Anaphylaxis: Early Recognition and Management

6

Won Young Kim

6.1 Introduction

Anaphylaxis is a serious systemic allergic reaction with a sudden onset after exposure to an offending agent [1]. Signs and symptoms can range from relatively mild to life threatening. About 2% of the population suffers from anaphylaxis during their lifetime; common causes are food, medications, and insect stings [2]. Recently the incidence of anaphylaxis is increasing in many countries; the prevention and treatment of anaphylaxis is an important clinical emergency which all healthcare professionals should be able to recognize and manage. Despite the release of a number of guidelines and updated practice on the management of anaphylaxis, there are identified gaps in knowledge and practice as well as barriers to care in emergency department (ED) [3]. Many of the gaps in the treatment of anaphylaxis included the lack of a practical definition of anaphylaxis as it related to physician.

The most well-known consensus clinical definition of anaphylaxis was proposed by Second National Institute of Allergy and Infection Disease/Food Allergy and Anaphylaxis Network Symposium (NIAID/FAAN) in 2005 [4]. The World Allergy Organization (WAO) Guidelines for the assessment and management of anaphylaxis (subsequently referred to as the Guidelines) were published on 3 March 2011 [1]. Recently, the European Academy of Allergy and Clinical Immunology (EAACI) released the EAACI Guidelines for Food Allergy to provide evidence-based recommendations for the recognition, risk assessment, and management of patients who are at risk of experiencing anaphylaxis [5].

The cornerstone of anaphylaxis management is the use of epinephrine as a first-line treatment while reserving H1-antihistamines and corticosteroids as second-line agents. Useful second-line interventions may include removing the trigger where possible, calling for help, correct positioning of the patient, high-flow oxygen, intravenous fluids, and inhaled short-acting bronchodilators. Biphasic anaphylactic reactions have been reported to develop in up to 20% of reactions although the evidence for this is of low quality. In general, patients with moderate respiratory or cardiovascular events should be monitored for at least 4–6 h and, if necessary, up to 24 h [6, 7]. In this chapter, we review and summarize the early recognition and management of anaphylaxis.

6.2 Pathophysiology

Anaphylaxis is an acute, potentially lethal, multisystem syndrome resulting from the sudden release of mast cell-, basophil-, and macrophage-derived mediators into the circulation [8]. The typical

W. Y. Kim
Department of Emergency Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

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pathophysiology of anaphylaxis involves immunoglobulin E (IgE). The term of anaphylactoid reaction has been used to describe IgE-independent events, although the two reactions are often clinically indistinguishable. The WAO dedicated to allergy and clinical immunology has proposed discarding this nomenclature [4]. The WAO categorizes anaphylaxis as either immunologic or non-immunologic. Immunologic anaphylaxis includes both IgE-mediated and IgG-mediated reactions, and immune complex/complement-mediated mechanisms [1]. Non-immunologic anaphylaxis is caused by agents or events that induce sudden, massive mast cell or basophil degranulation, without the involvement of antibodies [1]. Triger factors vary by region, age, and season. Food is the most common cause but drug and insect infestations are relatively common in older adults.

6.3 Initial Approach and Diagnosis

Traditionally, anaphylaxis was defined as based on mechanistically IgE-dependent reaction or on clinical reactions that range from urticarial to life threatening such as hypotension or shock. However, this definition is not useful for non-allergists. Anaphylaxis is defined as a "severe, life-threatening systemic hypersensitivity reaction"; this is characterized by being rapid in onset with life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes [1]. This definition suggests that the diagnosis of anaphylaxis is based on clinical symptoms and signs. The current clinical criteria for diagnosing anaphylaxis are published in NIAID/FAAN second symposium and WAO guidelines (Table 6.1). These widely accepted criteria significantly improve the identification of anaphylaxis and can lead to rapid management.

