.⁴ Infants cannot describe symptoms of epinephrine overdose, so it is particularly important to monitor clinically for manifestations of hypertension and pulmonary edema. For small children, clinicians may have difficulty choosing the correct device¹⁸ and thus may prescribe none at all. For example, EpiPen and EpiPen Jr are indicated for patients weighing ≥ 30 kg and 15 to 30 kg, respectively.²² Auvi-Q also has 2 dosage formulations for the same weight ranges; however, although they use different colors, the 2 products have the same name, which may cause confusion among prescribers, patients, and caregivers. It is critical not to confuse the 1:1000 epinephrine solution with the 1:10 000 solution typically used for cardiac emergencies.

Intramuscular (IM) administration into the midanterolateral thigh is preferred, although epinephrine may also be given by the IV, intratracheal, or intraosseous route.^{3,4} Among other reasons why the IM route is preferred is that it provides a faster rise in plasma and tissue concentrations than subcutaneous administration.^{3,4,18} With IM administration, injection into the thigh has shown peak serum concentrations about 5 times greater than when given via the deltoid muscle.¹⁸ The needle length of available EAIs may not be adequate to penetrate subcutaneous

fat in obese children¹⁸; however, force of administration is also a factor in the delivery of IM epinephrine.

Because of the short half-life of epinephrine and other factors, repeat dosing may be needed after 5 to 15 minutes.^{3,4} Up to 20% of patients may require >1 dose for resolution.³ The optimal time interval for repeat dosing has not been studied prospectively; however, redosing may occur >15 minutes after the first dose,³ and this almost certainly is too long.

Epinephrine often causes mild, transient adverse effects (eg, anxiety, tremor, headache, and dizziness) at therapeutic doses used for anaphylaxis.^{3,4} It rarely may cause severe cardiovascular adverse effects (eg, myocardial infarction, increased blood pressure, intracranial hemorrhage, and arrhythmias)^{3,4}; however, these are typically seen with overdose (eg, use of 1:1000 rather than 1:10 000 solution for IV administration).^{3,4} Concern over possible severe adverse effects may lead to delays in use by HCPs, but it must be stressed that there are no absolute contraindications to epinephrine in this setting, and it should be given when in doubt as to the diagnosis.³ It also should be noted that acute coronary syndrome may develop with anaphylaxis even in the absence of epinephrine, including in those with subclinical disease and children.⁴

Adjuncts

Other medications should be given only after epinephrine, but then may be given concurrently.³ Antihistamines may include H_1 blockers (eg, diphenhydramine and cetirizine) and/or H_2 blockers (eg, ranitidine).^{3,4} However, very little evidence supports their use for treatment of acute anaphylaxis; H_1 antihistamines are useful for urticaria, itching, and nasal/ocular symptoms, not respiratory, cardiovascular, or GI manifestations of anaphylaxis. Use of antihistamines is the most common reason for nonadministration of epinephrine, with their slow onset of action putting the patient at risk for progression to a life-threatening reaction.

There is also little evidence to either support or refute the use of corticosteroids, but their slow onset (4–6 hours) lends itself more to prevention of protracted or biphasic reactions than a benefit in the acute setting.^{3,4} If they are given, use should stop in 2 to 3 days, after the strongest potential for a biphasic reaction has passed. Like antihistamines, there is concern regarding inappropriate use as first-line therapy instead of epinephrine.

Inhaled β_2 -adrenergic bronchodilators (eg, albuterol) may help with lower respiratory tract symptoms.^{3,4} Other common adjunctive medications include vasopressors (other than epinephrine), atropine, and glucagon. Glucagon is used predominantly in patients

receiving β -blockers, who may be resistant to epinephrine and benefit from glucagon's β -receptor-independent cardiac effects.

Observation

There is no consensus regarding an observation period after resolution of the initial reaction^{3,18}; however, 4 to 6 hours seems reasonable to safely monitor for most biphasic reactions. Patients with severe or refractory symptoms should undergo prolonged observation or hospital admission.

Management After Discharge and Prevention of Recurrence

After discharge, every patient should have an anaphylaxis emergency action plan (EAP).^{3,4,23} Every plan should include symptoms of anaphylaxis; when to use an EAI, dosing, and so on; instructions to call for help (eg, 911 and rescue squad) in the event of an anaphylactic reaction; and directions to obtain medical information jewelry. In a study of 63 children with FA at an Atlanta clinic (mean age = 6.40 years), only 6% had a medical alert bracelet in the office,²⁴ demonstrating a need for significant improvement.

