



<http://dx.doi.org/10.1016/j.jemermed.2014.04.018>

Best Clinical Practice

ANAPHYLAXIS

Jeffrey Zilberstein, MD,* Michael T. McCurdy, MD,†‡ and Michael E. Winters, MD, FAAEM, FACEP†

*Department of Medicine, Division of Critical Care, Weiss Memorial Hospital, Chicago, Illinois, †Department of Emergency Medicine, and ‡Division of Pulmonary and Critical Care, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland
 Reprint Address: Michael E. Winters, MD, FAAEM, FACEP, Departments of Emergency Medicine and Medicine, University of Maryland School of Medicine, 110 S. Paca Street, 6th Floor, Suite 200, Baltimore, MD 21201

Abstract—Background: Anaphylaxis is the quintessential critical illness in emergency medicine. Symptoms are rapid in onset and death can occur within minutes. Approximately 1500 patients die annually in the United States from this deadly disorder. It is imperative, therefore, that emergency care providers be able to diagnose and appropriately treat patients with anaphylaxis. Any delays in recognition or initiation of therapy can result in unnecessary increases in patient morbidity and mortality. **Discussion:** Recent literature, including updated international anaphylaxis guidelines, has improved our understanding and management of this critical illness. Anaphylaxis is a multisystem disorder that can manifest signs and symptoms related to the cutaneous, respiratory, cardiovascular, and gastrointestinal systems. Epinephrine remains the drug of choice and should initially be administered intramuscularly, into the anterolateral thigh, as soon as the diagnosis is suspected. For patients unresponsive to repeated intramuscular injections, a continuous infusion of epinephrine should be started. Antihistamines and corticosteroids are second-line medications and should never be given in lieu of, or prior to, epinephrine. Aggressive fluid resuscitation should also be used to treat the intravascular volume depletion characteristic of anaphylaxis. Patient observation and disposition should be individualized, as there is no well-defined period of observation after resolution of signs and symptoms. **Conclusions:** For patients with anaphylaxis, rapid and appropriate administration of epinephrine is critical for survival. Additional therapy, such as supplemental oxygen, intravenous fluids, antihistamines, and corticosteroids should not delay the administration of epinephrine. © 2014 Elsevier Inc.

Keywords—anaphylaxis; anaphylactic shock; allergic reaction; epinephrine; antihistamines; corticosteroids; hypovolemic shock; cardiogenic shock; distributive shock

INTRODUCTION

In 1902, Portier and Richet observed a deadly reaction in dogs after repeated injections of sea anemone toxin. Building off the existing term *prophylaxis*, they coined the word *aphylaxis*, which later became *anaphylaxis* (1). Anaphylaxis is often considered the quintessential emergency medicine disease: symptoms are rapid in onset, and death can occur within minutes. Therefore, every acute care provider must be able to diagnose and treat patients with anaphylaxis promptly to minimize morbidity and mortality rates.

Although numerous questions regarding anaphylaxis remain, recent publications, including updated international guidelines, have improved our understanding and management of this deadly disorder. This article serves to update the acute care provider on the recognition and management of patients with anaphylaxis.

DISCUSSION

Definition

No universally accepted definition for anaphylaxis exists. In an effort to provide a single definition and encourage higher rates of diagnosis, participants from the Second

Symposium on the Definition and Management of Anaphylaxis, sponsored by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network, defined anaphylaxis as “a serious allergic reaction that is rapid in onset and may cause death” (2).

Epidemiology

The true incidence of anaphylaxis is unknown due to its varying definitions, the lack of confirmatory laboratory values, as well as under-recognition and under-diagnosis by clinicians. However, studies estimate the lifetime prevalence of anaphylaxis to be 0.5% to 2% (3). For patients with severe anaphylaxis, mortality rates range between 0.65% and 2% (4). In the United States, anaphylaxis is estimated to account for approximately 1% of emergency department (ED) visits and 1500 deaths annually (5,6). Risk factors associated with fatal anaphylaxis include infancy, old age, and concomitant diseases such as asthma, chronic respiratory disease, cardiovascular disease, mastocytosis, and severe atopy (7).