The first step of the diagnosis of anaphylaxis should be based on the detailed history of clinical symptoms and all substances such as food, exercise, and medications exposed within a few hours before symptoms appear. Symptoms and signs usually occur within 2 h of exposure to the allergen, usually within 30 min for food allergy and even faster with parenteral medication or insect stings [5]. In a large case series of fatal anaphylaxis, the median time from symptoms to

Table 6.1 Definition of anaphylaxis [1, 4]

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:	
Criteria 1	
Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., pruritus or flushing, swollen lips–tongue–uvula) And at least ONE of the following	(a) Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia) (b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
Or Criteria 2	
Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):	(a) Involvement of the skin–mucosal tissue (e.g., generalized hives, itch-flush, swollen lips–tongue–uvula (b) Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, hypoxemia) (c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) (d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
Or Criteria 3	
Reduced BP after exposure to known allergen for that patient (minutes to several hours):	(a) Infants and children: low systolic BP (age specific) or >30% decrease in systolic BP[a] (b) Adults: systolic BP of <90 mmHg or >30% decrease from that person's baseline

[a]Low systolic blood pressure for children is defined as <70 mmHg from 1 month to 1 year, less than (70 mmHg + [29 age]) from 1 to 10 years and <90 mmHg from 11 to 17 years

arrest has been reported as 30, 15, and 5 min for food, insect venom, and parenteral medication, respectively [9].

The clinical manifestations of anaphylaxis depend on the organ systems involved. Multiple symptoms occurring in at least two or more organs such as mucous membrane including skin, respiratory system, cardiovascular system, nervous system, and gastrointestinal system are typical. Thus, the second step of the diagnosis of anaphylaxis is detecting involved organ system. It should be noted that there are five types of involved system, but consensus definition of anaphylaxis classifies into four systems by combining cardiovascular and nervous system (Table 6.1). Among the symptoms of anaphylaxis, cutaneous manifestations occur in most cases. In a recent study describing a cohort of 340 adult patients with anaphylaxis, the skin and mucocutaneous such as pruritus or flushing and swollen lips–tongue–uvula were the most frequently affected organs (86%), followed by respiratory symptoms (68%), cardiovascular and neurologic symptoms (55%), and gastrointestinal symptoms (35%) [10]. However, the symptoms of anaphylaxis differ from person to person for the same cause. Attention should be paid that a patient can have anaphylaxis without shock. Moreover, the progression of anaphylaxis from itching to death is unpredictable. Even when the initial symptoms are mild, there is significant potential for rapid progression to a severe reaction. Thus physician should be familiar with the three diagnostic criteria of anaphylaxis and patients with these symptoms meeting the criteria should be treated as soon as possible.

Blood tests are not necessary for the diagnosis of anaphylaxis. However, measuring serum tryptase and histamine may help to distinguish other diseases with similar symptoms. Blood samples for measurement of tryptase levels are optimally obtained 15 min to 3 h after symptom onset. When the diagnosis is uncertain, serum tryptase greater than 2.0 μg/L at the time of symptom onset 1–2 h often supports the clinical diagnosis of anaphylaxis [11]. However, in anaphylaxis due to food or anaphylaxis without hypotension, tryptase may show normal results because basophils are more involved than mast cells [12].

6.4 Management

Anaphylaxis is a medical emergency. Prompt assessment and management are critically important. In this section of the Guidelines, we discuss a systematic approach to the basic initial management of anaphylaxis, emphasizing the primary role of epinephrine in treatment. It is also important to note that any delay in appropriate treatment increases the potential for morbidity and mortality [7, 13].

6.4.1 Airway Management

Although treatment of choice is epinephrine for anaphylaxis management, the immediate steps involve a rapid assessment of the patient's airway. Intubation should be performed in patients with developing airway compromise and early intubation should be considered if significant edema of tongue, uvula, or voice alteration has developed, especially in patients with short time since the exposure.

6.4.2 Epinephrine

The first-line use of epinephrine is the standard of care for anaphylaxis and is a clear directive in all gridlines [1, 14]. Delaying administration of epinephrine has been associated with increased reaction severity, increased morbidity, a greater likelihood of biphasic reactions, and an increased risk of fatality even in some cases in which the initial symptoms were mild [15–17]. However, recent analysis with nation-wide data on the management of anaphylaxis found that there is a distinct discrepancy between current guidelines and their implementation; for example only 13.0% received epinephrine [18]. To improve the treatment of anaphylaxis, they strongly recommend revision of medical education and practical training.

