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WILDERNESS MEDICAL SOCIETY CLINICAL PRACTICE GUIDELINES

Wilderness Medical Society Clinical Practice Guidelines on Anaphylaxis

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The Wilderness Medical Society convened a panel to review the literature and develop evidence-based clinical practice guidelines on the treatment of anaphylaxis, with an emphasis on a field-based perspective. The review also included literature regarding the definition, epidemiology, clinical manifestations, and prevention of anaphylaxis. The increasing prevalence of food allergies in the United States raises concern for a corresponding rise in the incidence of anaphylaxis. Intramuscular epinephrine is the primary treatment for anaphylaxis and should be administered before adjunctive treatments such as antihistamines, corticosteroids, and inhaled β agonists. For outdoor schools and organizations, selecting a method to administer epinephrine in the field is based on considerations of cost, safety, and first responder training, as well as federal guidelines and state-specific laws.

Keywords: epinephrine, autoinjector, food allergy, insect bites and stings, wilderness medicine

Introduction

Accounts of anaphylaxis date back to the earliest recorded history. Hieroglyphs from 2640 BC depict the pharaoh Menes dying after a wasp sting.[1] Today, anaphylaxis continues to be a serious medical issue. An estimated 2 to 5% of the US population has experienced anaphylaxis. In addition, between 1999 to 2010, there were a total of 2458 anaphylactic deaths, a figure that may reflect underreporting. Although such deaths appear to be rare, estimated at 0.1% of all emergency department (ED) visits and 1% of all hospital admissions for anaphylaxis, the potential for sudden and unpredictable fatality is an ever-present concern for at-risk individuals and their families.[2]

In remote areas or wilderness settings, access to standard medical care may be limited or delayed. To help increase the availability of life-saving treatment, the Wilderness Medical Society published clinical practice guidelines in 2010 and 2014 supporting the concept that nonmedical professionals whose duties include providing first aid or emergency medical care in the field also be trained to administer epinephrine for anaphylaxis.[3,4] Examples of such professionals include expedition leaders, outdoor instructors or guides, park rangers, and camp directors.

The current guidelines expand the focus from the administration of epinephrine by trained nonmedical professionals to the broader field treatment of anaphylaxis, with consideration for hospital-based treatment.

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Methods

Anaphylaxis, with its potentially drastic course, does not lend itself to study in randomized, controlled trials. The authors reviewed the literature for the best available evidence, including observational studies, case series, limited controlled trails, extrapolation from physiological data, and expert consensus. Practice recommendations were assigned a level of evidence according to the

methodology proposed by the American College of Chest Physicians (online Supplemental Table).[5]

Definitions and Scope

Emphasis in the guidelines is placed on the field treatment of anaphylaxis. Treatment of asthma and various non-anaphylactic allergic reactions are beyond the current scope. Nonetheless, the field practitioner will note some overlap in pathophysiology and treatment along the spectrum of allergic, asthmatic, and anaphylactic reactions.

- *Allergen.* An environmental substance that triggers an abnormal or heightened immune response in susceptible individuals. Common sources of allergens include foods, plant or animal elements, and medications.
- *Allergy.* An abnormal or heightened immune response against an allergen.
- *Anaphylaxis.* An acute, potentially-life threatening response to an allergen that progresses to involve multiple organ systems and is described in further detail later.
- *Asthma.* Abnormal bronchial constriction and inflammation arising from exposure to an inciting allergen, infection, extremes of temperature, or physical exertion.
- *Anaphylactoid reaction.* An acute inflammatory or anaphylaxis-like response without prior exposure to the inciting allergen.
- *Angioedema.* Subcutaneous or submucosal swelling and inflammation arising from exposure to an allergen or deficiency of an inflammatory inhibitor.
- *Antigen.* A substance or agent that incites an immune response with antibody production. An antigen may be environmental, as in allergens, bacteria, and viruses, or intrinsic to the body, as in autoimmune diseases.
- *Hypersensitivity reaction.* A heightened immune response against an antigen leading to inflammatory damage to the body. A hypersensitivity reaction may be immediate or delayed and is classified according to the specific types of antibodies or immune cells involved (Table 1).[6]

Epidemiology

In the United States, accurately determining the epidemiology of anaphylaxis is limited by the lack of a comprehensive national registry. National estimates of anaphylaxis are based on extrapolation from regional epidemiological surveys, with considerably varying results. A midrange estimate of the anaphylaxis risk in the US population is 1.6 to 2%.[7,8] Based on a population of 326 million (2020 US Census), 5.2 to 6.5 million individuals are theoretically at risk.

Exact numbers for anaphylactic deaths are also difficult to determine. In the United States, yearly estimates range from 205 (based on death certificate diagnoses) to 1500 (based on extrapolation from regional surveys).[9,10] Although the accuracy of individual estimates is questionable,[11] the range of 205 to 1500 deaths per year casts fatal anaphylaxis as a tragic but much smaller subset of the total incidence of anaphylaxis.

In children and adolescents, food allergies cause the majority of anaphylactic deaths, and asthma is a risk factor for fatal anaphylaxis.[12] The most common food allergies are to peanuts, milk, shellfish, and tree nuts. In adults and the elderly, medications and radiocontrast media cause the majority of anaphylactic deaths, often in hospital or healthcare settings. Penicillin and cephalosporin antibiotics are the medications most often implicated.[10] In both children and adults, *Hymenoptera* stings are the second leading cause of anaphylactic fatalities.[13] Overall, an estimated 45 to 150 deaths per year have been attributed to food allergies and insect stings, and 121 deaths to medications and radiocontrast media.[10,14]

The incidence of anaphylaxis specifically in wilderness settings is unclear, given the lack of a national reporting system. Illustrative examples, however, may be found in the injury and illness databases of 2 large, well-established schools in outdoor education and recreation.

NATIONAL OUTDOOR LEADERSHIP SCHOOL

Enrolling 5093±190 (mean±SD) students each year, the National Outdoor Leadership School (NOLS) teaches outdoor skills and leadership through wilderness-based courses and expeditions (https://nols.edu/en/). The majority of students have been young and healthy (median age: 20 y, IQR: 10). From 2005 to 2019, NOLS recorded 21 anaphylaxis cases in the field, occurring in approximately 0.03% of all students. In addition, 3 cases occurred among NOLS instructors and expedition leaders. Including both students and instructors, the total incidence of anaphylaxis was 24 cases per 2,431,591 person-days, or 10 per million person-days (1 student or 1 instructor in the field for 1 d=1 person-day) (Table 2).

