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Optimizing the clinical identification and management of patients at risk for anaphylaxis

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Introduction: What is anaphylaxis?

The National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (FAAN) define anaphylaxis as a "serious allergic reaction that is rapid in onset and may cause death." It is likely to be the diagnosis when there is involvement of skin or mucosal tissue (eg, hives, angioedema) and airway compromise (wheezing, dyspnea) and/or reduced blood pressure or associated symptoms (hypotension, syncope), along with a temporal relationship (minutes to several hours) to a potential causative agent.[1-3] Anaphylactic reactions, manifesting as systemic signs and symptoms, can be triggered from exposure to a wide range of allergens, including foods, insect stings and bites, and drugs.[1,3,4] The lifetime prevalence of anaphylaxis is estimated to be 0.05% to 2%, and the overall incidence of anaphylaxis appears to be increasing.[5-9] Furthermore, it is estimated that up to 16% of people may be at risk for anaphylaxis, and its risk persists over the long term.[2,9]

Anaphylaxis is often preventable. Anaphylaxis occurs most commonly in the community setting in the absence of a health care professional, so it is essential for patients at risk for anaphylaxis to be identified and prepared in the event of an emergency.[2,5,10] Patient-specific risk factors for a more severe anaphylactic reaction include age (teenagers and young adults are at an increased risk of anaphylaxis triggered by foods, and the elderly are at a greater risk of fatality from insect venom anaphylaxis and concomitant diseases), comorbidities (particularly asthma, especially if severe or uncontrolled),

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and concomitant chemical/medication use that may affect the recognition or increase the severity of anaphylaxis. Therefore, anaphylaxis should be considered a preventable, long-term disease for at-risk patients.[2]

Assessing anaphylaxis in patients with a confirmed history

Common triggers

The common triggers of anaphylaxis in the community include food, stinging and biting insects, and drugs. Foods including milk, egg, and peanuts account for the majority of anaphylactic reactions in young children, while peanuts, tree nuts (eg, pecans, walnuts, cashews, Brazil nuts, pistachios), and seafood (eg, fish, crustacean shellfish) account for the vast majority of reactions in teenagers and adults.[4,11,12]

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Venom from stinging insects (eg, honeybees, yellow jackets, yellow hornets, paper wasps, fire ants) or, less commonly, saliva from biting insects (eg, flies, mosquitoes, ticks) can also trigger anaphylaxis.[5,13] Although most insect stings produce a transient local reaction that might last up to several days and generally resolves without treatment, life-threatening systemic reactions may occur, and they are more common in adults than in children.[13]

Medication-triggered anaphylaxis can occur in patients of any age; however, it is particularly common in middle-aged and older adults. Penicillin is the most common cause of medication-induced anaphylaxis. The extent of allergic cross-reactivity between penicillin and other β-lactam antibiotics, particularly cephalosporins, is unknown but appears to be low. Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin and ibuprofen, constitute the second most common cause of medication-induced anaphylaxis.[4,5]

Additional triggers in the community can include natural rubber latex, exercise, and radiocontrast media, among other factors.[5]

Common signs and symptoms

Involvement of body organ systems varies among patients and even in the same patient, from one episode to another; however, review of anaphylaxis case series has revealed some general patterns. A minimum of 2 organ systems are needed to make the diagnosis of anaphylaxis. The majority of anaphylactic reactions (80% to 90%) involve the skin, manifesting as hives (urticaria), itching (pruritus), and flushing. The mucosal tissue may also be affected, involving pruritus and swelling of the lips, tongue, and uvula/palate.[2,5]

The airway is affected in 70% of reactions, including symptoms affecting the larynx (eg, pruritus and tightness in the throat, dysphonia, hoarseness) as well as the lungs (eg, dyspnea, chest tightness, wheezing/bronchospasm).[2,5] The gastrointestinal (GI) tract is affected in 30% to 45% of reactions, with typical GI-related symptoms including nausea, cramping, abdominal pain, vomiting, and diarrhea.[2,5] The cardiovascular system is affected in 10% to 45% of reactions, with chest pain, hypotension, tachycardia, weak pulse, dizziness, and fainting as potential symptoms.[2,5]