Patients should receive a prescription at discharge for at least 2 doses of an EAI.^{3,4} Dual doses should be kept together to address biphasic or protracted reactions, rather than split up and kept in different locations. A second dose may be needed within 5 to 15 minutes of the first. This should not be confused with a biphasic reaction, which may not manifest until hours after the initial reaction. Different EAI may be needed for multiple sites (eg, home, school, and parent's purse). Direct provision of EAI is preferred, with immediate filling of a prescription secondary. EAI are indicated for all patients after an anaphylactic reaction and selected patients with simple allergy.

Prior to discharge, all patients and caregivers should receive verbal training for their EAI, with accompanying visual aid (eg, pamphlet and DVD).^{3,4} Training should emphasize the importance of carrying the device at all times and what to do at school or day care (which will vary depending on state law). All caregivers (eg, family and friends) should subsequently be trained properly to use the EAI and recognize manifestations of anaphylaxis.

Different devices have unique steps for use. Devices currently approved in the US are EpiPen, EpiPen Jr, Auvi-Q, and an authorized generic of Adrenaclick (the brand name of which is no longer available). The approved generic device should not be considered a generic for EpiPen or EpiPen Jr and should not

be substituted automatically. Proper administration technique is specific for each device, so training must be individualized to the device prescribed. In addition, a rapidly dissolving sublingual formulation of epinephrine is under development as an alternative to an EAI, and other devices and formulations for epinephrine are in development. Clinicians themselves may be unable to properly use an EAI. In 1 study, only 21% of pediatricians could correctly demonstrate use of the device.¹⁸ When giving training, HCPs must know how to properly use all devices prescribed in their setting or used by their patients.

On parental questionnaires at the aforementioned Atlanta clinic, 79% reported that they had been trained in epinephrine use, but only 59% had the EAI present at the office visit,²⁴ a finding consistent with other studies. This correlated directly on multivariate analysis with training (OR = 8.74; 95% CI = 1.45, 52.60). Only 33% reported that an EAI was available during lunch, with a significant difference between children aged <5 years versus ≥ 5 years (school-aged) (42% vs 25%, $P = .002$).

In a report of 15 Swedish children and adolescents (median age = 8 years; range = 7-18 years), anxiety decreased after training to self-administer epinephrine.²⁵ Patients received education, including time to practice with an EAI trainer, and then were asked to self-administer epinephrine. There was a decrease in the number of patients reporting that they were anxious or very anxious from 7 prior to the initial injection to one 2 weeks later. The authors postulated that decreased anxiety may lead to increased use of an EAI.

As mentioned before, many pediatric patients do not use an EAI during an anaphylactic episode.²⁶ Among 969 children and adolescents (mean age = 8.6 years) in the United Kingdom, 48.1% had an allergic reaction within the past year, including anaphylaxis in 25.3%. Of those experiencing anaphylaxis, only 16.7% used an EAI, despite loss of consciousness, difficulty swallowing, or wheeze occurring frequently. Common reasons why an EAI was not used were that it was felt to be unnecessary (54.4%) or uncertainty about the need (19.1%). Other reasons included the following: ambulance called (7.8%), device unavailable (5.4%), too scared to use it (2.5%), untrained (2.5%), or EAI expired (1.0%). Other studies also have reported a high rate of nonuse for epinephrine during anaphylaxis, including preferential use of an antihistamine or lack of a prescription for an EAI.²⁷

In interviews with 26 Scottish adolescents aged 13 to 19 years with a history of anaphylaxis, most acknowledged that they only carried the device some of the time, with responses ranging from "at all times" to "rarely."²⁸ However, only 1 person reported a failure to use an EAI during anaphylaxis as a result of not having the device at

hand. Reasons for failure to carry an EAI at all times included the perception of risk in specific circumstances and the size of the device. Barriers also included failure to recognize anaphylaxis, uncertainty about EAI technique or when to use, and fear of use.

A plan must be established and adhered to for monitoring EAI expiration dates, which are potent for only 1 year.^{3,4} In addition, the color of the fluid in the device (which should be clear) should be checked prior to use.³ Ideally, the prescriber should see the patient annually and check expiration dates firsthand at that time³; however, reminder calls or e-mails from the prescriber and/or pharmacy may be used instead or in addition. Devices should be stored at room temperature to avoid degradation (eg, not in a medicine cabinet or car glove compartment).³

In a study of 14 677 patients who had an initial filling of EpiPen or EpiPen Jr from a US health maintenance organization in 2000 through 2006, only 46% had a refill.²⁹ Among patients in the cohort for ≥ 5 years, only 25% had multiple refills and 11% refilled consistently at all expected times. Children aged 7 to 12 years were less likely to have refills than those younger (57% vs 67%). Adolescents were not analyzed because the authors thought that this age group would be more likely to have an EAI in a school emergency kit.

