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Review

Anaphylaxis: recognition, treatment, and outcomes

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Abstract: Anaphylaxis is defined as an acute, life-threatening, systemic allergic reaction associated with a broad array of clinical manifestations. Anaphylaxis typically is a type 1 (IgE mediated) hypersensitivity reaction though other mechanism may also be involved. Patients most commonly present with cutaneous symptoms followed by respiratory and gastrointestinal symptoms. Prompt recognition and treatment can be life saving. Epinephrine is the drug of choice for treatment of anaphylaxis. It is imperative that patients and their caregivers are educated on the use of epinephrine autoinjectors and provided with an emergency action plan for managing anaphylaxis.

Keywords: anaphylaxis; life-threatening; hypersensitivity; epinephrine; action plan

Abbreviations: AAAAI: American Academy of Allergy, Asthma, and Immunology; ACE: Angiotensin converting enzyme; AIE: Auto-injectable epinephrine; BP: Blood pressure; CGRP: Calcitonin gene-related peptide; CT: Computerized tomography; EEG: Electroencephalogram; EIA: Exercise induced anaphylaxis; EKG: Electrocardiogram; ER: Emergency room; HAE: Hereditary angioedema; HCP: Health care professional; Ig: Immunoglobulin; MCT: Mast cell tryptase; NSAIDs: Non-steroidal anti-inflammatory drugs; PAF: Platelet Activating Factor; RCM: Radio-contrast media; TNF: Tumor necrosis factor; US: United States; USP: United States Pharmacopeia; UV: Ultra-violet; VCD: Vocal Cord Dysfunction; WAO: World Allergy Organization

1. Introduction

Anaphylaxis is an acute, life-threatening allergic reaction associated with wide array of systemic manifestations [1]. In most cases, it is an immunoglobulin (Ig) E–mediated reaction. However, other mechanisms may be involved such as IgG or complement-mediated immunologic reactions that result in degranulation and release of mediators from mast cells and basophils [1]. The most common cause of anaphylaxis is food allergy followed by drugs/medications [2]. Other common causes include insect stings and latex [2]. The most common foods causing anaphylaxis are cow's milk in infants, peanuts in children, and tree nuts and shellfish in young adults [2]. Beta-lactam antibiotics are the most common culprits of drug-induced anaphylaxis [2].

Patients with anaphylaxis commonly present with cutaneous symptoms followed by respiratory and gastrointestinal symptoms [2]. A diagnosis of anaphylaxis can also be established if hypotension is the only clinical manifestation following exposure to a known allergen for that individual. Epinephrine is the drug of choice for treatment of anaphylaxis. Delayed use of epinephrine has resulted in increased risk of hospitalization and death [2]. Thus, all patients diagnosed with anaphylaxis should be educated and provided with epinephrine autoinjectors as well as an emergency action plan for the management of anaphylaxis.

2. Epidemiology

Prevalence of anaphylaxis varies widely and has been increasing worldwide, particularly in developed countries [1,2]. Studies have shown that prevalence of anaphylaxis can vary between 1.6–5.1% [1,2]. Incidence of anaphylaxis has been estimated at 42 per 100000 person-years [3]. Hospitalizations related to anaphylaxis increased from 2000 to 2010, with children between 0–4 years of age being at highest risk of hospitalization [3]. Severe anaphylaxis has been associated with certain risk factors such as older age, asthma, cardiovascular disease, and other coexisting, comorbid conditions [4]. Atopy is a risk factor for food, exercise and latex associated anaphylaxis [5].

In US, the prevalence of fatal anaphylaxis is between 0.47–0.69 per million persons [6]. Most important causes of fatal anaphylaxis include drugs [such as beta-blocker and ACE inhibitor (Angiotensin converting enzyme)] (29–58.5%) [6], insect bites (3.3–54%) [7] and food (2–6.7%) [8]. Amongst these, drug-related anaphylaxis rates have increased [6]. Fatal drug-induced anaphylaxis increased significantly over 12 years: 0.27 (95% CI, 0.23–0.30) per million in 1999 to 2001 to 0.51 (95% CI, 0.47–0.56) per million in 2008 to 2010 ($P < 0.001$) [9]. Mast cell disease has also been recognized as a risk factor for fatal anaphylaxis [5].