Specific causes for the 24 cases are listed in Table 3. Overall, 13 cases (54%) were attributed to food-based allergies and 8 (33%) to *Hymenoptera* stings. Of note, 5 cases (21%) were first-time reactions in persons without a

Table 1. Hypersensitivity reactions

Reaction type	*Type I*	*Type II*	*Type III*	*Type IV*
Name	IgE-mediated hypersensitivity	IgG-mediated cytotoxic hypersensitivity	Immune complex–mediated hypersensitivity	Cell-mediated hypersensitivity
Mechanism	IgE antibodies activate mast cells	IgG antibodies activate T cells and complement	Antigen–antibody complexes activate complement and neutrophils	Antigens activate T cells and macrophages
Onset	Immediate (within minutes)	Intermediate (minutes to hours)	Intermediate (hours)	Delayed (48–72 h)
Clinical example	Anaphylaxis	Blood transfusion reaction	Serum sickness	Contact dermatitis, poison ivy

Adapted from Punt et al.[120]

known history of allergy. No anaphylactic deaths occurred among students or instructors. (All NOLS data provided by TS and DL)

OUTWARD BOUND—UNITED STATES

Enrolling 41,732±2427 (mean±SD) students each year, Outward Bound (OB) charters 11 regional schools across the United States that lead expeditions and outdoor-based courses in varied settings (https://www.outwardbound.org). The median student age is 16 y (IQR: 4). From 2005 through 2019, OB recorded 39 anaphylaxis cases in the field, occurring in approximately 0.01% of all students. In addition, there were 7 cases among field instructors. However, only the student incidence of anaphylaxis is available, which was 39 cases per 1,839,727 person-days, or 21 per million person-days (Table 2).

Specific causes for the 46 anaphylaxis cases among students plus instructors are listed in Table 3. These include 4 cases (9%) of students with a history of asthma who received epinephrine for respiratory distress, because distinguishing anaphylaxis with respiratory involvement from a severe asthma exacerbation may be difficult in the field. Overall, 11 cases (24%) were attributed to food-based allergies and 20 (43%) to *Hymenoptera* stings and insect bites. Of note, 10 cases (22%) were first-time reactions in persons without a known history of allergy. No anaphylactic deaths occurred among students or instructors. (All OB data provided by CBS)

Table 2. Anaphylaxis at the NOLS and OB, 2005 through 2019

	NOLS	*OB*
Students		
Annual enrollment (mean±SD)	5093±190	41,732±2427
Age, y (median) [IQR] (range)	20 [10] (6–84)	16 [4] (10–78)
Anaphylaxis cases in all students, n (%)	21 (0.03%)	39 (0.01%)
Field time (p-d)	1,945,057	1,839,730
Anaphylaxis incidence (per p-d)	1/96,622	1/46,173
(per million p-d)	10	21
Instructors		
Age, y (median) [IQR] (range)	32 [10] (20–72)	27 [7] (18–77)
Anaphylaxis cases in all instructors, *n*	3	7
Field time (p-d)	486,534	NA
Anaphylaxis incidence (per p-d)	1/162,178	NA
(per million p-d)	6	
Totals (students + instructors)		
Anaphylaxis cases, n	24	46
Field time (p-d)	2,431,591	NA
Anaphylaxis incidence (per p-d)	1/101,316	NA
(per million p-d)	10	
Cases per year (mean±SD) (range)	2±2 (0–10)	3±2 (0–8)
Anaphylaxis deaths	0	0

IQR, interquartile range; NA, not available; NOLS, National Outdoor Leadership School; OB, Outward Bound; p-d, person-day (1 student or 1 instructor in the field for 1 d).

Table 3. Causes of anaphylaxis at NOLS and OB, 2005–2019

Allergen	*Cases at NOLS n (%)*	*Cases at OB n (%)*
Hymenoptera/Insect stings	8 (33)	20 (43)
Peanuts/Tree nuts	8 (33)	7 (15)
Other foods	5 (21)	4 (9)
Plants/Pollen/Grasses	1 (4)	1 (2)
Marine life/Jellyfish	0 (0)	1 (2)
Asthma trigger	0 (0)	4 (9)
Unknown	2 (8)	9 (20)
Total	24 (99)	46 (100)

NOLS, National Outdoor Leadership School; OB, Outward Bound.

INCREASE IN THE FIELD REPORTING OF ANAPHYLAXIS BY NOLS AND OB

Since 1984, NOLS has noted a 12-fold increase in its field reporting of anaphylaxis (Table 4). Similarly, OB also has noted an increase, although exact comparative numbers are not currently available. To explain this, NOLS and OB leaders have proposed 3 theories, all of which may be contributing.

First is an increased incidence of anaphylaxis in this population, which is supported by a corresponding 3-fold increase at NOLS of nonanaphylactic, acute allergic reactions (Table 4). In particular, the number of NOLS and OB students reporting a history of food allergy has increased in recent years (Table 5 illustrates NOLS data). It is plausible that as the number of students with food allergy has increased, so has the number at risk for anaphylaxis. The rise in food allergy at NOLS and OB parallels an increased prevalence of food allergy in the general US population. Currently, an estimated 11% of adults and 8% of children in the United States have a food allergy, with an increased prevalence in children by 50% over a 15-y period.[15]

Table 4. Increase in incidence of anaphylaxis and allergic reactions at NOLS

NOLS injury and illness database	*2005–2019*	*1984–2004*
Total field time (p-d)	2,431,591	2,446,159
Anaphylaxis cases	24	2
Incidence per p-d	1/101,316	1/1,223,080
Allergic reactions	467	149
Incidence per p-d	1/5207	1/16,417

NOLS, National Outdoor Leadership School; P-D, person-days.

Table 5. Increase in food allergies at NOLS

Year	*NOLS students with food allergy, n (%)*	*Nut allergy (% of total allergies)*
2015	37 (0.7)	65
2016	65 (1.2)	71
2017	116 (2.2)	71
2018	192 (3.6)	58
2019	140 (2.7)	54

NOLS, National Outdoor Leadership School.

Second, the increase in anaphylaxis may be due to increased recognition by instructors, perhaps as the result of specialized training, as well as the indirect effect of heightened public awareness of food allergies and anaphylaxis. On the other hand, internal quality-assurance reviews of field reports by each school have suggested that instructors appropriately identified and generally did not overdiagnose anaphylaxis.

Third, veteran OB leaders have observed that more parents and physicians are allowing students with a food allergy or anaphylaxis history to participate in remote wilderness-based courses and expeditions compared to the past. Caretakers may have found reassurance in the increased public awareness of food allergy and anaphylaxis, as well as emergency care plans for the immediate availability of prehospital epinephrine, whether administered by trained, onsite first responders or self-injected by students. As more individuals at risk for food allergy and anaphylaxis feel comfortable enrolling in NOLS and OB courses, a slight selection bias may be contributing to the increased field incidence of these conditions.

Pathophysiology

The vast majority of allergic and anaphylactic responses are IgE-dependent, immediate (Type I) hypersensitivity reactions (Table 1). An allergen exposure in a susceptible host stimulates B lymphocytes to produce specific IgE antibodies that bind to receptors on mast cells and, to a lesser extent, basophils. If the same allergen is later reintroduced into the body, it binds to the previously formed IgE-receptor complex, triggering a release of multiple preformed mediators such as histamine, tryptase, and proteases. Neutrophils, eosinophils, monocytes, and platelets can also be activated in the process.[16]

Limited, focal release of preformed mediators such as histamine leads to the relatively minor expressions of allergy such as allergic conjunctivitis and rhinitis, as well as urticaria.