6.4.2.1 Mechanisms of Action

Epinephrine is lifesaving because of its alpha-1 adrenergic vasoconstrictor effects in most body organ systems (skeletal muscle is an important exception) and its ability to prevent and relieve airway obstruction caused by mucosal edema, and to prevent and relieve hypotension and shock [1, 15, 19]. Other relevant properties in anaphylaxis include its beta-1 adrenergic agonist inotropic and chronotropic properties leading to an increase in the force and rate of cardiac contractions, and its beta-2 adrenergic agonist properties such as decreased mediator release, bronchodilation, and relief of urticaria [20, 21].

6.4.2.2 Route and Dose

Epinephrine should be injected by the intramuscular route in the mid-anterolateral thigh as soon as anaphylaxis is diagnosed or strongly suspected, in a dose of 0.01 mg/kg of a 1:1000 (1 mg/mL) solution, to a maximum of 0.5 mg in adults (0.3 mg in children) [4, 6, 20, 22, 23]. Depending on the severity of the episode and the response to the initial injection, the dose can be repeated every 5–15 min, as needed. Most patients respond to one or two doses of epinephrine injected intramuscularly promptly; however, more than two doses are occasionally required. Failure to inject it promptly is potentially associated with fatality.

Epinephrine can be given by slow intravenous infusion with diluted solution 1:10,000 (0.1 mg/mL), ideally with the dose titrated according to noninvasive continuous monitoring of cardiac rate and function [22]. For example, if shock is imminent or has already developed or cardiac arrest is impending, an intravenous bolus dose of epinephrine is indicated; however, in other anaphylaxis scenarios, this route of administration should be avoided [20].

6.4.2.3 Adverse Effect

Transient pharmacologic effects after a recommended dose of epinephrine by any route of administration include pallor, tremor, anxiety, palpitations, dizziness, and headache [15, 19, 20]. These symptoms indicate that a therapeutic dose has been given. Serious adverse effects such as ventricular arrhythmias, hypertensive crisis, and pulmonary edema potentially occur after an overdose of epinephrine by any route of administration. Typically, they are reported after intravenous epinephrine dosing [9, 20]. Moreover intravenous epinephrine injection can lead to dosing error and epinephrine overdose [24]. Physician should be aware that there are no absolute contraindications to the use of epinephrine for anaphylaxis and serious adverse effects are very rare when epinephrine is administrated at the appropriate intramuscular doses for anaphylaxis.

6.4.3 Intravenous Fluids

Patients with anaphylaxis should not suddenly sit, stand, or be placed in the upright position because massive fluid shifts can occur in anaphylaxis. All patients with orthostasis, hypotension, or incomplete response to epinephrine should receive large-volume fluid resuscitation with isotonic saline or normal saline. The rate of administration should be titrated according to the blood pressure, cardiac rate and function, and urine output. All patients receiving such treatment should be monitored for volume overload. Normotensive patients should receive normal saline to maintain venous access in case their status deteriorates.

6.4.4 Second-Line Pharmacologic Treatment

6.4.4.1 H1-Antihistamine

H1-antihistamines relieve itching, flushing, urticaria, angioedema, and nasal and eye symptoms; however, they should not be substituted for epinephrine because they are not lifesaving; that is, they do not prevent or relieve upper airway obstruction, hypotension, or shock [4, 20, 22, 23]. Moreover it does not inhibit mediator release from mast cells and basophils and rapid intravenous administration may increase hypotension. Some guidelines do not recommend H1-antihistamine treatment in anaphylaxis, citing lack of supporting evidence from randomized controlled trials that meet current standards [25]. Current systematic

review reported that no high-quality evidence was found to support the use of H1-antihistamines in the treatment of anaphylaxis [26].

6.4.4.2 H2-Antihistamine

An H2-antihistamine, administered concurrently with an H1-antihistamine, potentially contributes to decrease in flushing, headache, and other symptoms; however, H2-antihistamines are recommended in only a few anaphylaxis guidelines [22, 27]. Moreover, rapid intravenous administration of cimetidine has been reported to increase hypotension [22] and anaphylaxis to ranitidine has been reported [28].