3. Pathogenesis

Anaphylaxis typically is a type 1 (IgE mediated) hypersensitivity reaction which is associated with release of mediators such as histamine, tryptase, from mast cells and basophils [1,10]. These mediators are responsible for various clinical manifestations of anaphylaxis including hives, itching, bronchospasm and hypotension. In animal models, immune complex and IgG mediated immunologic reactions have been shown to cause anaphylaxis.

Non-immunologic mechanisms can also be involved in pathogenesis of anaphylaxis [10]. These include direct activation of mast cell and basophils as well as the complement cascade.

Non-immunologic mechanisms usually are involved in anaphylaxis caused by opioids, radio-contrast media (RCM), ethanol, physical activity, cold, heat and sunlight/ultra-violet (UV) radiation. Previously these types of reactions were termed anaphylactoid reactions, but that term has now been eliminated. The World Allergy Organization (WAO) has classified anaphylaxis as allergic when the reaction is immune mediated (IgE, IgG, or immune-complex) and nonallergic anaphylaxis when the reaction is not immunologically mediated [2]. Both the IgE-mediated and non-IgE-mediated mechanisms release platelet-activating factor, whereas only the IgE-dependent mechanism releases histamine. Regardless of the pathogenesis, the symptoms of anaphylaxis are identical in IgE mediated as well as non-IgE mediated anaphylaxis [11].

4. Etiology

Anaphylaxis can occur following various exposures. Common causes include foods, medications, insect sting/bites and exercise. Foods and insect bites are the most common triggers amongst children and adolescents while amongst adults, medications and insect bites are the most common causes [1,12]. In general, food allergy is the most common cause of anaphylaxis and affects up to 8 to 11% children and adults. Anaphylaxis related to food allergy accounts for almost 50% of emergency room (ER) visits amongst anaphylaxis cases in US [13]. In children, food induced anaphylaxis is the most common trigger and accounts for 37–85% cases [14]. In adults, food allergens are the 3rd most common cause of anaphylaxis accounting for 16% of cases [15]. Fatal food-induced anaphylaxis has been associated with certain risk factors such as adolescent age, asthma, peanuts/tree nut allergy, past history of anaphylactic reaction and absence of cutaneous manifestations [16].

Drug allergy is the second most common cause of anaphylaxis. Adverse drug reactions affect up to 10% population and accounts for 20% of hospitalizations [13]. Beta-lactam antibiotics, followed by non-steroidal anti-inflammatory drugs (NSAIDs) are the most common causes of drug-induced anaphylaxis which is IgE mediated. Opioids and RCM cause direct mast cell activation which results in symptoms of anaphylaxis. Use of non-ionic low osmolality RCM can minimize contrast media mediated reactions. Perioperative anaphylaxis can be due to multiple agents such as antibiotics, neuromuscular blocking agents, natural rubber latex, blood products and chlorhexidine [9,17].

Venom hypersensitivity reactions affects 0.5–3% of the population in US. Of note, most fatalities have been reported in patients who have not previously experienced systemic reaction to Hymenoptera [13].

Exercise induced anaphylaxis (EIA) occurs after physical activity and is often associated with direct mast cell activation [17]. EIA can occur after ingestion of some foods such as wheat and celery [17].

Idiopathic anaphylaxis is usually a diagnosis of exclusion. It tends to be rare in pediatric age group. Amongst adults, the underlying cause is not determined in almost two-third of the cases [10]. These patients should be evaluated for underlying mast cell diseases [10].

Table 1 elucidates the common causes of anaphylaxis [1,12].

Table 1. Common causes of anaphylaxis.

Cause	Example	Mechanism
Foods	Peanut, Tree nuts, Egg, milk, fish, shellfish	IgE mediated
Medications	-B lactam antibiotics, NSAIDs, Biologic agents -Vancomycin, RCM, Opioids	-IgE mediated -Non-IgE mediated
Hymenoptera	Honeybee, Yellow jacket, wasp, hornet, imported fire ant	IgE mediated
Exercise Induced	Physical activity	Non-IgE mediated

Note: NSAID: Non-steroidal anti-inflammatory drugs; RCM: Radio-contrast media.