In acute asthma, allergens that enter the airways induce T-helper cells to produce cytokines, stimulate B cells to release IgE, and cause mast cells to release leukotrienes and histamine—all of which trigger bronchoconstriction and initiate airway inflammation. Ongoing, subacute release of inflammatory mediators occurs in

chronic asthma, with associated mucus hypersecretion as well as airway edema and remodeling.[17]

Large-scale release of preformed mediators, together with the synthesis and release of inflammatory mediators such as prostaglandins, cytokines, and leukotrienes, lead to the clinical signs and symptoms of anaphylaxis. Histamine induces vasodilation and increases capillary vascular permeability, causing fluid to extravasate from the intravascular to the extravascular space. Tryptase stimulates additional mast cell degranulation and downstream activation of the complement and coagulation pathways, as well as the kallikrein-kinin system, triggering an amplified, overwhelming inflammatory cascade.[18]

The role of IgE-independent pathways in anaphylaxis is less clearly understood, but it may involve the release of preformed mediators by mast cells and basophils through direct activation of the complement system. Reactions involving IgM and IgG antibodies also have been demonstrated in animal models.[16]

Histamine and other inflammatory mediators can be released directly from mast cells without an antigen-antibody interaction or prior exposure to an antigen. Such direct release has been called an anaphylactoid reaction, although some experts now discourage use of this term because the clinical symptoms and severity may be identical to IgE-mediated anaphylaxis.[19] Non-IgE anaphylaxis or anaphylactoid reactions are most commonly associated with certain pharmaceuticals, such as nonsteroidal anti-inflammatory drugs and radiocontrast agents.[20]

Histamine also contributes to allergic angioedema, a form of submucosal tissue swelling typically affecting the face, oropharynx, and larynx and sometimes presenting as extremity or abdominal wall edema. Angioedema also can develop in nonallergic conditions, including hereditary angioedema, acquired C1-inhibitor deficiency, and drug-related angioedema, such as that caused by angiotensin converting enzyme (ACE) inhibitors. In these conditions, the cause is excess production or decreased clearance of bradykinin, a vasoactive peptide.[19,21]

Certain cofactors augment allergy symptoms in susceptible individuals who ingest a food-based allergen. These cofactors include exercise, alcohol, and nonsteroidal anti-inflammatory drugs, all of which are thought to enhance intestinal permeability and allergen absorption. In addition, exercise has been associated with 2 subtypes of anaphylaxis: exercise-induced anaphylaxis (EIA) and food-dependent, exercise-induced anaphylaxis (FDEIA). A hypothesis for the pathophysiology of EIA is that physical activity, in the absence of an environmental allergen, increases plasma osmolarity, which in turn causes mast cells to degranulate, releasing histamine and other cell mediators. FDEIA is an IgE-mediated food allergy that occurs when exercise is performed shortly after ingestion, activating the histamine-based cellular cascade.[22-24]

A food allergy to red meat such as beef, pork, or lamb may develop in individuals who form an IgE antibody response to the mammalian glycoprotein component galactose-α-1,3-galactose after a tick bite. This is associated with the Lone Star tick (*Amblyomma americanum*) in the United States and other species worldwide. Symptoms of α-gal allergy characteristically develop 3 to 5 h after ingestion as the meat is digested and absorbed through the gastrointestinal tract and range from mild to severe, including anaphylaxis.[25]

Clinical Manifestations

Anaphylaxis is a systemic reaction, usually of rapid onset, that progresses to affect multiple organ systems. Medical organizations have published clinical algorithms to aid in diagnosis, emphasizing early recognition. In 2020, based on evidence review and expert consensus, the World Allergy Organization proposed that anaphylaxis be diagnosed when 1 of 2 criteria is met, in the context of known or highly probable allergen exposure[26]:

1. Cutaneous or mucosal signs that occur suddenly, progress within minutes to hours, and are accompanied by respiratory compromise, hypotension, or persistent gastrointestinal symptoms.
2. Acute onset of hypotension or respiratory compromise, including severe bronchospasm or laryngeal involvement, even in the absence of skin involvement.

As exceptions, and described in the previous section, the diagnosis of EIA does not require exposure to an environmental allergen, and symptoms of α-gal allergy typically develop 3 to 5 h after ingestion.

Cutaneous or mucosal involvement is the most frequent sign of anaphylaxis and includes urticaria, flushing, pruritus, oropharyngeal swelling, or angioedema.[27] Urticaria (hives) is a blanching, erythematous rash with transient wheals that is typically pruritic. However, skin involvement is not required for the diagnosis; up to 10 to 20% of anaphylaxis cases have absent or unrecognized skin and mucosal findings.[28]

Respiratory involvement can present as sneezing, nasal congestion, cough, hoarse voice, angioedema, bronchospasm, wheezing, stridor, dyspnea, and hypoxemia. The most common gastrointestinal symptoms are nausea, vomiting, abdominal pain or cramping, and diarrhea. Cardiovascular signs and symptoms include tachycardia, dysrhythmias, lightheadedness, syncope, chest pain, and hypotension. Neurologic symptoms such

as lightheadedness, impending sense of doom (*angor amini*), and confusion may be present. Patients may also report a metallic taste or appear extremely anxious.[26]

Anaphylactic fatalities result from respiratory or cardiovascular effects. Angioedema and bronchospasm lead to airway obstruction and ventilatory failure. In the cardiovascular system, a sudden and massive increase in capillary permeability causes hypotension and shock. Up to 35% of intravascular fluid may extravasate within 10 min of allergen exposure, leading to decreased venous return and cardiovascular collapse.[27]

The majority of anaphylactic reactions resolve with appropriate treatment. Certain patient characteristics, however, increase the risk of severe or fatal anaphylaxis.[29] Infants and young children are less able to communicate symptoms and may have unrecognized abnormal vital signs. Their narrower airways are more susceptible to obstruction by swelling and increased secretions. Elderly patients are at increased risk owing to underlying comorbidities or medication use. Those with cardiovascular or pulmonary disease, for example, may not tolerate the increased stress on these organ systems. In addition, patients with heart disease have more mast cells in their coronary arteries, which may lead to increased coronary vasoconstriction during anaphylaxis.[30] For patients on antihypertensive medications, beta blockers may blunt the therapeutic response to epinephrine and ACE inhibitors may interfere with the degradation of inflammatory mediators.[19,26]