6.4.4.3 Glucocorticoids

Glucocorticoids switch off transcription of a multitude of activated genes that encode proinflammatory proteins. Extrapolating from their use in acute asthma, the onset of action of systemic glucocorticoids takes several hours [29]. Although they potentially relieve protracted anaphylaxis symptoms and prevent biphasic anaphylaxis [20, 22], these effects have never been proven. Therefore, glucocorticoid is not lifesaving in initial hours of an anaphylactic episode. Current systematic review failed to identify any evidence to confirm the effectiveness of glucocorticoids in the treatment of anaphylaxis, and raised concerns that they are often inappropriately used as first-line medications in place of epinephrine [30].

6.4.4.4 Bronchodilators

Selective beta-2 adrenergic agonists such as salbutamol (albuterol) are sometimes given in anaphylaxis as additional treatment for wheezing, coughing, and shortness of breath not relieved by epinephrine. Although this is helpful for lower respiratory tract symptoms, these medications should not be substituted for epinephrine because they have minimal alpha-1 adrenergic agonist vasoconstrictor effects and do not prevent or relieve laryngeal edema and upper airway obstruction, hypotension, or shock [20] (Table 6.2).

Table 6.2 Initial management and medications of anaphylaxis [20]

Basic initial management
1. Remove exposure to the trigger, if possible For example, discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms
2. Assess circulation, airway, breathing, mental status, skin, and body weight
3. Call for help (resuscitation team in hospital or emergency medical services in community setting), if available
4. Inject epinephrine intramuscularly in the mid-anterolateral aspect of the thigh, 0.01 mg/kg of a 1:1000 (1 mg/mL) solution, to a maximum of 0.5 mg (adult) or 0.3 mg (childe); record the time of the dose and repeat it in 5–15 min, if needed; most patients respond to one or two doses
5. Place patient on the back, or in a position of comfort if there is respiratory distress and/or vomiting; elevate the lower extremities; fatality can occur within seconds if a patient stands or sits suddenly
6. Give high-flow supplemental oxygen (6–8 L/min) by face mask or oropharyngeal airway
7. Establish intravenous access with wide-bore cannula. When indicated, give 1–2 L of 0.9% (isotonic) saline rapidly (e.g., 5–10 mL/kg in the first 5–10 min to an adult, or 10 mL/kg to a child)
8. When indicated at any time, prepare to initiate cardiopulmonary resuscitation with continuous chest compressions
Medications
1. First-line (priority) medication – Epinephrine 1:1000 (1 mg/mL) intramuscular injection 0.01 mg/kg, to a maximum of 0.5 mg (adult), 0.3 mg (child)
2. Second-line medications – H1-antihistamine for intravenous infusion For example chlorpheniramine 10 mg (adult), 2.5–5 mg (child) or diphenhydramine 25–50 mg (adult) (1 mg/kg, maximum 50 mg [child]) – ß2-adrenergic agonist For example salbutamol (albuterol) solution, 2.5 mg/3 mL or 5 mg/3 mL (adult), (2.5 mg/3 mL [child]) given by nebulizer and face mask – Glucocorticoid for intravenous infusion For example hydrocortisone 200 mg (adult), maximum 100 mg (child); or methylprednisolone 50–100 mg (adult); 1 mg/kg, maximum 50 mg (child) – H2-antihistamine for intravenous infusion For example, ranitidine 50 mg (adult) or 1 mg/kg, maximum 50 mg (child)

6.4.5 Management of Refractory Anaphylaxis

A minority of patients do not respond to timely, basic initial anaphylaxis treatment with epinephrine by intramuscular injection, supplemental oxygen, intravenous fluid resuscitation, and second-line medications. In these refractory anaphylaxis patients with shock, no clear superiority of dopamine, dobutamine, norepinephrine, phenylephrine, or vasopressin (either added to epinephrine alone or compared with one another) has been demonstrated in clinical trials. Physicians suspect patients taking a beta-adrenergic blocker or other medications that interfere with epinephrine effect. Glucagon, a polpypeptide with non-catecholamine-dependent inotropic and chronotropic cardiac effects, is sometimes needed in patients taking a beta-adrenergic blocker who have hypotension and bradycardia and who do not respond optimally to epinephrine [31].