5. Clinical presentation

Anaphylaxis is associated with a broad array of clinical manifestations. Most common clinical findings include involvement of skin/mucosal surfaces (62–90%) followed by respiratory (45–70%), gastrointestinal (25–45%) system and neurological (5–15%) systems [10,18].

Cutaneous manifestations include urticaria, pruritus, flushing and angioedema. Patients may present with swelling of eyelids, lips, tongue and uvula. Occasionally, larynx may be involved which can be life threatening [10,18].

Symptoms of respiratory system involvement include stridor, congestion, rhinitis, dyspnea, sensation of throat closing, cough, wheezing and hypoxia. Patients may develop gastrointestinal symptoms such nausea, vomiting and abdominal pain. Neurological symptoms such as headache, confusion, and hypotonia may be present. A small subset of patients (10%) may present with profound shock in the absence of any cutaneous manifestations which can make the diagnosis of anaphylaxis very difficult. Table 2 summarizes clinical symptoms of anaphylaxis [10,18].

Table 2. Clinical presentation.

Organ system	Frequency	Symptoms
Cutaneous	62–90%	Urticaria, pruritus, flushing and angioedema of eyelids, lips, tongue, uvula
Respiratory	45–70%	-Upper airway—Stridor, congestion, rhinitis, choking -Lower airway—dyspnea, wheezing
Gastrointestinal	25–45%	Nausea, vomiting, diarrhea, abdominal pain
Cardiovascular	10–45%	-Chest pain, diaphoresis, tachycardia, hypotension -Occasionally, bradycardia may be present (caused by Bezold-Jarisch reflex)
Neurological	5–15%	Headache, confusion, hypotonia, incontinence, seizure, unconsciousness
Other		Metallic taste in mouth, uterine cramping/bleeding

Biphasic anaphylaxis is defined as second anaphylactic reaction which occurs within 1 to 72 hours of the initial reaction in the absence of allergen exposure. This can occur in up to 0.4–23%

patients presenting with anaphylaxis [17]. Patients who present with severe anaphylaxis and/or require more than 1 dose of epinephrine are at risk for biphasic anaphylaxis. Other risk factors for biphasic reaction include unknown trigger of anaphylaxis, drug as a trigger in children, cutaneous signs and symptoms, and wide pulse pressure. On the other hand, in patients with protracted anaphylaxis, symptoms of anaphylaxis can last from hours to several days [17].

Certain factors can increase the severity of anaphylaxis such as age, atopy, asthma, exposure to ingested allergens, certain drugs, mastocystosis, and comorbid conditions [9,17]. Certain age groups are more prone to have more severe episodes. In infants, diagnosis of anaphylaxis may be missed while in teenagers, increased risk may be related to risky behavior. At old age, comorbidities and certain medications (β-blockers, ACE inhibitors) can increase severity of an episode as well as complicate treatment. Presence of asthma increases risk of fatal anaphylaxis. Mastocytosis is associated with increased frequency as well as severity of cardiovascular manifestations. Comorbidities such as chronic renal and pulmonary conditions as well as cardiovascular diseases can also increase risk of fatal events [9,17].

6. Diagnosis

Anaphylaxis is usually diagnosed based on clinical presentation. Laboratory tests are usually not required [2,17].

6.1. Clinical diagnosis

Anaphylaxis is likely when one of the following three criteria outlined in Table 3 are fulfilled [9,17,19].

Table 3. Diagnosis of anaphylaxis.