The biphasic reaction is an anaphylaxis variant, reported to occur with a wide range of incidence from <1 to 15%, although larger cohorts have reported 4 to 6%.[31-35] After treatment and apparent resolution of anaphylaxis, symptoms can recur within 1 to 78 h without antigen re-exposure. A multinational registry found that the second phase of symptoms occurred within 12 h in 60% of patients; from 12 to 24 h in 24% of patients; and >24 h in 16% of patients.[34] Risk factors associated with the development of a biphasic reaction have included history of anaphylaxis, elderly age, cardiovascular disease, regular use of beta-blockers, onset of symptoms >30 min from allergen exposure, nut allergy, unknown allergen, medication allergy in children, severe initial reaction with multiorgan involvement, delay in epinephrine administration, and requirement of multiple epinephrine doses.[13,34]

Exercise-induced anaphylaxis occurs less commonly than other causes of anaphylaxis, but it is relevant to the physical activities of outdoor recreation. Activity of any intensity may induce symptoms in the absence of an environmental allergen; however, jogging and aerobic exercise appear to be the most common causes.[23] Symptoms occur shortly after the onset of exercise and include rhinorrhea, pruritus, flushing or urticaria, abdominal cramping with nausea, vomiting or diarrhea, cough, wheezing, and shortness of breath. Symptoms of EIA (and FDEIA) typically resolve with rest and prompt cessation of activity. Patients who have persistent or worsening signs and symptoms, including respiratory compromise or hypotension, should be treated with the standard therapies discussed later.[23,24,26] Mortality attributed to EIA has been reported only in a handful of cases, although it is speculated that EIA may be underreported as a cause of sudden death with exercise.[24]

Anaphylaxis is a syndrome with a variable presentation, and therefore the differential diagnosis is broad. It includes conditions affecting the respiratory system, such as asthma, acute pulmonary edema, foreign body aspiration, pulmonary embolism, and vocal cord dysfunction. Acute coronary syndrome, cardiogenic shock, sepsis, hypoglycemia, hyperventilation, panic attack, and vasovagal reactions should also be considered. Hereditary angioedema, ACE-inhibitor induced angioedema, and diffuse urticaria may share similar skin findings with anaphylaxis. Less common mimics involve excess histamine release such as scombroid, mastocytosis, and drug-related red man syndrome. Pronounced flushing of the skin also may be caused by rare syndromes such as pheochromocytoma and carcinoid.[20,26]

Treatment

GENERAL CONSIDERATIONS AND DECONTAMINATION

As with any potentially serious illness or injury in the field, care begins with an assessment of scene safety followed by a primary evaluation of the patient with interventions as needed to support airway, breathing, and circulation. Epinephrine should be given as soon as possible once anaphylaxis has been identified. Additional interventions depend on first responder training as well as local resources and equipment.

Removal of the inciting allergen is appropriate in certain circumstances. For example, immediately removing an insect stinger from the skin may prevent additional injection of venom (avoiding pressure, if possible, on the venom sac). Exposure to aerosolized, food-based allergens should be stopped by discontinuing on-site cooking of the associated food (eg, steaming of shellfish) and, if feasible, distancing of the patient. Inducing vomiting for food-based allergens, however, has not been proven effective and may delay treatment with epinephrine.[35]

EPINEPHRINE (ADRENALINE)

Ideally, the treatment of anaphylaxis should stabilize mast and other immune cells, reverse vascular dilation and increased permeability, and relieve airway constriction. Epinephrine accomplishes all these tasks through agonist effects at α_1 receptors in the vascular system and β_2 receptors in the lungs and mast cells.[36] Its worldwide acceptance as the primary anaphylaxis treatment is based on years of clinical experience and theoretical mechanisms of action rather than controlled human trials.[13,26,37,38] Unfortunately, epinephrine is still viewed by some as a temporizing rather than definitive treatment and is withheld while other medications are given first.[39-42] Delay in epinephrine administration has been repeatedly associated with fatal anaphylaxis.[43]

Recommendations: Epinephrine is the essential, primary treatment that should be given once anaphylaxis has been diagnosed (1A). If possible, separating the patient from the inciting allergen is prudent, but vomiting should not be induced to eliminate a food-based allergen (1C).

Routes of Administration

Intramuscular (IM) injection of epinephrine is used in the prehospital and hospital settings to treat anaphylaxis immediately before intravenous (IV) access is established. Based on experimental IM studies, injection into the anterior lateral thigh delivers the highest serum levels of epinephrine in the shortest time and is strongly preferred.[44] If the anterior lateral thigh is inaccessible (eg, because of body position, injury, thick clothing, or protective gear), then the deltoid is acceptable. Subcutaneous (SQ) deltoid injection has been proposed as an alternative to IM injection, although current evidence favors muscle tissue for its greater vascularity, which enhances medication absorption.[45]

Although they are widely available, over-the-counter, metered-dose inhalers of epinephrine have not been found to be a practical or effective treatment for anaphylaxis. In a pharmacological study on children, achieving weight-based doses of epinephrine required a high number of puffs (11±2 [mean±SD]) and was hampered by the adverse effects of bad taste, cough, and dizziness. As a result, most of the children were not able to achieve therapeutic plasma levels.[46]

The US Food and Drug Administration (FDA) has given expedited review to intranasal formulations of epinephrine based on preliminary trials that demonstrated effective absorption equivalent to IM injection.[47] In the future, sublingual administration also may become an option.[48]

Epinephrine may be given IV as a continuous infusion or intermittent boluses when anaphylactic shock is refractory to repeated IM injections (see "Dosage" and "Refractory Anaphylaxis" sections).

Recommendations: Given its effectiveness and rapid administration, IM epinephrine is the first-line treatment for anaphylaxis. The preferred injection site is the anterior lateral thigh, followed by the deltoid (1B). Over-the-counter, metered-dose inhalers of epinephrine have not been found to be a practical or effective treatment for anaphylaxis (1B).

Epinephrine Injection Devices

Various devices are available to inject epinephrine (Table 6), each with advantages and disadvantages. NOLS outfits its trips with a preassembled kit containing an insulin-type syringe with needle and a 1-mL ampule of epinephrine. OB primarily uses epinephrine autoinjectors (EAIs) in addition to prefilled syringes and the syringe-plus-ampule or vial method. Regardless of the device used, with regular training, instructors from both schools have had an excellent safety record on correctly administering epinephrine.