Clinical Features

Anaphylaxis is a multisystem disorder that produces clinical signs and symptoms centered on the skin, respiratory, cardiovascular, gastrointestinal, and central nervous systems (Table 1). Importantly, up to 20% of patients with anaphylaxis do *not* manifest the characteristic cutaneous signs or symptoms (e.g., urticaria, angioedema). Cutaneous manifestations are commonly absent in people experiencing an allergic reaction to food (8). Gastrointestinal symptoms are associated with more severe reactions (9). The route of antigen exposure often determines how quickly symptoms manifest. In one case series, intravenous medications caused symptoms within 5 min, insect stings caused symptoms within 15 min, and ingestion caused symptoms within 30 min (10).

Diagnostic Criteria

Anaphylaxis is a clinical diagnosis. In addition to proposing a universal definition for anaphylaxis, participants from the Second Symposium on the Definition and Management of Anaphylaxis put forth formal diagnostic criteria to identify patients with anaphylaxis (11). These diagnostic criteria were recently incorporated into international guidelines, which are listed in Table 2 (7).

Traditional laboratory values (e.g., complete blood count, comprehensive metabolic panel) are unreliable and impractical in the identification of anaphylaxis; however, serum tryptase values can facilitate the diagnosis.

Table 1. Signs and Symptoms of Anaphylaxis

Skin, subcutaneous tissue, and mucosa (80–90%)
Urticaria
Angioedema
Flushing
Pruritus
Periorbital
Lips, tongue, palate
External auditory canal
Genitalia
Palms, soles
Morbilliform rash
Respiratory (70%)
Rhinorrhea, congestion, sneezing
Stridor
Dysphonia, hoarseness
Shortness of breath
Chest tightness
Bronchospasm
Cyanosis
Cardiovascular (45%)
Chest pain
Tachycardia
Bradycardia
Hypotension
Dysrhythmias
Cardiac arrest
Gastrointestinal (45%)
Abdominal pain
Nausea, vomiting
Diarrhea
Central nervous system (15%)
Sense of impending doom
Altered mental status
Dizziness
Confusion
Headache

Tryptase, found in mast cells and basophils, is released after mast cell activation, peaks within 60 to 90 min after mast cell degranulation, and remains detectable for approximately 5 h (12). Interestingly, serum tryptase levels are elevated in patients experiencing anaphylaxis from insect stings and in those who are hypotensive, yet the levels can be normal in the setting of food-induced anaphylaxis. Serum histamine, another potential laboratory marker for anaphylaxis, can also be measured (13). Histamine levels can increase within 15 to 60 min after symptom onset. Because evidence regarding serum tryptase and histamine is limited, current guidelines emphasize that normal values for either laboratory parameter do not exclude anaphylaxis (7).

Etiology

Although any substance can elicit a hypersensitivity reaction severe enough to result in anaphylaxis, the three most common causes of anaphylaxis are food, medications, and insect stings and bites (14). For particular allergens, the time course and symptoms associated with the reaction often can be predicted.

Table 2. Diagnostic Criteria for Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to hours) with involvement of the skin, mucosal tissue, or both AND AT LEAST ONE OF THE FOLLOWING:
 - a. Respiratory compromise (e.g., dyspnea, bronchospasm, stridor, hypoxemia)
 - b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope)
2. Two or more of the following that occur rapidly (minutes to hours) after exposure to a likely allergen for that patient:
 - a. Involvement of the skin-mucosal tissue (e.g., urticaria, angioedema, pruritus)
 - b. Respiratory compromise (e.g., dyspnea, bronchospasm, stridor, hypoxemia)
 - c. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope)
 - d. Persistent gastrointestinal symptoms (e.g., abdominal pain, vomiting)
3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to hours)
 - a. Infants and children: low systolic blood pressure (age-specific) or > 30% decrease in systolic blood pressure
 - b. Adults: systolic blood pressure < 90 mm Hg or > 30% decrease for that patient's baseline

Food is the most common cause of anaphylaxis. An estimated 1% to 3% of adults have a confirmable food allergy (8). The incidence and severity of food allergies have risen inexplicably over the past several decades. Interestingly, sensitization to food allergens is not limited to the gut. It can also develop from topical (e.g., body products containing peanut oil) and inhalational (e.g., dust mite aeroallergens) exposures, both of which have been implicated in shellfish sensitization (8,15). Nuts (i.e., tree nuts and peanuts), fish, and shellfish are the most common agents, but dairy products, eggs, fruits, and vegetables are also occasional triggers (14).