Numbers	Clinical manifestations
1. Acute onset of symptoms (within minutes to several hours) with	-Involvement of skin/mucosa(urticarial, itching, angioedema) And -Either respiratory involvement(dyspnea, wheezing, stridor, hypoxia) Or -Hypotension/end-organ dysfunction(collapse, syncope, incontinence)
2. or more of the following after exposure to *likely* allergen for that patient	-Involvement of skin/mucosa (urticarial, itching, angioedema) -Respiratory involvement (dyspnea, wheezing, stridor, hypoxia) -Hypotension/end-organ dysfunction (collapse, syncope, incontinence) -Persistent GI symptoms (vomiting, diarrhea, crampy abdominal pain)
3. Following exposure to known allergen for that patient (within minutes to several hours)	-Hypotension (Infants and children—Low systolic blood pressure (BP) or more than 30% decrease in Systolic BP; Adults—Systolic BP less than 90 mm Hg or more than 30% decrease in Systolic blood pressure)

However, World allergy organization(WAO) combined criteria 2 and 3 and proposed following diagnostic criteria in 2020 [20] outlined in Table 4. Anaphylaxis is very likely when patient exhibits even one of the following 2 criteria.

Table 4. WAO Diagnostic criteria for anaphylaxis.

Numbers	Clinical manifestations
I.	I. Acute onset of an symptoms (within minutes to several hours) involving skin or mucosal tissue, or both (hives, pruritus, swelling) AND at least one of these a. Respiratory involvement (stridor, bronchospasm/wheezing, hypoxemia, difficulty in breathing) b. Hypotension or manifestations of end-organ dysfunction (incontinence, collapse, syncope) c. Gastrointestinal involvement (severe abdominal pain, vomiting) particularly after exposure to allergens other than food.
II.	II. Acute onset (within minutes to several hours) of hypotension/ bronchospasm/laryngeal involvement following exposure to a *known or highly* probable allergen for that patient, even in the absence of cutaneous manifestations

6.2. Laboratory tests

Certain laboratory tests can be used to establish a diagnosis of anaphylaxis. Many mediators are linked to pathophysiology of anaphylaxis. Amongst these, histamine is one of the most important mediators and accounts for most symptoms such as urticaria, itching, flushing, bronchospasm and hypotension. Serum histamine levels tend to remain elevated for less than an hour of onset of anaphylaxis and thus are usually not helpful [17]. Obtaining 24-hour levels of urinary histamine metabolites (N tau- methylhistamine and N tau- methylimidazoleacetic acid) are more helpful than serum histamine levels in evaluation of these patients. Another sample should be collected 24 hours after symptoms resolve.

Serum mast cell tryptase (MCT) levels are often elevated in patients presenting with anaphylaxis. However it is not detectable in all anaphylactic events. Tryptase levels tend to peak in 60–90 minutes after onset of symptoms and remain elevated for up to 6 hours. Studies have shown correlation between elevated tryptase level and severity of an anaphylactic reaction [21,22]. Elevated serum tryptase levels along with elevated levels of other mediators such as histamine, IL-6, IL-10, and tumor necrosis factor (TNF)-receptor 1 have been shown to correlate with degree of hypotension which is a symptom of severe anaphylaxis [23].

Mast cell disorders should be suspected if serum tryptase level remains elevated for more than 24 hours after the resolution of symptoms. These patients can present with recurrent idiopathic anaphylaxis. These conditions are also associated with elevated baseline serum tryptase, plasma histamine levels or 24-hour urinary histamine metabolites [9,17].

Other mediators may also be involved in anaphylaxis such as Platelet Activating Factor (PAF). Studies shave shown highest correlation between increased PAF levels and severe anaphylaxis as compared to histamine and tryptase levels [24].

Skin prick tests and allergen-specific serum IgE levels can be performed to identify the cause of anaphylaxis. However, such testing should be done only as suggested by history [10,17]. Patients should not be tested for broad allergen panels as it can result in false positive results. Evaluation by an allergist should be considered to identify the culprit agent [25]. Typically, skin prick testing is delayed for 6 weeks after anaphylaxis because of the possibility of false negative reaction due to consumption of specific IgE that occurs during the reaction; however, the evidence supporting this practice is controversial. Allergen component testing can be done for allergies related to foods, insect venoms and pets. Component testing helps to identify the specific protein in the food or venom that the patient might be allergic. Allergy to some specific proteins correlates with more severe reactions.

If these tests are not conclusive, challenge can be done to the suspected agents under supervision. These can be done via oral, inhalational or intravenous route [25].