Autoinjectors; Prefilled Syringes

Fixed-dose EAIs have become widely available in hospitals, clinics, emergency medical services, certain public venues, and the field.[49] They are effective, convenient to carry, and eliminate the need to draw medication into a syringe, which may decrease the risk of incorrect dosage.[50] Many can be discharged through clothing, although thicker clothing would likely decrease the depth of delivery. Currently, EAIs are available in 0.1, 0.15, 0.3, and 0.5 mg doses, outfitted with a variety of needle lengths, and manufactured in different styles, depending on the country of origin (Table 6). Their disadvantages include cost, which is compounded by a limited shelf life. The manufacturer's wholesale list price of EpiPen, a widely used brand in the United States, is $609 for a package containing 2 autoinjectors (0.3 or 0.15 mg doses). The list price for a generic dual-pack is $300.[51] (Medical insurance and other factors, however, may greatly decrease the final consumer cost.) In addition, without proper training that is periodically reinforced, both prescribers and patients may use the devices incorrectly[52,53] or cause unintended medication discharge and needle injury.[54-57]

Epinephrine is also available in sterile, prefilled syringes (0.3 and 0.15 mg doses) with a manual plunger and preattached needle. The list price is $250 for a package containing 2 syringes (Symjepi).[51]

To help prevent accidental needle sticks, manufacturers have developed safety features, such as needles that automatically retract after medication discharge (eg, Auvi-Q)

Table 6. Sample epinephrine delivery devices

Name	*Mechanism; medicine container*	*Dose (mg)*	*Needle length (mm)*	*Safety features post-injection*	*Manufacturer*
Autoinjectors					
EpiPen (G)	Spring; cartridge	0.15 0.3	12.7 15.2	Automatic needle guard	Meridian Medical Technologies, United States
Auvi-Q (United States), Allerject (Canada)	Compressed gas; cartridge	0.1 0.15 0.3	7.4 12.7 15.7	Automatic retractable needle	Kaléo, United States
Adrenaclick (G)	Spring; syringe	0.15 0.3	12.7 12.7	Carrier case for syringe + exposed needle	Meridian Medical Technologies, United States
Emerade	Spring; syringe	0.15 0.3 0.5	16 23 23	Automatic needle guard	Medeca Pharma, Sweden
Jext	Spring; cartridge	0.15 0.3	13 15	Automatic needle guard	ALK-Abelló, Denmark
Anapen	Spring; syringe	0.15 0.3 0.5	12.7 12.7 12.7	Manual sliding needle guard	Bioprojet, United Kingdom
Manual injectors					
Symjepi	Plunger; fixed-dose syringe	0.15 0.3	15.9 15.9	Manual sliding needle guard	Adamis Pharmaceuticals, United States
Epi Kit	Plunger on 1 mL syringe; 1 mg epinephrine in 1 mL vial	Variable, up to 1 mg	25.4	Manual sliding needle guard	Curaplex, United States

G, generic versions available.
In a syringe-based autoinjector, the medicine container is connected directly to the base of the needle. In a cartridge-based autoinjector, the medicine container is propelled during injection to connect with the base of the needle. Product specifications subject to change.

and guards that slide over the needle either automatically (eg, EpiPen) or manually (eg, Symjepi).[51]

Vials or Ampules

Epinephrine manually drawn into a syringe at the time of injection is a viable and less expensive alternative to EAIs. The list price for generic epinephrine (1 mg·mL^{-1} concentration) is approximately $3 for a 1 mL vial and $10 to $18 for a 30 mL multidose vial.[58] For cost savings, the vial or ampule plus syringe method is becoming more commonly used among basic life support practitioners in emergency medical services.[59,60] A possible disadvantage to this method is operator error or time delay while calculating the dose and drawing epinephrine into a syringe, especially during an anaphylaxis emergency.[50] The risk of operator error can be lessened by prefilling syringes with epinephrine before a trip or field deployment. With proper technique and storage, the risk of medication inactivation and contamination is reported to be minimal for up to 90 d.[61] In addition, stocking field medical kits with ampules or vials containing 1 mL of epinephrine rather than 30 mL multidose vials limits the total amount of medication that may be given in overdose.

Recommendations: An organization's choice of an epinephrine delivery device depends on considerations of cost, operator training, and safety for both patient and first responder (1C). Autoinjectors may be less prone to dosage error, but they require periodic training to use correctly and avoid injury. With regular training, the ampule or vial and syringe method has been safely used for decades in field conditions by NOLS and OB. A third option involves prefilled or fixed-dose syringes with epinephrine.

Dosage

In the United States, epinephrine is available in 2 concentrations, 1 mg·mL^{-1} and 1 mg·mL^{-1} (formerly 1/1000 and 1/10,000 concentrations, respectively).[62] The standard initial adult dose for anaphylaxis is 0.3 to 0.5 mg IM in the United States and 0.5 mg in Europe (1 mg·mL^{-1} concentration) (Table 7). Clinical experience has

Table 7. Summary of pharmacological treatments for anaphylaxis, with examples in each drug class

Medication	*Route*	*Dosage*	*Indication*	*Recommendation*
Epinephrine (Adrenaline)	IM: anterior lateral thigh > deltoid	0.01 mg·kg^{-1}, up to 0.3-0.5 mg per dose Q 5-15 min PRN	Initial treatment	1A (Epinephrine) 1B (choice of anterior lateral thigh)
	IV	Infusion: 0.1 microgram·kg^{-1}·min^{-1}, titrate to clinical effect Bolus: 50–100 microgram·min^{-1}	Refractory cases	1C
H_1 antihistamines	Diphenhydramine PO, IM, IV	25–50 mg Q 4–6 h Peds: 1 mg·kg^{-1} per dose	Secondary treatment; cutaneous manifestations (rash, edema, pruritis)	1C
	Certirizine PO, IV	10 mg QD Peds: <6 y: 2.5 mg; 6–11 y: 5–10 mg QD		
H_2 antihistamines	Famotidine PO, IV	20 mg BID Peds >3 mo: 0.25 mg·kg^{-1} dose BID	Possible synergistic effect with H_1 antihistamines	2B
β2 agonist	Albuterol		Secondary treatment; bronchospasm	1C
	Metered-dose inhaler, 90 microgram·actuation^{-1}	2 inhalations; frequency varies with severity		
	Nebulizer solution	≥12 y: 2.5–5 mg 5–12 y: 1.25–2.5 mg; 1–5 y: 1.25 mg		
Corticosteroids	Prednisone PO	1-2 mg·kg^{-1}, up to 50–60 mg QD Peds: ÷ Q12–24 h	Secondary treatment; bronchospasm; asthmatic patient; possible prevention of biphasic reaction	1C
	Methylprednisolone PO, IM, IV	1–2 mg·kg^{-1}, up to 40-60 PO/IM QD, 80-125 mg IV QD Peds: ÷ Q12–24 h		
	Dexamethasone PO, IM, IV	6–9 mg QD Peds: 0.3 mg·kg^{-1} QD		
Glucagon	IV	Initial dose: 1–5 mg Peds: 0.02–0.03 mg·kg^{-1}, up to 1 mg per dose Subsequent infusion at 5–15 microgram·min^{-1}, titrate to clinical effect	Refractory cases in patients on β blockers	2C
Desensitization therapy	SQ, PO	Protocol of sequentially increasing antigen dose.	Prior anaphylaxis to *Hymenoptera* venom or peanuts	1B

BID, twice per day; IM, intramuscular; IV, intravenous; Peds, pediatric dose; PO, orally; PRN, as needed; Q, every; QD, per day; SQ, subcutaneous.
Unless otherwise specified, the maximum pediatric dose is the adult dose. Duration of treatment with antihistamines and corticosteroids is generally 3 to 5 d (1–2 d with dexamethasone). Dosing reference: Kleinman et al.[121]

