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Anaphylaxis: Etiology, Clinical Manifestations, Diagnosis and Management

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1. Introduction

Anaphylaxis is an acute systemic allergic reaction that can potentially be life-threatening. Therefore it has to be diagnosed and treated promptly. It can occur after exposure to various triggers or spontaneously and can potentially affect multiple organ systems and prompt and definite treatment may be life saving. In this chapter, possible triggers of anaphylaxis, clinical manifestations, diagnosis and management will be discussed.

2. Epidemiology

Anaphylaxis is defined as a "severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance" (Sampson et al., 2006). As there is no unified method of obtaining data about anaphylaxis, its incidence is very difficult to evaluate clearly. A substantial portion of the existing data on the epidemiology of anaphylaxis has come from investigations that have limited scope population sources, such as surveys and volunteer registries (Harduar-Morano et al., 2011). Lifetime prevalence is estimated as 0.05% to 2% (Simons, 2008). Recent studies confirm that the incidence of anaphylaxis, particularly food-induced anaphylaxis, is increasing world-wide (Chiu & Kelly, 2005). A very recent study investigated a large diverse population with anaphylaxis diagnosed in emergency departments using rigorous descriptive and analytic evaluation of risk factors, such as sex, race, ethnicity, and age (Harduar-Morano et al., 2011). In this study the highest observed rates were among the youngest male subjects (8.2/100,000 aged 0-4 years) and among adult female subjects (15-54 years) grouped in 10-year age categories (9,9-10.9/100,000). Previous epidemiologic studies also suggested that until age 15 years, there is a predilection for males, but after age 15 years, there is a predilection for females. Different trigger factors predominate in different age groups; for example, fatalities from food-induced anaphylaxis peak in adolescents and young adults, and fatalities from anaphylaxis triggered by insect stings, diagnostic agents, and medications predominate in middle-aged and older adults (Simons, 2008). Atopy is an associated risk factor for anaphylaxis triggered by food, exercise, and latex but not for anaphylaxis triggered by insect stings, β-lactam antibiotics (Chiu and Kelly, 2005). In addition, asthma was reported in 23% of 142 patients with anaphylaxis who presented to an emergency department from 1998 to 1999 (Brown et al., 2001).

3. Pathogenesis

The underlying pathogenesis of human anaphylaxis commonly involves an immunologic mechanism in which IgE is synthesized in response to allergen exposure and becomes fixed to high affinity receptors for IgE (FcεRI receptors) on the surface membranes of mast cells and basophils (Simons, 2010). Other potential immunologic mechanisms in anaphylaxis include involvement of immune aggregates, IgG, IgM, platelets, and T cells; shift in eicosanoid metabolism toward leukotriene formation; and activation of the complement or coagulation systems (Simons, 2008).

The mast cells and basophils are central players in allergic reaction (Rivera & Gilfillan, 2006). Activation of these cells induces the release of preformed inflammatory mediators localized in specialized granules and the de novo synthesis and secretion of cytokines, chemokines, and eicosanoids. Appropriate activation of mast cells is mediated by a number of factors, including the cells' ability to distinguish activating or inhibiting stimuli and the strength and duration of stimulus. FcεRI on mast cells is comprised of an IgE- binding α chain, a 4-transmembrane spanning β chain and a monodimer of γ chains. The β chain functions as an amplifying modul for this receptor. The γ chain monodimer imports signaling competence to this receptor. It has been demonstrated that both the β and γ chains function to generate positive signals that are key in initiating and amplifying the mast cells' effector responses. However, recent evidence suggests that these two chains can also function to negatively regulate cell activation and effector responses (Rivera & Gilfillan, 2006).

Current knowledge suggests that mast cell's response to a stimulus is very complex. A number of molecules play role in the coordination and control of degranulation. FcεRI-mediated activation of mast cells requires both Lyn and the related Src PTK Fyn as receptor-proximal kinases. Fyn-deficient and Lyn/Fyn double deficient mice showed defective passive systemic anaphylaxis responses indicating a positive role for Fyn in promoting mast cell degranulation in vivo (Rivera & Gilfillan, 2006).