Other tests include serum IgE to alpha gal and occasionally, bone marrow biopsy. Presence of IgE to alpha gal has been shown to be associated with 2 types of anaphylactic events—an immediate reaction to cetuximab and a delayed onset, usually 3–6 hours after consumption of mammalian meat such as beef and pork. This mechanism has now been recognized as an underlying etiology for some of the idiopathic anaphylactic reactions [26].

6.3. Differential diagnosis

Certain conditions can closely mimic anaphylaxis and should be considered when evaluating a patient with anaphylaxis [17,20]. Table 5 [17,20] outlines some of those conditions.

Table 5. Differential diagnosis of anaphylaxis.

Condition	Clinical presentation	Laboratory tests
Vasodepressor (vasovagal) reactions	-Hypotension, diaphoresis, nausea, vomiting, pallor, weakness. -Cutaneous manifestations of anaphylaxis are absent (urticaria, angioedema, flush, and pruritus) -Bradycardia	-Non-specific tests
Flushing syndromes	-Absence of pruritus or urticaria	
-Carcinoid	-Flushing, diarrhea, difficulty breathing, tachycardia	-Chromogranin A
-Vasointestinal polypeptide tumors	-Abdominal pain, nausea, diarrhea and intermittent episodes of flushing.	-Neuroendocrine hormones (vasointestinal polypeptide, neurokinin A, substance P, pancreastatin.)

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Condition	Clinical presentation	Laboratory tests
Flushing syndromes	-Absence of pruritus or urticaria	
-Mastocytosis and mast cell activating syndrome	-Hives, itching, diarrhea, abdominal pain, flushing	-Elevated serum tryptase, plasma histamine, 24-hour urinary histamine metabolites, prostaglandin D2
-Medullary carcinoma of the thyroid	-Facial flushing, diarrhea, bone pain, weight loss, lethargy	-Serum calcitonin, calcitonin gene-related peptide(CGRP)
-Drugs(ACE inhibitors, niacin, nicotine, catecholamines)/Ingestants	-Flushing with history of exposure to ACE inhibitors, niacin, nicotine, or catecholamines/Alcohol	-Non-specific tests
-Pheochromocytoma	-Flushing, headaches, diaphoresis, tachycardia, with hypertension.	-Increased neuropeptide levels
Postprandial or restaurant syndromes		
-Monosodium glutamate	-Symptoms typically develop after eating food from Chinese restaurant. Flushing, nausea, diaphoresis, headache, numbness, burning in oral cavity	-Normal serum tryptase level
-Scombroidosis	-Symptoms develop after eating spoiled, scombroid fish (tunas, bonitos, mackerels). Symptoms are seen in more than 1 person. -Flushing (sunburn like) rather than urticaria.	
-Sulfites	-Symptoms develop after eating foods, beverages and medications that contain sulfites	
Non-organic disease		
-Vocal Cord Dysfunction (VCD)	-Throat tightness, stridor, dysphonia, dyspnea, coughing, wheezing. Cutaneous symptoms are absent.	-Non-specific tests -Pulmonary function test show extra thoracic airway obstruction with flattening of the inspiratory loop. -Flexible laryngoscopy shows abnormal adduction of vocal cords

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Condition	Clinical presentation	Laboratory tests
Non-organic disease		
-Panic attacks	-Acute episodes of excessive fear, diaphoresis, palpitations, dyspnea in absence of cutaneous findings -Possible mild flushing	-Non-specific tests
-Munchausen stridor (factitious anaphylaxis)	-Patients fake symptoms of illness for secondary gain. Typically, symptoms of vocal cord dysfunction.	-Non-specific tests
Miscellaneous		
-Red man syndrome	-Flushing and pruritus on the face, neck, and upper body following vancomycin administration. Patients may also have hypotension.	-Non-specific tests
-Capillary leak syndrome	-Shock with hemoconcentration, gastrointestinal symptoms, recurrent angioedema in association with monoclonal gammopathy	-Non-specific tests
-Hereditary angioedema (HAE) with rash	-Non-pruritic, recurrent episodes of angioedema. Family history of angioedema may be positive in some cases	-C1 esterase inhibitor level and function
Some common diagnoses		
-Asthma	-Wheezing, difficulty breathing, cough	-Based on symptoms, Spirometry
-Generalized urticaria	-Hives, itching	-Non specific tests
-Foreign body aspiration	-Choking, coughing, difficulty breathing	-Chest X-rays, CT scan
-Cardiovascular (myocardial infarction, pulmonary embolus)	-Difficulty breathing, sweating, pallor	-EKG, Echocardiography, CT scan
-Neurologic events (seizure, cerebrovascular event)	-Loss of consciousness, pallor	-EEG