The natural history of anaphylaxis resulting from food allergy includes a relatively rapid onset of symptoms, with an average latency period of approximately 15 min (8). In a study by Sampson et al., all children with severe anaphylaxis reactions had symptoms within 30 min of exposure, and the majority had symptoms within the first 5 min after ingestion of the causative food (16). In general, the most severe reactions occur relatively quickly. If several hours elapse prior to the onset of symptoms, the presentation tends to be less severe. The most common symptoms occur in the cutaneous (76%) and respiratory (80%) systems. Not surprisingly, the gastrointestinal system is involved more frequently with food allergies than with any of the other forms of anaphylaxis (17). Notably, almost all food allergy-related anaphylactic deaths occur in individuals with asthma (18).

Insect stings are another common cause of anaphylaxis. The most clinically important insects are bees (e.g., honeybees, bumblebees), vespids (e.g., yellow jackets, hornets, wasps), and stinging ants (19). At least 50 fatal sting reactions occur each year in the United States, and half of these individuals had no known history of sting reactions (20). Over 99% of individuals with a history of systemic reactions to insect stings do not develop more severe reactions with subsequent stings (21,22).

Medications are frequently implicated as a cause of anaphylaxis. Although penicillins are believed to account

for approximately 40% of medication-related instances of anaphylaxis, virtually any medication in any form (e.g., inhalational, rectal, topical, intra-articular) can cause an allergic reaction (4). It is important to consider anaphylaxis any time a reaction occurs after the administration of a medication.

Finally, 6% to 27% of anaphylaxis cases are idiopathic (23,24). Idiopathic anaphylaxis is a frightening entity because, without an identifiable trigger, a sensitized individual does not know what allergen to avoid. Ditto and colleagues highlighted the danger of idiopathic anaphylaxis (25). All of the 335 patients in their case series developed either urticaria or angioedema, and almost a quarter presented with syncope or hypotension. Interestingly, half of the patients had a history of atopy; therefore, a high level of suspicion for potential idiopathic anaphylaxis should be maintained in such individuals.

Risk Factors

Numerous factors can increase the severity of anaphylaxis episodes. These include extremes of age, cardiovascular diseases, chronic respiratory diseases, mastocytosis, mast cell disorders, and severe atopic disease (7). Patients taking β -adrenergic blockers or angiotensin-converting enzyme inhibitors might also be at increased risk for severe episodes (7). In addition to predisposing patients to severe episodes of anaphylaxis, a number of factors can amplify the actual event. These include concurrent acute upper respiratory illness, alcohol ingestion, emotional stress, disruption of normal daily activities (e.g., travel), and use of nonsteroidal anti-inflammatory medications (7).

Initial Management

Management of the patient with anaphylaxis should begin with a careful assessment of the airway, breathing, and circulation. Given the rapid progression of the disease, a low threshold for intubation should be maintained

in patients with respiratory distress, altered mental status, or progressive upper airway obstruction. Although patients try to compensate for upper airway edema with positioning and muscular control, rapid sequence intubation (RSI) medications eliminate these compensatory maneuvers and may lead to complete airway occlusion. Due to the inherent dangers of RSI in this situation, prudence dictates preparation for a difficult airway. Therefore, awake fiberoptic intubation should be considered, rescue equipment should be readily available at the bedside, and a low threshold should exist for cricothyroidotomy. If no clear airway compromise exists, administer supplemental oxygen and monitor the patient with continuous pulse oximetry during the initial assessment. Because hypoxemia is a late finding of airway compromise, we recommend the use of continuous capnography, if available, to monitor for early ventilatory impairment.

The pathophysiology of circulatory shock in anaphylaxis is complex and includes elements of hypovolemic, distributive, and cardiogenic shock (26). The cardiovascular evaluation should include continuous cardiac monitoring and frequent measurements of arterial blood pressure and signs of perfusion (e.g., mentation, urine output, capillary refill). Large-bore intravenous (i.v.) lines (14- to 16-gauge) should be placed promptly to allow administration of boluses of isotonic crystalloid fluid (5–10 mL/kg) within the first few minutes, even if the patient's vital signs are normal (7). The need for volume was underscored by a series of 205 patients who experienced anaphylactic shock during general anesthesia. In this group, up to 35% of circulating blood volume extravasated into the interstitial tissues within 10 min after the onset of anaphylaxis (27). To avoid the cardiovascular collapse experienced by some patients within minutes after assuming an upright posture, supine positioning and leg elevation are simple but important steps to take to improve preload in those with anaphylaxis (7,28).