Patients suffering from refractory anaphylaxis have been resuscitated with extracorporeal membrane oxygenation (ECMO) or operative cardiopulmonary bypass. ECMO is becoming increasingly available in ED and should be considered in patients unresponsive to complete resuscitative efforts in institutions with experience in this technology. The decision to initiate ECMO should be considered early in patients unresponsive to traditional resuscitative measures, before irreversible ischemic acidosis develops.

6.5 Disposition

The duration of monitoring of the developing biphasic anaphylaxis after initial treatment varies from patient to patient. In general, patients with moderate respiratory or cardiovascular events should be monitored for at least 4 h, and if indicated for 8–10 h or longer, and patients with severe or protracted anaphylaxis might require monitoring and interventions for days. For the biphasic anaphylaxis, timely epinephrine administration appears to have a role, but the role of steroids has been called into question and is an opportunity for future investigation.

6.5.1 Biphasic Reaction

6.5.1.1 Incidence and Risk Factor

A biphasic anaphylactic reaction was first described in 1984 and was defined as the recurrence of symptoms after complete resolution of initial anaphylactic without re-exposure to the trigger [32]. The reported incidence rate varies from 3 to 20% depending on the study population, and recent systemic review of 4162 patients showed a 4.6% rate of biphasic reaction [32]. It may occur from 1 to 72 h after the first anaphylactic reaction. Guidelines about optimal duration of observation vary considerably in their recommendations: the United States recommend 6 h of observation after the initial anaphylactic episode due to the risk of a biphasic reaction [7], and Europe recommends up to 24 h of observation [6]. Identifying patients who are most likely to benefit from a longer period of observation is important. However, risk factors for developing a biphasic anaphylaxis have not been well studied due to the uncommon occurrence. In observational studies with 415 anaphylaxis patients from Korea, history of drug anaphylaxis (odds ratio 14.3, 95% CI 2.4–85.8) was a contributing factor to the development of the biphasic reaction [33]. A recent systemic review found that initial presentation with hypotension (odds ratio 2.18, 95% CI 1.1–4.2) was associated with the development of the biphasic reaction and anaphylaxis due to food was associated with decreased risk (odds ratio 0.62, 95% CI 0.4–0.94) [32]. In addition, the single pediatric study showed that biphasic reactions seem to be associated with the severity of the initial anaphylactic reactions [34]. More studies regarding the identification of anaphylaxis patients at higher risk for biphasic anaphylaxis may be warranted.

6.5.1.2 Prevention

Steroid use and early epinephrine administration have been theorized to decrease biphasic anaphylaxis [35]. However, contemporary stud-

ies have failed to find compelling evidence of a protective effect of steroids for preventing biphasic reactions [33, 36]. Recent study of corticosteroid use for the patients with allergy or anaphylaxis did not decrease ED return visits within 7 days [37].

Delayed epinephrine treatment for the initial reaction has been reported as an associated factor with a biphasic reaction [38]. A recent observational study reported that a subgroup of patients who had delays in their initial epinephrine administration were more likely to develop biphasic reactions [34]. The role of other allergy medications in the prevention of biphasic anaphylaxis is not well studied.

6.5.2 Epinephrine Auto-Injector

In patients with anaphylaxis, it can be recurred due to re-exposure to the substance or stimulant. Therefore, patients with anaphylaxis, even after initial successful treatment, should be educated to avoid antigen and usage of epinephrine auto-injector. Patients should be advised that they have experienced a potentially life-threatening medical emergency ("killer allergy"), and that if their symptoms recur within the next 72 h they should inject epinephrine and call emergency medical services or be taken to the nearest emergency facility [20].

6.6 Future

Inappropriate treatment of anaphylaxis can be caused by failure of early recognition. We believed that the early recognition with three clinical diagnostic criteria, use of epinephrine as soon as possible, and appropriate discharge plans were the most critical recommendations for ED health professionals. At a time when anaphylaxis is increasing, physicians also should recognize that anaphylaxis may not appear life threatening and that the patients may present without respiratory or cardiovascular symptoms. For the biphasic anaphylaxis which is a debating issue, timely epinephrine administration appears to have a role, but the role of steroids has been called into question and is an opportunity for future investigation. Moreover, studies regarding the identification of anaphylaxis patients at higher risk for biphasic anaphylaxis may be warranted.

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