Note: ACE: Angiotensin converting enzyme; CGRP: Calcitonin gene-related peptide; VCD: Vocal Cord Dysfunction; HAE: Hereditary angioedema; EKG: Electrocardiogram; CT: Computerized tomography; EEG: Electroencephalogram

7. Treatment

Epinephrine is the drug of choice for acute treatment of anaphylaxis, irrespective of the underlying trigger. Epinephrine should be administered intramuscularly, in the mid-outer thigh as a single dose of 0.01 mg/kg (maximum dose 0.5 mg in adults and 0.3 mg in children). It can also be administered intravenously, in case of availability of an intravenous access. However, it should not be administered subcutaneously owing to poor blood supply in the subcutaneous tissue. Epinephrine administration can be repeated up to 3 times every 5 to 15 minutes if the patient is not improving clinically. Glucagon can be given to patients who are using β-blockers if they do not respond to epinephrine [9,17,20].

Prompt recognition of anaphylaxis and early administration of epinephrine is life saving and thus strongly recommended. Delayed use of epinephrine has been associated with increased morbidity and mortality [1].

Immediate medical attention should be sought after administration of Epinephrine. Cardiopulmonary resuscitation should be initiated including assessment of airway, breathing and circulation [17]. Patients with laryngeal edema may need advanced airway management and mechanical ventilation. Children should be placed in a comfortable position. Adolescents and adults should be placed in a recumbent position while pregnant women should be placed on the left side. A patient who is experiencing anaphylaxis should be positioned according to the presenting features. The patient should be kept still and avoid sudden abrupt change to a more upright positioning. If the patient is in respiratory distress, sitting position may be preferred as it may help with respiratory effort. In the absence of respiratory distress, patient should be placed in a supine position. If the patient is pregnant she should be positioned in a semi- recumbent position on the left side. An unconscious patient should be placed in the recovery position [19]. The benefit of elevating lower extremities or placing patient in Trendelenburg position is controversial [17].

An infant experiencing anaphylaxis should be held in a supine or semi-reclining position in the caretaker's arms [27].

Intravenous access should be established and fluid replacement started for hypotension. Refractory hypotension may require aggressive fluid resuscitation, epinephrine infusion and dopamine [17]. Oxygen supplementation should be started simultaneously in hypoxic patients. Bronchodilators (nebulized albuterol) should be used for patients who are wheezing and have lower airway obstruction. These can be repeated every 15 minutes, if needed. Patients, who are unresponsive to resuscitative measures, may respond to additional life saving treatment modalities such as extra-corporeal membrane oxygenation [17].

Corticosteroids and antihistamines (H1 and H2 blockers) can be used as adjunctive therapies in management of an acute episode. They should not be used for initial treatment or to replace epinephrine. Because many other mediators in addition to histamine are involved in the pathogenesis of anaphylaxis, antihistamines may not be effective in all patients [28]. H1 antihistamines do not have any effect on airway obstruction or hypotension that occurs during anaphylaxis. They do not inhibit mast cell degranulation though their antihistaminic effect helps to relieve some cutaneous symptoms such as itching and urticaria. Moreover, they tend to have a slow onset of action. Use of Epinephrine, thus, should not be delayed while awaiting response to antihistamines. First and second generation H1-antihistamines can be used. The recommended dose for diphenhydramine, an H1

antihistamine, is 1 to 50 mg/kg (pediatric) and 25–50 mg (adults). There is no proven role of H2 antihistamines in management of anaphylaxis [2,17].