Table 8. Recommended minimum needle length (22–25 gauge) for IM injection of patients according to body weight

Weight kg (lb)	*Minimum needle length for IM injection (mm)*
Female or male <60 (130)	16
Female or male 60–70 (130–152)	25
Female 70–90 (152–200)	25
Male 70–118 (152–260)	25
Female >90 (200)	38
Male >118 (260)	38

Adapted from: National Center for Immunization and Respiratory Diseases.[122]

confirmed the safety and efficacy of this dose range.[13] The pediatric IM dose is 0.01 mg·kg^{-1} of body mass until the adult dose is reached.[63] For pediatric EAIs, 0.15 mg is an accepted dose for patients weighing 7.5 to 25 kg.[64] For both children and adults, there is no cumulative maximum dose. Repeat IM doses can be given as needed every 5 to 15 min if there has been no improvement.[13]

Although the majority of cases resolve after 1 dose, a reported 8 to 12% of ED adult and pediatric anaphylaxis patients have required 2 or more epinephrine doses during initial treatment (not for a biphasic reaction).[65,66] In urban pediatric EDs, 6 to 19% of anaphylaxis patients have required 2 or more initial doses.[63]

For adult IV administration, generally in hospital settings for refractory anaphylaxis (see the following), 1 mg of epinephrine may be added to 1 L of normal saline, producing a concentration of 1 microgram·mL^{-1} and started at a drip of 0.1 microgram·kg^{-1}·min^{-1}, with careful hemodynamic monitoring. Alternatively, 1 mg of epinephrine may be added to 10 mL of normal saline, producing a concentration of 0.1 mg·mL^{-1}, and given slowly via IV bolus starting at 50 to 100 microgram·min^{-1} (0.5–1 mL·min^{-1}). Subsequent rates and doses are titrated to effect. In infants and small children, the concentrations of IV epinephrine solutions are weight-based and adjusted so as to not infuse an excess amount of fluid.[67]

Recommendations: Standard IM doses of epinephrine may be repeated every 5 to 15 min for an inadequate response to initial anaphylaxis treatment or hours later for a biphasic reaction (1B).

Needle Length

In the United States, the EpiPen needle length is 16 mm for adults and 13 mm for pediatrics. In Europe, needle length in adult EAIs may reach 23 mm (eg, Emerade). Studies using ultrasound to measure adipose thickness in the adult lateral thigh have questioned whether the 16 mm needle is long enough to deliver epinephrine into the muscle layer of many female patients (who may have a thicker adipose layer at the thigh compared to males) as well as patients with obesity.[45,68,69] These concerns, however, are based on a surrogate marker of clinical effectiveness (thickness of adipose tissue) rather than on actual clinical outcomes or pharmacological studies. In actual use, EAIs compress the SQ tissue and also deliver medication with propulsive force, both of which contribute to the depth and effectiveness of injection.[70] Therefore, the available pharmacological studies suggest that EAIs administered into the anterior lateral thigh deliver an effective medication dose in the majority of patients.[47] Although certain adult patients with obesity or thick adipose tissue in the thigh may benefit from a longer needle (23–25 mm), current evidence does not exactly characterize such patients. On the other hand, a 16 mm or longer needle may be too long for small children and risk penetrating bone.[71]

For injections using a manual syringe with plunger, published guidelines for needle length needed to reach muscle tissue are based on vaccine administration in outpatient settings. The recommended needle length varies from 16 to 38 mm depending on body weight and sex (Table 8). A 22- to 25-gauge needle is acceptable for all needle lengths. A 16 mm needle may deliver an effective IM dose of epinephrine in fit adolescents and young adults, but 25 mm should be considered in large adults or obese patients. Compressing the SQ tissue and pushing the plunger with propulsive force may render the 16 mm needle effective in large adults or obese patients, but this has not been definitely studied in anaphylaxis.

Recommendations: In general, an EAI with a 16 mm needle delivers an effective dose of medication in adult patients (1B), although obese patients may benefit from a longer needle (2B). For manual syringes, a 16 mm needle delivers an effective IM dose in fit adolescents and young adults, though a 25 mm or longer needle should be considered in large adults or obese patients (1C).

Storage

Environment

Manufacturers recommend keeping epinephrine at temperatures between 20 and 25°C (Meridian Medical Technologies, Columbia, MD). These conditions cannot always be met in the field. Limited research, however, suggests that temperatures exceeding this range will have little impact on potency over short durations. As an extreme example, EAIs experimentally stored at 70°C for 5 d delivered 97±4% of labeled dose compared to room temperature controls.[72] Conversely, freezing neither inactivates epinephrine[73,74] nor damages an EAI (EpiPen) for use after thawing.[75]

Insulated carrying cases designed to protect medications from high temperatures are available (Frio, Walnut Creek, CA) but require independent field testing and additional corroboration of efficacy.

Expiration Dates

For disaster or austere conditions, multiple reports suggest that acceptable epinephrine potency is retained as long as 24 mo beyond the expiration date.[76-79] The US Army Health Command in Europe has extended the expiration dates of EAIs by 6 mo due to manufacturing shortages.[80] In the United States, the FDA has extended the expiration dates of EAIs by 4 mo and prepackaged epinephrine syringes by 9 mo due to similar shortages.[81]

Recommendations: During manufacturing shortages, US government agencies have approved the use of epinephrine for up to 9 mo past the expiration date. This extension provides a potential rationale, but not regulatory approval, for the use of recently expired epinephrine in shortages associated with austere or disaster conditions (2C). In addition, uncontaminated epinephrine may retain its potency despite short excursions to high or low temperatures as may occur in the field (2B).

Complications

National and international guidelines note the lack of absolute contraindications for epinephrine in anaphylaxis.[13,26,63] Serious adverse events with therapeutic dosing, including arrhythmias, stroke, and myocardial infarction, are rare and generally have affected the elderly or individuals with a history of coronary artery or cerebrovascular disease.[82,83] A few cases of myocardial infarction in young, healthy patients have been reported, presumably due to coronary artery vasospasm.[84] On the other hand, cardiac complications attributed to epinephrine may result instead from the effects of anaphylaxis itself.[85,86]

Cases of cardiac dysrhythmias and myocardial infarction have been associated with IV epinephrine and attributed to accidental overdose, rapid administration, or insufficiently diluted medication.[87-90]

Complications also may result from mechanical operation of the EAI. Lacerations and embedded needles have occurred in children who have forcefully withdrawn from the autoinjector needle. To decrease the risk of such injury, caregivers should receive education on firmly immobilizing the limb during injection. In addition, the EAI should be pressed against the skin only with the force required to deploy the spring or cartridge-loaded needle (1-3.5 kg [2-8 lb] of pressure) and only for the time required to deliver the medication (about 3 s).[91] Inadvertent digital injection of epinephrine has occurred from handling the needle end of the autoinjector after safety lid removal. The resulting local vasoconstriction and ischemia have been treated effectively with warm compresses, topical nitroglycerin, or, in severe cases, phentolamine injected into the affected finger. Digital necrosis or permanent injury from inadvertent epinephrine injection has not been reported.[55]

Recommendations: Absolute contraindications to epinephrine in anaphylaxis are lacking; however, IV administration carries additional risks and generally requires advanced medical expertise and monitoring (1C). Proper limb immobilization and injection technique may decrease the risk of EAI-associated injuries, especially in children. For inadvertent digital injection of epinephrine, treatment options include warm compresses, topical nitroglycerin, and, in severe cases, local phentolamine injection (1C).