Approximately 10% to 15% of anaphylactic reactions involve the central nervous system (CNS), with symptoms including uneasiness, throbbing, headache, dizziness, confusion, and tunnel vision.[2,5] In particular, symptoms involving the throat, lung, and heart can be potentially life-threatening and, therefore, should not be ignored.[14]

The continuum of anaphylaxis

Anaphylaxis often produces signs and symptoms within minutes of exposure to an allergen, but some reactions might develop later (eg, >30 minutes after exposure). The more rapidly anaphylaxis occurs after exposure to an offending stimulus, the more likely the reaction will be severe and potentially life-threatening; therefore, prompt recognition of signs and symptoms of anaphylaxis is crucial.[4]

Food-induced anaphylaxis often occurs immediately after allergen exposure; symptoms may then subside, only to recur several hours later. This is known as biphasic anaphylaxis, characteristic of approximately 20% of food-induced anaphylaxis[15] and defined as symptom recurrence 1 to 72 hours (usually within 8 hours) after resolution of the initial symptoms, despite no further exposure to the trigger. For this reason, and because there are no reliable predictors of biphasic ana-

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TABLE 1 Clinical criteria for diagnosing anaphylaxis[3]

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus, 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 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); respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) B. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) C. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): A. Infants and children: low systolic BP (age-specific) or >30% decrease in systolic BP* B. Adults: systolic BP of <90 mm Hg or >30% decrease from that person's baseline

* Low systolic BP is defined as <70 mm Hg for children ages 1 month to 1 year; < (70 mm Hg + [2 X age]) for ages 1 to 10 years; and <90 mm Hg for ages 11 to 17 years.

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

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phylaxis on the basis of initial clinical presentation, observation periods in the office must be individualized.[4,5] Most importantly, anaphylactic reactions may not always follow the same pattern, as fatalities have often occurred in people whose previous reactions were mild.[15]

Diagnostic criteria

The diagnosis of anaphylaxis is based on clinical findings and a detailed description of the acute episode, in association with a known or suspected allergen exposure. Diagnostic criteria published in 2006 (**TABLE 1**) set out to capture more than 95% of cases of anaphylaxis.[3,11]

Criterion 1 should identify at least 80% of anaphylactic reactions, even when the allergic status of the patient and potential cause of the reaction might be unknown.[3] However, cutaneous symptoms might be absent in up to 20% of anaphylactic reactions in children with food allergy or insect sting allergy.[3] In patients with a known allergic history and possible exposure, criterion 2 should provide ample evidence that an anaphylactic reaction is occurring. Lastly, criterion 3 should identify the rare patients who experience an acute hypotensive episode after exposure to a known allergen.[3]

The medical history is essential in establishing a diagnosis of anaphylaxis. It is important to inquire about key aspects of the episode, including allergen exposure prior to the episode; the timing and duration of the event; the presence of cutaneous manifestations; sign of airway obstruction involving either the upper or the lower airway; presence of syncope or presyncopal symptoms; treatment required (if any); the recurrence of symptoms after remission; and the history of atopic disease (ie, asthma, eczema). Asking these questions will help obtain a more accurate diagnosis and establish the appropriate preventive measures.[4,11] Patients with a history of anaphylaxis should be considered for referral to an allergist-immunologist, particularly in cases involving an unknown causative allergen, an in-

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TABLE 2 Patient-specific risk factors for anaphylaxis severity and fatality

Age	Comorbidities	Concurrent medication/chemical use
• Adolescent/young adult: Increased risk of anaphylaxis triggered by foods –Inconsistent behaviors regarding allergen avoidance and carrying epinephrine auto-injector • Elderly: Greater risk of fatality from insect venom anaphylaxis and concomitant diseases (eg, COPD, CVD)	• Asthma, especially if severe or uncontrolled • CVD • Allergic rhinitis and eczema: Atopic diseases are a risk factor for anaphylaxis triggered by food, exercise, and latex • Psychiatric disease (may impair recognition of symptoms)	• May affect recognition of anaphylaxis: Ethanol, sedatives, hypnotics, antidepressants, recreational drugs • May increase the severity of anaphylaxis: β-blockers, ACE inhibitors