Recent investigations showed that stem cell factor and its receptor Kit are fundamentally important in IgE/antigen-induced mast cell activation, and concurrent inhibition of Kit- and FcεRI-mediated signaling achieves coordinated suppression of human mast cell activation (Jensen et al., 2007). Inhibitory sialic acid-binding immunoglobulin-like lectins are expressed on human mast cells, on which Siglec-8 engagement results in inhibition of FcεRI-dependent mediator release without apoptosis (Yokoi et al., 2006). Sphingosine kinases are reported to be determinants of mast cell responsiveness (Olivera et al., 2007).

In some individuals described as having idiopathic anaphylaxis, FcεRI receptors may be aggregated through autoimmune mechanisms (Simons, 2010). Nonimmunological factors, which activate mast cells by mechanisms not yet fully understood, include exercise, cold air or water exposure, radiation, ethanol, insect venom, constituents, radiocontrast media and medications such as opioids and vancomycin (Simons, 2010). Regardless of the immunologic or nonimmunologic triggering mechanism, and regardless of whether FcεRI or other receptors such as G protein-coupled receptors or Toll-like receptors are activated, mast cells and basophils play an important role in initiating and amplifying the acute allergic response. They release mediators of inflammation including histamine, proteases such as tryptase, mast cell carboxypeptidase A3 and chymase, lipids such as platelet activating factor (PAF), prostaglandines (PGD2) and leukotrienes (LTC4) as well as chemokines and cytokines (Simons, 2008).

3.1 Animal models

Studies with murine models demonstrate 2 pathways of systemic anaphylaxis: one mediated by IgE, FcεRI, mast cells, histamine, and platelet-activating factor (PAF), and the other mediated by IgG, FcγRIII, macrophages, and PAF. The former pathway requires much less antibody and antigen than the latter. As a result, IgG antibody can block IgE-mediated anaphylaxis induced by small quantities of antigen without mediating FcγRIII-dependent anaphylaxis (Finkelman et al., 2005).

The IgE pathway is most likely responsible for most human anaphylaxis, which generally involves small amounts of antibody and antigen; similarities in the murine and human immune systems suggest that the IgG pathway might mediate disease in persons repeatedly exposed to large quantities of antigen. Antigen cross-linking of antigen specific IgE bound to mast cell FcεRI stimulates mast cell degranulation, with the rapid release of histamine and serotonin and the synthesis and secretion of platelet activation factor (PAF) and leukotrienes. These mediators act on target cells to increase vascular permeability which cause depletion of intravascular volume. The resulting decrease in vital organ perfusion is the primary cause of the symptoms that characterize murine anaphylaxis (Finkelman et al., 2005).

The other pathway in mouse is Ig-E independent pathway. As contrary of clasical pathway, at first immunized and antigen challenged mice had anaphylaxis despite the absence of mast cells, FcεRI and IgE. This pathway is also complement independent but requires IgG antibody, macrophages, FcγRIII and PAF. Regardless which pathway takes place, mouse anaphylaxis occurs in very short time and displays similar symptoms. Potentially important differences between mouse and human anaphylaxis are proposed as follows: 1. Mouse IgG has some ability to activate mast cells, an effect that is not shared by any human IgG isotype, 2. IgE binds weakly to murine, but not human low-affinity FcγRs, 3. Human but not mouse macrophages, Langerhans cells and dendritic cells can express FcεRI, and 4. Human platelets, B cells and natural killer cells, and neutrophils express low affinity IgG receptor (FcγRIIA, FcγRIIC, and FcγRIIIB, respectively) that are not expressed in mouse (Finkelman et al., 2005).

Less antibody and antigen are required to trigger IgE dependent anaphylaxis then IgG mediated anaphylaxis. IgG and IgA blocking antibodies inhibit the ability of small quantities of antigen to induce IgE dependent anaphylaxis by neutralizing antigen before it can cross link mast cell associated IgE. IgG antibodies also inhibit IgE-dependent anaphylaxis by mediating an interaction between FcεRI and FcγRIIb on mast cells. In mice the predominant determinants that influence whether IgE dependent anaphylaxis is induced appear to be the quantity of antigen specific IgG antibody produced and the quantity of antigen used to challenge immunized mice. This suggests that IgG antibodies, in addition to mediating IgE- independent anaphylaxis, can block IgE-dependent anaphylaxis and provide the rationale for investigating the function of blocking antibody. Gastrointestinal anaphylaxis is induced by IgE/ FcεRI/mast cell/PAF plus serotonin pathway and can cause systemic symptoms if levels of blocking antibodies are low (Finkelman et al., 2005).