Epinephrine is the treatment of choice for anaphylaxis and should be administered as soon as the diagnosis is suspected (7,29). Epinephrine, through its α - and β -agonist effects, reverses pathologic vasodilation, decreases angioedema, provides positive chronotropic and inotropic support, and reverses bronchoconstriction. In addition, epinephrine can inhibit further mediator release by mast cells, thereby attenuating symptom severity (30).

No absolute contraindications to the use of epinephrine for anaphylaxis have been identified (7,31). Unfortunately, epinephrine remains underutilized in anaphylaxis (7). The lack of, or delay in, epinephrine administration accounts for the majority of deaths caused by anaphylaxis (10). Current guidelines recommend that epinephrine initially be administered at a dose of 0.01

mg/kg of a 1:1000 solution (to a maximum of 0.5 mg for adults and 0.3 mg for children) into the intramuscular (i.m.) space of the mid-anterolateral thigh (7). In contrast to subcutaneous administration in the deltoid muscle, injection into the lateral thigh has been shown to provide more rapid absorption (32). Intramuscular doses of epinephrine can be repeated every 5 to 15 min as needed (7). Generally, patients with anaphylaxis respond to one or two doses of intramuscular epinephrine (7). For patients unresponsive to two doses of i.m. epinephrine, or for those with circulatory shock, i.v. epinephrine should be administered (7). Adverse events reported with i.v. epinephrine have occurred almost exclusively with intermittent i.v. bolus dosing or the administration of the wrong epinephrine concentration (33). As a result, we prefer a continuous infusion of epinephrine rather than intermittent boluses. An epinephrine infusion should be started at 1 μ g/min and increased 1 μ g/min every 5 to 10 min to a maximum of 10 μ g/min. For clinicians unable to initiate an epinephrine infusion, 0.1 mg of a 1:10,000 solution can be administered i.v. every 5 min. Although epinephrine-induced myocardial ischemia has been reported, epinephrine is *not* contraindicated in patients with known or suspected coronary artery disease, and clinicians should not hesitate to treat any anaphylactic patients with epinephrine (Table 2) (7,34).

Second-line Medications

Despite widespread use of antihistamines in the management of anaphylaxis, a 2007 Cochrane review found no evidence to support or refute the use of this class of medications for this purpose (35). Notwithstanding, H1 and H2 antihistamines can relieve cutaneous symptoms of anaphylaxis. If cutaneous symptoms are present, many experts recommend diphenhydramine, 25 to 50 mg i.v. (1 mg/kg, up to 50 mg for children), with the optional addition of ranitidine (11). Importantly, antihistamines will not reverse the cardiovascular, pulmonary, or gastrointestinal manifestations of anaphylaxis. As such, antihistamines should be considered second-line medications for anaphylaxis and should never be given in lieu of epinephrine.

Corticosteroids, like antihistamines, are often given to patients with anaphylaxis, but they are not life-saving in the initial hours of the illness. A Cochrane review found no evidence for the effectiveness of corticosteroids in anaphylaxis (36). The common practice of prescribing steroids to mitigate biphasic or protracted symptoms is extrapolated from their use in acute asthma exacerbations, but they have not been shown to decrease the incidence of biphasic symptoms (37). Despite the lack of proven benefit, corticosteroids have minimal short-term effects and may be beneficial in select patients. The

recommended steroids are methylprednisolone (1–2 mg/kg) or hydrocortisone (200 mg) (38).

β_2 -Agonists can be given to patients with wheezing, shortness of breath, or cough, but only limited data are available to support their use in anaphylaxis.

Refractory Anaphylaxis

In a small number of patients, anaphylaxis will progress despite early use of epinephrine, appropriate fluid administration, patient positioning, supplemental oxygen, and second-line medications. For these rare patients, further treatment options are limited. Endotracheal intubation should be considered if not already performed. For those who do not respond to an i.v. infusion of epinephrine, additional vasopressor medications (e.g., dopamine, norepinephrine, vasopressin, phenylephrine) can be considered. Atropine (0.02 mg/kg) or transcutaneous pacing can also be used in the unstable patient with hypotension and bradycardia (7).