Abbreviations: ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

dication for a special procedure (eg, desensitization, immunotherapy), and/or the presence of comorbidities that may impact or complicate treatment.[4]

Identifying the at-risk patient goes beyond a history of anaphylaxis

There are key risk factors beyond a history of anaphylaxis that may increase a patient's risk of experiencing a more severe anaphylactic reaction or that may lead to fatality due to anaphylaxis (**TABLE 2**). Teenagers and young adults are at increased risk for anaphylaxis triggered by foods, because of inconsistent behaviors with regard to avoiding their confirmed relevant triggers.

> Asthma, in particular (especially if severe or uncontrolled), is an important comorbidity that may increase the risk of life-threatening or fatal anaphylaxis.

Elderly patients may be at an increased risk of fatality due to anaphylaxis because of concomitant diseases such as chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD), as well as the medications used to treat them. Concomitant diseases also increase the risk of a more severe anaphylactic reaction. Asthma, in particular (especially if severe or uncontrolled), is an important comorbidity that may increase the risk of life-threatening or fatal anaphylaxis; CVD is also implicated.[5] Atopic diseases such as allergic rhinitis and eczema may increase the risk of anaphylaxis triggered by food, exercise, and latex but not the risk of anaphylaxis triggered by insect stings and β-lactam antibiotics.

In patients of any age, diseases that impede prompt recognition of triggers or symptoms potentially place patients at increased risk for anaphylaxis. These include impaired vision or hearing, neurologic disorders, psychiatric disorders (including depression), and use of medications such as first-generation H_1-antihistamines (eg, diphenhydramine, chlorpheniramine), antidepressants, sedatives, hypnotics, or CNS-active chemicals such as ethanol or recreational drugs. Concurrent medications such as β-blockers and angiotensin-converting enzyme inhibitors may increase the severity of anaphylaxis, and β-blockers potentially make anaphylaxis more difficult to treat.[5,11,14,15-18]

Long-term risk reduction: Management of patients at risk for anaphylaxis in the community

Allergen avoidance

Allergen avoidance measures are often difficult to implement and maintain in the real-world setting. For example, food avoidance measures potentially decrease the quality of life for those at risk for anaphylaxis and for their caregivers because of lifestyle changes that disrupt activities, elicit confusion regarding advisory labeling, and concern about the risk of accidental exposures. Strict avoidance of foods also potentially leads to nutritional deficiencies.[5,11,19,20] Nevertheless, it is important to educate patients and/or caregivers on appropriate avoidance measures; those specific to food-induced anaphylaxis include menu planning,

reading and interpreting food labels, avoiding risky eating behaviors, inquiring about ingredients in restaurant meals, and informing school personnel about food allergies.[15] The FAAN (www.foodallergy.org) and the Allergy and Asthma Network Mothers of Asthmatics (AANMA; www.aanma.org) are excellent resources for patients and their caregivers to learn more about how to best manage their severe allergies.

> Epinephrine is the cornerstone of emergency treatment for anaphylaxis.

The role of epinephrine as first-line treatment

Immediate intervention for anaphylaxis includes rapid assessment and maintenance of airway, breathing, circulation, and level of consciousness, followed by epinephrine administration.[4] Epinephrine is the cornerstone of emergency treatment for anaphylaxis.[4,5,21] In patients with anaphylaxis, epinephrine has potent, lifesaving, α_1-adrenergic vasoconstrictor effects on the small arterioles and precapillary sphincters in most body organ systems, increasing blood pressure and preventing and relieving hypotension and shock.[5]

Epinephrine also decreases mucosal edema, thereby preventing and relieving upper airway obstruction. In addition, its β_2-adrenergic effects lead to increased bronchodilation and decreased release of mediators, such as histamine and tryptase, from mast cells and basophils. Clinical implications of these effects include reduced wheezing and hives. Epinephrine also has β_1-adrenergic effects, leading to increased force and rate of cardiac contractions.[5]