Legal Considerations

Historically, training nonmedical first responders to inject epinephrine has involved controversy and uncertainty, especially in light of different state regulations. Controversies have included whether such training promotes practicing medicine without a license, as well as the liability implications of a provider writing, and a pharmacist dispensing, a prescription to an organization rather than an individual. To some extent, these concerns have been addressed by the Federal School Access to Emergency Epinephrine Act of 2013, which supported trained lay providers administering epinephrine for anaphylaxis in elementary through secondary schools. Expanding upon this act, individual states have passed legislation (commonly known as "stock epinephrine entity laws") to include other locations where anaphylaxis may occur, including daycare centers, recreational camps, theme parks, and sporting events.[92] In general, state laws on stocking emergency epinephrine in public venues have favored EAIs or FDA-approved prefilled syringes to help reduce the risk of a dosing error or needle injury that may occur when manually drawing medication from a vial into a syringe. An exception is illustrated by the state of Alaska, which has approved the use of vials and syringes by lay providers who have obtained state-approved certification.[93]

Regardless of the epinephrine delivery device chosen, the US Occupational Safety and Health Administration has issued guidelines requiring the use of engineering controls and standard procedures to protect worker safety by reducing the risk of needle injury and transmission of bloodborne pathogens.[94] Outdoor schools and organizations that carry epinephrine into the field therefore must consult and follow both the relevant federal guidelines as well as state-specific laws.

SUPPLEMENTARY TREATMENTS

National and international guidelines list antihistamines, corticosteroids, and inhaled β agonists as acceptable secondary treatments for anaphylaxis that should not substitute or delay epinephrine administration.[13,26,63,95] Table 7 lists representative medications, administration routes, and dosages.

Antihistamines

H_1 antihistamines such as diphenhydramine bind to and block H_1 histamine receptors in mast cells, smooth muscle, and endothelium. They improve the cutaneous manifestations and pruritus of allergic reactions.[96] Early administration of antihistamines with epinephrine has been associated with blunting the overall severity of anaphylaxis and reducing the total number of epinephrine doses needed.[66] On the other hand, antihistamines do not reverse vascular dilation and airway constriction or edema, nor do they inhibit the release of other inflammatory mediators.[97] Their role in preventing a biphasic reaction is possible but uncertain.[13,66]

Potential side effects include sedation and anticholinergic reactions, such as dry mouth, tachycardia, and urinary retention. Second generation antihistamines such as loratadine are less likely to cause sedation. In hospital and certain prehospital settings, IV administration of H_1 antihistamines may cause vascular dilation if injected too rapidly.[98]

H_2 antihistamines such as famotidine or ranitidine have been used in combination with H_1 antihistamines to treat allergic reactions with improved outcomes compared to H_1 use alone.[99] Evidence to support an additive therapeutic effect specifically in anaphylaxis, however, is inconclusive.[100]

Recommendations: Antihistamines may help blunt the overall severity of anaphylaxis when given early with epinephrine (1C). Non-sedating antihistamines may be preferred in the field to help keep the patient alert and potentially able to walk (2B). The addition of an H2 antihistamine to an H1 antihistamine has improved outcomes in allergic reactions and may be beneficial in anaphylaxis, but the exact incremental benefit is unknown (2B).

Inhaled β Agonists

This class of medications is a mainstay for the treatment of asthma exacerbations but an adjunct to treating the lower airway constriction and wheezing that may occur in anaphylaxis.[63,95,101] Possible side effects include tachycardia and a temporary decrease in serum potassium (which shifts into cells) and increase in serum glucose.[102]

Recommendations: Inhaled β-agonists may be administered as adjunctive treatment for wheezing, especially in a person with a history of asthma (1C).

Corticosteroids

The anti-inflammatory effects of corticosteroids stabilize mast cells and blunt the cascade of inflammatory mediators. Corticosteroids have been used in anaphylaxis based on their efficacy in asthma[103] as well as theoretical mechanisms of action. The onset of their anti-inflammatory effect may not occur for several hours, regardless of oral or parenteral administration.[104] Studies have suggested that corticosteroids diminish the possibility of a biphasic reaction, although this finding has not been consistently replicated.[31,105,106] In 1 review, prehospital administration of corticosteroids for anaphylaxis was associated with increased hospital or ICU admission; however, confounding variables and selection bias may have contributed.[66]

The optimal route and dose for steroids in anaphylaxis have not been established. Common practice in the ED is 50 to 60 mg of oral prednisone for stable adult patients who are not vomiting, or 80 to 125 mg of methylprednisolone IV for severely ill patients. The pediatric dose is 1 to 2 $mg{\cdot}kg^{-1}$ orally or IV until the adult dose is reached. The total duration of steroid treatment (commonly with antihistamines) is generally 3 to 5 d (1–2 d for dexamethasone, given its long half-life) with the theoretical aims of reducing the risk of biphasic reaction and offsetting any lingering allergen effect, especially with gastrointestinal absorption that may continue past the day of ingestion.[35] Side effects are uncommon with short-term use and may include blood glucose elevation in diabetic patients, agitation in the elderly, exacerbation of peptic ulcer disease, and increased infection risk in immunosuppressed patients.[104]

Recommendations: Evidence of benefit for corticosteroids in anaphylaxis is inconsistent; however, pending conclusive evidence, continued empiric use is reasonable given the potential for benefit paired with a low side-effect profile (1C). In particular, corticosteroids should be given for anaphylaxis with a respiratory component in asthmatic patients (1C).

FIELD PROTOCOLS

Both the NOLS and OB field protocols (see online Appendix 1 and 2) stipulate that individuals who have been treated with epinephrine for anaphylaxis be evacuated from the field. The actual decision to evacuate, however, as well as the modality (eg, air or ground) and

timing of evacuation depend on multiple factors. These include environmental and safety considerations, such as the local terrain, weather, visibility, and distance to definitive care. Medical factors should also be considered, including the severity of the reaction; patient comorbidities and risk factors for a biphasic reaction; medical training of field providers; availability of medical control; and contents of the medical kit, including additional doses of epinephrine. Preparations for litter transportation should be made for patients with ongoing cardiovascular or respiratory symptoms. Patients should be transported in a position of comfort—those with hypotension may benefit from recumbency, whereas those with breathlessness may not tolerate a supine position.[2]

As a potentially life-saving measure in the field, off-label techniques have been described for disassembling an EAI after IM administration to obtain an additional epinephrine dose when no other source is available.[107,108] This procedure involves a significant risk of injury from the spring or cartridge-loaded needle, which remains under tension even after medication discharge, and requires practice under controlled conditions. Knowledge of this procedure, however, should never replace proper planning for an adequate, reliable supply of medication in the field.