If refractory anaphylaxis develops in a patient taking a β -adrenergic receptor antagonist, glucagon should be administered (7). Glucagon bypasses the β -receptor, has direct inotropic and chronotropic effects, and might restore hemodynamic stability. For adults with anaphylaxis, the recommended dose of glucagon is 1 to 5 mg i.v. over 5 min, followed by an infusion of 5 to 15 μ g/min. For children, the dose is 20 to 30 μ g/kg to a maximum of 1 mg.

Disposition

The decision to discharge a patient treated for anaphylaxis should include consideration of the potential for biphasic or protracted symptoms. Biphasic anaphylaxis, in which symptoms resolve but then recur in 1 to 72 h, emerges in as many as one in five cases (39). Protracted anaphylaxis can last as long as 32 h (40). Unfortunately, accurately determining whether a patient will experience a discrete, biphasic, or protracted episode of anaphylaxis is impossible (41). The symptoms of biphasic anaphylaxis can be the same or more severe than those of the first reaction (42). Some experts recommend a 24-h observation period after the first episode, whereas others recommend a variety of other periods of observation (43,44). Because no standard exists, current guidelines recommend that the duration of monitoring be individualized (7). For example, patients presenting with risk factors for severe anaphylaxis or those requiring multiple doses of epinephrine should be observed for a longer period than those who had less severe signs and symptoms.

Follow-up with a physician within 24 to 48 h after an episode of anaphylaxis is critical. If the patient is unable to see his primary care physician within this time frame,

he should be instructed to return to the ED for a repeat evaluation. At the time of follow-up, the primary care physician can refer the patient to an allergy specialist. Finally, and perhaps most importantly, a self-injectable dose of epinephrine (e.g., administered with an EpiPen®; Mylan, Canonsburg, PA) should be given to the patient upon discharge from the ED. Patients must be taught to use the device and demonstrate the ability to do so prior to discharge.

CONCLUSION

Anaphylaxis is the quintessential critical illness in emergency medicine. Signs and symptoms develop rapidly, and death can occur within minutes. Epinephrine is the drug of choice and should be administered as soon as the diagnosis is suspected. For patients who do not respond to repeated i.m. injections, a continuous infusion should be started. Antihistamines and corticosteroids are second-line medications and should never be given in lieu of, or prior to, epinephrine. Aggressive fluid resuscitation should also be used to correct the intravascular volume depletion characteristic of anaphylaxis. Patient observation and disposition should be individualized, as there is no well-defined period of observation after resolution of signs and symptoms, but the potential for biphasic symptoms exists. Patients appropriate for ED discharge should be given self-injectable epinephrine and must successfully demonstrate its proper use.

Acknowledgment—This manuscript was copyedited by Linda J. Kesselring, MS, ELS, the technical editor/writer in the Department of Emergency Medicine at the University of Maryland School of Medicine.

REFERENCES

1. Portier P, Richet C. De l'action anaphylactique de certains venins [French]. *Soc Biol (Paris)* 1902;54:170–2.
2. Sampson HA, Muñoz-Furlong A, Bock SA, et al. Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 2005;115:584–91.
3. Lieberman P, Camargo CA Jr, Bohlke K, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol* 2006;97:596–602.
4. Moneret-Vautrin DA, Morisset M, Flabbee J, et al. Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy* 2005;60:443–51.
5. Gaeta TJ, Clark S, Pelletier AJ, et al. National study of US emergency department visits for acute allergic reactions, 1993 to 2004. *Ann Allergy Asthma Immunol* 2007;98:360–5.
6. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. *Arch Intern Med* 2001;161:15–21.
7. Simons FE, Arduoso LR, Bilò MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011;4:13–37.