Glucocorticoids also have a slow onset of action (4–6 hours) and thus have no role in the management of an acute episode. They can be administered via intravenous route (1.0 to 2.0 mg/kg per dose of methylprednisolone or equivalent) or orally (1.0 mg/kg, up to 50 mg prednisone). Use of glucocorticoids in anaphylaxis has been extrapolated from studies regarding their role in acute asthma. The use of steroids for preventing biphasic or protracted anaphylaxis is also not strongly supported in many studies [29,30].

After initial treatment, all patients should be kept under direct observation and monitored until their symptoms have completely resolved. Patients who present with severe anaphylaxis and/or require more than 1 dose of epinephrine are at risk for biphasic anaphylaxis and should be observed for extended period of observation, up to 6 hours [31]. In absence of these risk factors, patients should be monitored for 1 hour. Steroids and/or antihistamines have not shown to prevent biphasic anaphylaxis. However, they can be used as secondary or adjuvant treatment [30].

8. Management

Patient education is a key tool in long term management of anaphylaxis. Patient education should focus on avoidance measures of known and likely triggers of anaphylaxis. This should include hidden triggers as well as cross-reactive foods and medications. All patients with anaphylaxis should be referred to an allergist for further evaluation.

All patients with anaphylaxis should be provided with anaphylaxis action plan. Anaphylaxis action plans available at the American Academy of Allergy, Asthma, and Immunology (AAAAI) web site (www.aaaai.org) should be provided to all patients and reviewed during follow-up visits. These plans should be personalized and list triggers of anaphylaxis, common signs and symptoms, instructions for how to use an auto-injectable epinephrine AIE [25]. Patients can use medic alert bracelets or anaphylaxis wallet card listing their triggers and concurrent medications [17,29]. Families should be educated and provided with specific information regarding the triggers and their avoidance [25].

Auto-injectable epinephrine (AIE) should be prescribed to all patients who have experienced anaphylaxis. Under prescription and underuse of epinephrine has been recognized as the most important obstacle for long-term management of anaphylaxis. Patients should be educated that the AIE should be used immediately for the treatment of anaphylaxis. They should also be educated about symptoms of anaphylaxis and also how and when to use AIE. Each patient should carry 2 AIEs as up to 30% patients may require second dose [17]. It should be emphasized to the patient and their family that use of an AIE is not a substitute for immediate medical attention and that they should be evaluated by a health care professional(HCP) soon after using an AIE. Some patients may require more than 2 doses of epinephrine which should be done only under supervision of a HCP. All patients and their caretakers should be provided education regarding recognition of symptom and management of anaphylaxis including calling for help, positioning of patient and administration of self-injectable epinephrine. Patients should be educated to always carry the EAI. Instructions about when and how to use an EAI should be reiterated during follow up clinic visits. They should be provided with educational material regarding the use of an EAI [19].

In the United States, AIEs are available in 2 doses: 0.15 mg (weight <30 kg) and 0.3 mg (weight of ≥30 kg) [18,23]. In recent years, 0.1-mg dose AIE was approved for children who weigh 7.5 to 15 kg. Table 6 [18,23] shows the different types of AIEs available in US.

Table 6. Types of AIEs.

Type of AIE	Dose available
-Adrenaclick	0.15 mg, 0.3 mg
-Auvi-Q	0.1 mg, 0.15 mg, 0.3 mg
-Epinephrine injection, USP auto-injector (generic)	0.15 mg, 0.3 mg
-Epipen	0.15 mg, 0.3 mg

These AIEs differ in shape, needle size, portability, method and ease of use [1,30]. They should be stored at room temperature (20℃ to 25℃) in order to prevent degradation of the medication. Exposure to high temperatures can cause degradation of epinephrine. If the AIE is exposed to freezing temperatures for few days, it should be completely thawed before use [18,23]. HCPs should be familiar with the device prescribed and able to instruct patients and parents in its use.

There are some limitations to the currently available AIEs. The needle length of most AIEs is 1.43 cm which may be too short and medication may not be delivered intramuscularly [29]. For most teenagers and adults as well as obese children, a single dose of 0.3 mg may be sub-therapeutic and they may thereby require a repeat dose. HCP can choose to prescribe slightly higher dose for some patients with a maximum single dose of 0.5 mg [17]. Higher dose EAI [500 mg (0.5 mg)] has been recommended in older children and adults >50 kg, however they are not available in most countries [19].