When a patient fulfills any of the 3 criteria of anaphylaxis outlined in **TABLE 1**, the patient should receive epinephrine immediately. However, there undoubtedly will be patients who present with symptoms not yet fulfilling the diagnostic criteria of anaphylaxis, yet for whom it would be appropriate to initiate therapy with epinephrine, such as a patient with a history of near-fatal anaphylaxis to peanuts who ingests peanuts and is experiencing urticaria and generalized flushing within minutes.[3] Prompt recognition of signs and symptoms of anaphylaxis is crucial. If there is any doubt, it is generally better to administer epinephrine, as there is no absolute contraindication to its use.[4]

Prompt epinephrine injection is important, as delayed injection may be associated with fatality and also contributes to the increased likelihood of biphasic anaphylaxis.[4,5] Approximately 20% of patients who receive an initial dose of epinephrine for the treatment of anaphylaxis in the community are reported to require a second dose, either because of ongoing symptoms or due to biphasic anaphylaxis.[5] Additional criteria potentially warranting a second dose of epinephrine include comorbid asthma, younger age-group, food- or insect-induced anaphylaxis, rapid symptom progression, or living in a remote area, farther than 10 to 15 minutes from a health care facility.[5,22-24]

Patients at risk for anaphylaxis severity and fatality in the community (**TABLE 2**) should be provided an epinephrine auto-injector. People in the community who are at risk for anaphylaxis or who care for children or other at-risk individuals require training and regular coaching in the use of epinephrine auto-injectors. Such training may not be routinely provided, which is reflected in patients' lack of knowledge on the appropriate administration technique for these devices.[25,26] Adequate training has been shown to increase patients' comfort level with using an epinephrine auto-injector.[27] The increasing annual incidence of unintentional injections from epinephrine auto-injectors can potentially be reversed by more vigilance in training and coaching, as well as improved epinephrine auto-injector design (eg, needle protection).[25]

Epinephrine dosage, administration, and storage

The first-aid dose of epinephrine is 0.01 mg/kg of a 1-mg/mL (1:1,000) dilution to a maximum dose of 0.5 mg in an adult or 0.3 mg in a child. This dose can be repeated every 5 to 15 minutes, as needed.[5] Commercially available epinephrine auto-injector devices are dosed according to patient body weight, with the 0.15-mg dose used for patients who weigh approximately 15 to 30 kg (~33-66 lb) and the 0.30-mg dose used for patients who weigh ≥30 kg (~66 lb).[28-30] Potential adverse events at usual doses of epinephrine include anxiety, tremor, palpitations, dizziness, and headache.[5] Intramuscular administration into the anterolateral aspect of the thigh is the preferred route and site of epinephrine injection, as epinephrine has a

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TABLE 3 Adjunctive medications for the management of anaphylaxis in the community[5]

	H_1-antihistamines (eg, cetirizine, diphenhydramine)	H_2-antihistamines (eg, ranitidine)	β_2-agonists (eg, albuterol)	Glucocorticoids (eg, prednisone)
Pharmacologic effects	Reduction in itch (skin, mucus membranes), flush, hives, sneezing, and rhinorrhea	Reduction in gastric acid secretion, vascular permeability, hypotension, flushing, headache, mucus production (airway)	Increase in bronchodilation	Reduction in late-phase allergic response to allergen
Practical aspects/role in anaphylaxis	Reduction in itch and hives; lack lifesaving effects Should not be used alone in anaphylaxis	Small additive effect (~10%) when used in conjunction with H_1-antihistamines to reduce vascular permeability, flushing, and hypotension Should not be used alone in anaphylaxis; if used, should be given in conjunction with an H_1-antihistamine; not mentioned in most guidelines	Reduction in wheeze, cough, and shortness of breath; do not decrease upper airway obstruction or relieve hypotension; lack lifesaving effects	Late onset; used to prevent biphasic anaphylaxis, although no clinical evidence has demonstrated this effect Unlikely to play a role in the initial minutes to hours of an anaphylactic episode
Potential adverse effects (usual doses)	First generation: sedation; impair cognitive function	Hypotension (ranitidine)	Tremor, tachycardia, dizziness, jitteriness	Unlikely to occur during a short 1- to 3-day course