8. Keet CA, Wood RA. Food allergy and anaphylaxis. *Immunol Allergy Clin North Am* 2007;27:193–212.
9. Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;114:371–6.
10. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;30:1144–50.
11. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–7.
12. Ogawa Y, Grant JA. Mediators of anaphylaxis. *Immunol Allergy Clin North Am* 2007;27:249–60.
13. Simons FER. Anaphylaxis: recent advances in assessment and treatment. *J Allergy Clin Immunol* 2009;124:625–36.
14. Simons FER. Anaphylaxis. *J Allergy Clin Immunol* 2008;121 (2 Suppl):S402–7.
15. Roberts G, Lack G. Relevance of inhalational exposure to food allergens. *Curr Opin Allergy Clin Immunol* 2003;3:211–5.
16. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380–4.
17. Novembre E, Cianferoni A, Bernardini R, et al. Anaphylaxis in children: clinical and allergologic features. *Pediatrics* 1998;101: E8.
18. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191–3.
19. Golden DBK. Insect sting anaphylaxis. *Immunol Allergy Clin North Am* 2007;27:261–72.
20. Barnard JH. Studies of 40 Hymenoptera sting deaths in the United States. *J Allergy Clin Immunol* 1973;52:259–64.
21. Golden DBK, Breisch NL, Hamilton RG, et al. Clinical and entomological factors influence the outcome of sting challenges. *J Allergy Clin Immunol* 2006;117:670–5.
22. van der Linden PW, Hak CE, Struyvenberg A, et al. Intentional diagnostic sting challenges: an important medical issue. *J Allergy Clin Immunol* 1994;94:563–4.
23. Lin RY, Schwartz LB, Curry A, et al. Histamine and tryptase levels in patients with acute allergic reactions: an emergency department-based study. *J Allergy Clin Immunol* 2000;106: 65–71.
24. Brown AF, McKinnon D, Chu K. Emergency department anaphylaxis: a review of 142 patients in a single year. *J Allergy Clin Immunol* 2001;108:861–6.
25. Ditto AM, Harris KE, Krasnick J, et al. Idiopathic anaphylaxis: a series of 335 cases. *Ann Allergy Asthma Immunol* 1996;77: 285–91.
26. Brown SG. The pathophysiology of shock in anaphylaxis. *Immunol Allergy Clin North Am* 2007;27:165–75.
27. Fisher MM. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesth Intensive Care* 1986;14:17–21.
28. Pumphrey RS. Fatal posture in anaphylactic shock. *J Allergy Clin Immunol* 2003;112:451–2.
29. Kemp SF, Lockey RF, Simons FE. World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy* 2008;63:1061–70.
30. Chong LK, Morice AH, Yeo WW, et al. Functional desensitization of beta agonist responses in human lung mast cells. *Am J Respir Cell Mol Biol* 1995;13:540–6.
31. Winters ME. Anaphylaxis. In: Field JM, ed. *The textbook of emergency cardiovascular care and CPR*. Philadelphia: Lippincott Williams & Wilkins; 2009:530–7.
32. Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol* 2001;108:871–3.
33. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006;110:7–14.
34. Cunningham C, McDonald JE, Singh RK. Epinephrine-induced myocardial infarction in severe anaphylaxis: is nonselective α -blockade a contributory factor? *Am J Emerg Med* 2013;31: 759.e1–2.
35. Sheikh A, Ten Broek V, Brown SG, et al. H1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review. *Allergy* 2007;62:830–7.
36. Choo KJ, Simons E, Sheikh A. Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review. *Allergy* 2010;65: 1205–11.
37. Popa VT, Lerner SA. Biphasic systemic anaphylactic reaction: three illustrative cases. *Ann Allergy* 1984;53:151–5.
38. De Bisschop MB, Bellou A. Anaphylaxis. *Curr Opin Crit Care* 2012;18:308–17.
39. Lieberman P. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol* 2005;95:217–26.
40. Kemp SF, Lockey RF. Anaphylaxis: a review of causes and mechanisms. *J Allergy Clin Immunol* 2002;110:341–8.
41. Ellis AK, Day JH. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. *Ann Allergy Asthma Immunol* 2007;98:64–9.
42. Kemp SF. Office approach to anaphylaxis: sooner better than later. *Am J Med* 2007;120:664–8.
43. Brazil E, MacNamara AF. “Not so immediate” hypersensitivity—the danger of biphasic anaphylactic reactions. *J Accid Emerg Med* 1998;15:252–3.
44. Smit DV, Cameron PA, Rainer TH. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. *J Emerg Med* 2005;28:381–8.