A plan should also be devised before discharge for further evaluation at a later date. Patients should follow up with their primary physicians within 1 to 2 weeks of an acute event, with referral considered to an allergist/immunologist.^{3,5} Triggers should be clarified through testing, optimally 3 to 4 weeks after an acute event.⁴

With chronic care, one of the challenges physicians face is deciding at what age to transfer responsibility for epinephrine self-injection over to the patient. Members of the American Academy of Pediatrics (AAP) Section on Allergy and Immunology were surveyed regarding their individual practices.³⁰ Among 88 pediatric allergists who responded, most expected patients aged 12 to 14 years to take over some responsibilities, such as description of anaphylaxis symptoms (95.4%), demonstration of how to use an EAI trainer (93.1%), carrying an EAI (88.2%), and recognition of the need for epinephrine (88.1%). Very few respondents expected younger patients to transfer responsibilities.

Prior to discharge, patients and caregivers also should receive printed information regarding anaphylaxis and its treatment.^{3,4} Patient-directed education should be age appropriate.⁴ The NIAID has recommended the SAFE mnemonic³: (1) Seek support, (2) Allergen identification and avoidance, (3) Follow up with specialty care, and (4) Epinephrine for emergencies. Other sources of information are available on the Internet (eg, the AAP at <http://www.healthychildren.org/english/health-issues/conditions/allergies-asthma/Pages/default.aspx>).

Prevention of recurrence must include optimal management of comorbid diseases (eg, asthma and mastocytosis) and drugs (eg, β -blockers and ACE [angiotensin-converting enzyme] inhibitors) that may exacerbate anaphylaxis.⁴ The benefits of immunotherapy/immunomodulation should be considered. Patients treated with many biological agents (eg, omalizumab for asthma) or immunotherapy for allergy should be taught how to recognize anaphylaxis and correctly use an EAI.⁵ If a trigger medication is necessary, consider desensitization, which provides temporary tolerance until treatment is interrupted.⁴ For radiocontrast dye, premedication with an antihistamine and corticosteroid or other agents may be used, but the effectiveness is controversial.^{4,5} For mast cell activation syndrome (with no known trigger), prophylactic omalizumab or the combination of an antihistamine and corticosteroid has shown benefit.⁴

Each patient should receive personalized written directions about avoidance of known triggers, with regular review at physician visits.⁴ Caregivers and patients should be educated about alternative names for foods (eg, casein for milk) and cross-reacting allergens. With FA, reading of food labels must be reinforced. However, studies have shown that parents do not adhere consistently to food labels and that labels may be confusing.³¹ Dietary restrictions may lead to nutritional deficiencies, so children must be monitored for gains in height/weight, and consultation with a nutritionist should be considered when appropriate.⁴ Patients should follow up with physicians at least annually to review symptoms of anaphylaxis, avoidance of allergens, use of epinephrine, and the expiration dates of EAIs.^{3,4}

Management in Schools

Although anaphylaxis in schools is itself rare, about 20% of cases may first occur on school grounds,^{32,33} and about 1 in 25 children have FA.³² EAPs for schools are often nonexistent or deficient, and availability of epinephrine and trained school staff are frequently limited.³⁴ A thorough review of this subject was published in 2009.

The AAP and the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²LEN) both have recently produced papers regarding the allergic child at school.^{32,33} Especially critical to note is that school fatalities have been associated with delayed administration of epinephrine.³² Recommendations from the AAP include³² the following:

- notification of the school by parents of an allergic child, which may take the form of a written EAP;

- appropriate substitutions may be required by physicians for food programs;
- prescription of an EAI, which may include 1 for the child to carry and 1 for the health office, the latter of which may be useful for a biphasic reaction;
- considering that one-quarter of anaphylactic reactions occur in patients without a history, an EAI prescription for general use may be written, consistent with all local regulations and laws;
- because prompt administration of epinephrine is critical, children should be encouraged to self-carry an EAI (as age appropriate), and EAI should be stored in secure and readily accessible locations; procedures should dictate responsibility for replacing expired medication and ensuring access during field trips; and
- special attention should be paid to adolescents, including education directed toward coaches and other extracurricular staff.