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rapid, vasodilatory effect in the skeletal muscle (which is well vascularized), thus rapidly reaching the central circulation.[5]

Patients should be instructed to periodically visually inspect the epinephrine solution in their auto-injector devices for particulate matter and discoloration. The epinephrine solution should be clear; if the solution contains particulate matter, develops a pinkish color, or becomes darker than slightly yellow, the patient should immediately contact the clinician for a replacement, since these changes indicate that the effectiveness of the drug may be decreased. Patients should also be instructed to replace their auto-injector device prior to the expiration date. These devices should be protected from light, stored at room temperature (68º-77ºF), and should not be refrigerated.[28-30]

Adjunctive medications

Adjunctive medications for the management of anaphylaxis include antihistamines, β_2-agonists, and glucocorticoids (**TABLE 3**). Since H_1-antihistamines are commonly used for anaphylaxis in the community, it is important to communicate to patients and/or caregivers *not* to depend on these agents alone in anaphylaxis.[5] In fact, the use of antihistamines is the most commonly reported reason for not administering epinephrine, and it may place the patient at a significantly increased risk for progression toward a life-threatening reaction.[11] H_1-antihistamines lack the lifesaving effects associated with epinephrine; these agents do not prevent or relieve upper or lower airway obstruction, hypotension, or shock.[5] After oral administration, their onset of action ranges from 1 to 3 hours. The rapid improve-

ment in symptoms sometimes attributed to oral H_1-antihistamines likely reflects spontaneous resolution of the severe allergic episode. First-generation, potentially sedating H_1-antihistamines, such as diphenhydramine, chlorpheniramine, and promethazine, have a poor benefit/risk ratio. When self-administered in patients with anaphylaxis, these medications potentially impair self-recognition of symptoms. H_1-antihistamines might be useful as an adjunctive measure to relieve residual hives that have not disappeared after epinephrine injection.[4,5,31,32]

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Anaphylaxis action plan

Anaphylaxis action plans are an essential component for emergency preparedness in the community. Most plans list common signs and symptoms of anaphylaxis and emphasize the importance of using the epinephrine auto-injector promptly and of calling 911 or emergency medical services promptly. Plans should be personalized for each at-risk patient by listing comorbidities and concurrent medications, describing the epinephrine auto-injector and dose prescribed for the patient, and providing appropriate contact telephone numbers, such as those of family members. Plans need to be updated and discussed with the patient, and if relevant, his or her caregivers, on a regular basis.[5] A sample anaphylaxis action plan is available for download at the American Academy of Allergy, Asthma, and Immunology website (www.aaaai.org/members/resources/anaphylaxis_toolkit/action_plan.pdf).

Medical identification

Medical identification is also an important component of emergency preparedness in the community. Persons at risk for anaphylaxis in the community should wear medical identification (eg, MedicAlert jewelry; anaphylaxis wallet cards, available at www.aaaai.org) providing an accurate and up-to-date listing of their confirmed triggers, relevant comorbidities, and concurrent medications.[2,5]

Conclusions

Anaphylaxis is a serious, systemic allergic reaction that is rapid in onset and can cause death.[2,3] Anaphylaxis occurs most commonly in the community setting in the absence of a health care professional, so it is essential for patients at risk for anaphylaxis to be identified and prepared in the event of an emergency.[2,5,10] Identifying at-risk patients goes beyond a history of anaphylaxis; it is important to identify patients who may be at risk for a more severe anaphylactic reaction.[5,33] Epinephrine is the cornerstone of emergency treatment for anaphylaxis. Patients at risk for anaphylaxis should be provided an epinephrine auto-injector and appropriately trained in its use in the community setting.[4,5] ■

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