Adverse effects associated with use of Epinephrine are usually mild and transient including pallor, tremor, headache, anxiety and palpitations. Cardiac effects may also occur such as cardiac arrhythmias and myocardial infarction. However, untreated anaphylaxis can be associated with more severe cardiac complications. Overdose as well as rapid intravenous infusion can cause more serious effects such as pulmonary edema. There are no absolute contraindications to use of epinephrine.

Patients with EIA should always exercise with a partner and carry epinephrine autoinjector. They should avoid doing exercise after eating, and quit exercise at earliest signs of anaphylaxis.

9. Specialist referral

Any patient who has experienced an anaphylactic reaction should be referred to an allergist for identification of the triggers. This has shown to improve clinical outcome, prevented recurrence of similar episodes as well as decreased hospitalizations [1,9,17].

9.1. Avoidance of food

Identification and avoidance of food triggers is the cornerstone of management of food-induced anaphylaxis. However, accidental exposures can still occur [32]. Patients with food-induced anaphylaxis should be evaluated by an allergist including skin testing, component testing and/or oral food challenge as guided by history to identify the culprit allergen. Families should also be educated on how to read food labels, notify restaurants about their food allergies while dining out, avoiding

cross- reactive foods as well as cross-contamination while preparing food. All patients with IgE mediated food allergy should be prescribed an AIE and educated regarding their use. Patients should be instructed to have the AIE readily accessible at all times [17,25].

Patients should be referred to an allergy specialist dietitian who can help patients identify food triggers and also provide advice regarding allergen avoidance [9,17,19]. An allergy specialist dietitian can assess patients' nutritional intake and provide recommendations for appropriate food allergen substitution, thereby avoiding nutritional deprivation. This may be particularly more important for patients with higher caloric/nutritional needs such as children and pregnant women. Thus, regular monitoring by a dietitian should be an integral part of management of these patients which can help to lessen risks of food elimination such as nutritional deficiencies or malnutrition [33].

9.2. Avoidance of drug

Evaluation by an allergist can help to confirm diagnosis of drug allergy, particularly penicillin, using skin prick and intradermal test as well as graded challenge. Similarly, allergists can recommend desensitization procedure if the culprit drug is deemed necessary for treatment and cannot be avoided [18,25]. Patients with drug-induced anaphylaxis should be educated regarding strict avoidance of the culprit drug and all cross-reacting medications. They should be provided a list of medications to be avoided. Patients should be treated with a non-cross-reacting medication from a different class.

9.3. Venom/Hymenoptera

Patients with venom-induced anaphylaxis should be evaluated by an allergist for venom testing and immunotherapy. Venom immunotherapy (VIT) has proven to be safe and effective in reducing severe systemic reactions to subsequent stings [34]. Venom skin testing and immunotherapy are recommended for all patients with venom induced anaphylaxis. Patients who experience only cutaneous systemic reaction without any systemic manifestations are considered as low risk for anaphylaxis and do not require VIT [34]. Patients who develop only large local reactions without any systemic manifestations after insect stings do not require testing or immunotherapy as the risk of anaphylaxis is very low except in certain populations such as bee-keepers [34].

10. Summary

Anaphylaxis is an acute, life-threatening reaction. Thus, prompt recognition and treatment are essential. Foods, medications and insect stings are the most common causes of anaphylaxis. Patients typically present with urticaria, angioedema, respiratory distress, and hypotension. A small subset of patient does not have cutaneous manifestations which can often lead to misdiagnosis or delayed diagnosis. Epinephrine is the mainstay of treatment. Delayed administration of epinephrine is associated with increased morbidity and mortality. All patients with anaphylaxis should be prescribed epinephrine autoinjectors and provided with an emergency action plan. Patient education is a key tool in long term management of anaphylaxis and should focus on avoidance measures of known and likely triggers of anaphylaxis. Patients should be referred for evaluation by an allergist whenever possible. Evaluation by an allergist helps in identification of culprit agent and thus has shown to improve clinical outcomes and reduced hospital admissions.

Conflict of interest

The authors declare no relevant conflict of interest.

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