Recommendations: In the field, medical evacuation is generally recommended after treatment of anaphylaxis (2C). The actual decision to evacuate, however, may be influenced by case-specific factors, such as geography, weather, field capabilities, and patient characteristics and response to treatment. These factors also may influence the timing and method of evacuation. For austere or disaster conditions, off-label techniques for disassembling an EAI after IM administration to obtain another epinephrine dose are available and should be considered an inherently risky but potentially life saving measure when no other source is available (2C).

REFRACTORY ANAPHYLAXIS

Refractory anaphylaxis has been defined as requiring 3 or more epinephrine doses during initial treatment and occurs in approximately 1% of cases.[65,66] In contrast, persistent anaphylaxis has been defined as lasting 4 or more hours despite initial treatment.[109] Epinephrine may be given every 5 to 15 min IM to treat refractory anaphylaxis, along with the secondary treatments of antihistamines and corticosteroids, as well as inhaled β agonists for patients with bronchospasm. Where available, supplemental oxygen should be given for hypoxia and crystalloid solutions for volume replacement and hypotension. Persistent shock or hypoxia requires critical-care measures including positive-pressure ventilation, intubation, and advanced cardiovascular monitoring, generally in hospital settings. In these instances, epinephrine may be given IV as a continuous infusion or with slow boluses. Other vasopressors should also be considered.[20,26,35,95,110] For patients on β blockers, a few case reports have suggested that glucagon may be beneficial in refractory anaphylaxis.[111,112]

Recommendations: Epinephrine may be given every 5 to 15 min IM to treat refractory anaphylaxis, along with the secondary treatments of antihistamines and corticosteroids, as well as inhaled β agonists for patients with bronchospasm (1C). For hypotension after epinephrine administration, IV crystalloids may be given with additional doses of IM epinephrine (1C). For persistent hypotension, IV epinephrine or an alternative vasopressor may be considered, in addition to standard critical-care measures (1C). For patients on long-term β blocker medication with refractory hypotension, glucagon is an option (2C).

POST-TREATMENT OBSERVATION PERIOD

The length of observation for patients after successful treatment of anaphylaxis is not clearly established, although there is consensus that it should vary with the severity of the initial reaction and risk factors for a biphasic reaction.[31] Ideally, observation should occur in a hospital or setting able to treat recurrence of symptoms with additional epinephrine, as well as the ability to address respiratory or hemodynamic decompensation. A recent meta-analysis concluded that 1 h of observation post-treatment achieved a 95% negative predictive value for detecting a biphasic reaction, and 6 and 8 h of observation achieved a 97% and 98% negative predictive value, respectively.[113]

Based on these findings, the American Academy of Allergy, Asthma, and Immunology has proposed that patients with nonsevere presentations, a prompt response to treatment, and low risk for a biphasic reaction be observed in a medical center for 1 h before discharge. Patients with a more severe presentation, significant comorbidities, or requiring multiple doses of epinephrine may benefit from a prolonged observation period up to 6 h or longer.[13] In addition, European guidelines have suggested a minimum monitoring period of 6 to 8 h for patients presenting with respiratory compromise and 12 to 24 h for patients with hypotension.[110] After observation and discharge, patients should receive an epinephrine prescription and be advised to follow up for allergy testing and consideration of immunotherapy.[114]

Recommendations: The length of observation after treatment of anaphylaxis depends on the severity of the initial reaction and risk factors for a biphasic reaction (1C). In patients with nonsevere reactions, a prompt

response to treatment, and low risk for a biphasic reaction, observation for 1 h may be sufficient (2B). Patients with more severe presentations, significant comorbidities, or requiring multiple doses of epinephrine may benefit from a minimum observation period of 6 h, or 12 to 24 h for presentations that involve cardiovascular compromise and hypotension (2B). Before discharge from a medical center, patients should receive an epinephrine prescription and be advised to follow up for allergy testing and consideration of immunotherapy (1C).

Prevention

The most important preventive strategy is avoidance of known allergens. This is not always possible, especially with *Hymenoptera* encounters in the outdoors. Desensitization protocols with SQ insect venom injections have been effective for at-risk individuals with a history of moderate to severe reactions.[115,116] For food-based allergies such as peanut, desensitization may be based on gradually increasing doses of prescription oral antigen. Of note, all desensitization protocols may reduce rather than eliminate allergic symptoms.[117]

Avoidance of food-based allergens is achieved by careful pre-trip medical screening of participants followed by appropriate selection of group provisions. All participants should be informed of the allergies present and advised of the importance of not exposing those at risk. Even with such measures, however, avoidance of allergens is challenging because many foods are produced in facilities that process a range of ingredients and may contain traces of potential allergens—an effect known as cross-contamination. The FDA does not require manufacturers to declare potential cross-contamination on food labels, although many do.[118]

Although pretreatment with antihistamines and steroids is widely used to prevent an allergic reaction to radiocontrast injection in the short term, a similar protocol has not been developed for the prevention of anaphylaxis to environmental or food-based allergens. In particular, the use of antihistamines to prevent allergic reactions or anaphylaxis in asymptomatic individuals prior to allergen exposure has shown inconsistent results.[119]

Recommendations: Desensitization protocols to *Hymenoptera* venom and peanuts are available and should be considered in patients with prior anaphylactic reactions to these antigens (1B).

Conclusions

Based on the injury and illness databases of NOLS and OB, anaphylaxis occurs in 0.01 to 0.03% of students in outdoor education courses, but its incidence appears to be increasing in recent decades. This increase is associated with a rise in the prevalence of food allergies among students in both schools, as well as children in the general US population. Since 2010, the Wilderness Medical Society has supported the concept that nonmedical professionals such as outdoor educators and guides whose work responsibilities include providing emergency medical care in the field also be trained to appropriately administer epinephrine for anaphylaxis. This position is strengthened by the finding that over 20% of the anaphylaxis cases in the NOLS and OB databases were first-time reactions in individuals without a known history of allergy or need to carry their own epinephrine. The top causes of anaphylaxis were food-based allergens or insect stings and bites.

The primary prehospital or field treatment for anaphylaxis is IM epinephrine. An organization's choice of an epinephrine delivery device depends on multiple factors, including cost, safety, provider training, as well as federal and state regulations. Antihistamines, corticosteroids, and inhaled β agonists are supplemental treatments for anaphylaxis that should not delay epinephrine administration. Formulations of intranasal and sublingual epinephrine are currently under development and may provide alternatives to needle-based devices in the future.

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Supplemental Material(s)

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