Readers are encouraged to familiarize themselves with the additional guidance in this report.

Ethical principles should guide school policies.³⁵ Confidentiality of children should be protected, with secure medical information and staying away from special food lines. Policies should have equal benefits and burdens. Undue burdens should be avoided regarding eating habits (eg, same quality meals as for nonallergic children), and policies should be enacted that will apply to all allergens, rather than focusing on any one (eg, peanuts). Finally, school personnel and students should be empowered through education, allowing children to self-carry EAI and taking seriously any bullying that results from special conditions.

Policies and practices vary substantially among states and individual school districts. In the Canadian province of Ontario, Sabrina's Law was enacted to address anaphylaxis in schools.³⁶ The law requires public school boards to establish policies that include minimization of allergen exposure, regular management training for school personnel, and establishment of individualized EAPs. The law also permits use of an EAI for anaphylaxis in previously undiagnosed students and grants legal immunity for "good Samaritan" use of an EAI. A study compared Ontario with several nonlegislated provinces. Of a possible score of 0 to 13 when compared with Canadian anaphylaxis guidelines (13 = greatest consistency with Canadian anaphylaxis guidelines), Ontario boards scored 8.8 compared with 6.1 in other provinces ($P = .009$). However, Ontario policies still usually did not have clauses allowing EAI use in

undiagnosed students or good-faith use. Compared with nonlegislated provinces, Ontario schools were more likely to be:

- have a written policy to address life-threatening allergy; despite >90% of Ontario schools having policies, only slightly >50% of parents and school personnel knew that they existed;
- ask parents to submit an EAP; although >78% of parents reported completing EAPs in all provinces, only about 40% of staff had personal copies available; commonly reported omissions from EAPs included location of the EAI and treatment steps;
- train staff on use of EAI (reported by 95.1% of staff in Ontario vs 81.1% elsewhere, $P < .001$); however, when asked to demonstrate technique, only 39% of Ontario staff scored a perfect 4 (vs 26% in nonlegislated provinces, $P < .002$), a disparity between reporting and practice that has been noted in other studies.

Thus, legislation may improve anaphylaxis practices, yet substantial gaps can remain. In response to school fatalities in the United States caused by anaphylaxis, a growing number of states (eg, Illinois and Virginia) also have enacted comprehensive legislation pertaining to allergy, including requiring EAI in schools. The current laws in each state and policies for individual school districts should be known to pediatricians. A curriculum in Washington State has been described that prepares school nurses to train other school personnel about anaphylaxis.³⁷ In addition, the National Association of School Nurses has a toolkit on its Web site for management of FAs and anaphylaxis in the school setting (see <http://www.nasn.org/ToolsResources/FoodAllergyandAnaphylaxis>).

Conclusion

Multiple studies have noted the adverse effects of allergy on quality of life in children, adolescents, and parents.^{3,9,38,39} With FA, this is partially related to the stress of preparing and selecting allergen-free foods.³ Caregivers reported that having children with FA adversely affected family activities, with >60% reporting alterations in food preparation, and nearly 50% noting an effect on social events; a tenth chose to home school children. In a survey of 2945 parents of children with FA from across the United States, parents agreed with the following statements: some relatives do not accommodate the child's FA (51%); hostility has been experienced from other parents in accommodating the child's FA (40%); the child's FA causes strain on

marriage/relationship (29%); the child's friends treat him/her differently because of FA (26%); and career has suffered because of child's FA (25%).³⁸ Fewer than 20% thought that FA was taken seriously. Parents and children can benefit from both live and Web-based support initiatives in terms of improved self-confidence and self-care skills and decreased anxiety.⁴⁰

Several recent studies have reaffirmed that knowledge is limited among pediatric patients, caregivers, and HCPs about recognition and management of anaphylaxis, including when to use epinephrine and how to use an EAI.^{24,26-28,41} Recent studies have also shown that educational activities and information support can improve this knowledge.^{24,42-44}

Although acute care often occurs in other settings, and allergists may be involved in assessment and chronic management, the pediatrician is most likely to see children and adolescents regularly. In light of this, it is particularly important for this group to have expertise in the recognition and treatment of allergy and anaphylaxis, including review with the patient and caregiver at each office visit of overall anaphylaxis knowledge and proper use and maintenance of an EAI. It is vital to recognize changing needs as the patient ages, such as expression of symptoms, transition to self-care, and risk factors for exposure.

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