3.2 Cytokines

The development and severity of anaphylaxis depend not only on the presence of the required IgE or IgG antibodies, inflammatory cells that express receptor for these antibodies and mediators that are released by these cells but also on the responsiveness of cells that are targeted by these mediators. This last factor is influenced by IL-4 and IL-13, cytokines that are also important in the initial generation of the antibody and inflammatory cell responses

that mediate anaphylaxis to a considerable extent. These effects depend on IL-4Rα-dependent IL4/IL13 activation of transcription factor signal transducer and activator of transcription 6 and thus likely depend on new gene expression and protein synthesis even though they develop within 1-2 hours after mice are treated with either cytokine. The most dramatic and rapid effect of IL-4 on anaphylaxis is a 3-to-6 fold enhancement of responsiveness of targeted cells to vasoactive mediators, including histamine, serotonin, PAF and cysteinyl lekotrienes (Finkelman et al., 2005).

4. Clinical aspects

Currently, there is no universally accepted clinical definition of anaphylaxis. Because of large variability in presenting clinical signs and symptoms, a clear definition of anaphylaxis is difficult. It is likely that anaphylaxis is under diagnosed, especially if it is a patient's first episode, if there is a hidden or previously unrecognized trigger, or if symptoms are mild, transient, or skin signs are absent. Patients might not be able to describe their symptoms if awareness, recognition, and judgment are impaired or if they are dyspneic or becoming unconscious. Symptoms may be suppressed by other medications such as first-generation H1- antihistamines. Health care providers may fail to recognize symptoms of anaphylaxis without obtaining a detailed history and full physical examination. Even after a detailed history and examination, the diagnosis may be overlooked when hives or other skin manifestations are absent. The guidelines published in 2006 by the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) have partially responded to this difficulty (Sampson et al., 2006) (Table 1). However, new large studies are necessary to evaluate current situation.
For the diagnosis of anaphylaxis, a detailed and comprehensive clinical history is essential. Such a history may disclose exposure to potential triggering agents or events, time elapsed between exposure and symptom onset, and evolution of the episode over minutes or hours.

5. Anaphylaxis triggers

The triggering factors of anaphylaxis are listed on Table 2. Foods, medications, and venom continue to be leading causes of anaphylaxis (Boden & Burks, 2011).

5.1 Foods

Food allergy is the most common trigger of children presenting with anaphylaxis (Boden & Burks, 2011). Although most episodes of food-induced anaphylaxis occur within minutes of ingestion, anaphylaxis triggered by mammalian meat may be delayed by several hours. Although, the most common food triggers are reported to be peanut, tree nuts, shellfish, fish, milk, egg, and sesame; there are important variations between the populations from different geographic regions (Sicherer & Sampson, 2006). Any food can potentially trigger anaphylaxis, including previously unrecognized triggers, or some fresh red meats containing carbohydrates. Food triggers can be hidden (eg, substituted foods, cross-reacting foods, and cross-contacting foods). Food triggers also include additives, such as spices, vegetable gums, and colorants (eg, carmine [cochineal]); contaminants, such as dust mites; and parasites, such as the live sea fish nematode Anisakis simplex. Although some food allergies resolve with age others persist. An estimated 80% of children with anaphylaxis to milk or egg are able to tolerate ingestion by age 16 years (Sampson & Burks, 2009).

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:	
1.	Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, and swollen lips-tongue-uvula) AND at least 1 of the following:
	A. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
	B. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2.	Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
	A. Involvement of the skin–mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
	B. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
	C. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
	D. Persistent gastrointestinal symptoms (eg, cramping abdominal pain, vomiting)
3.	Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours):
	A. Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
	B. Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Table 1. Clinical criteria for diagnosing anaphylaxis (Sampson et al., 2006 with permission)

Immunologic mechanisms (IgE dependent)
Foods and food additives Medications Venoms, such as stinging insects (Hymenoptera) Natural rubber latex Occupational allergens Seminal fluid (prostate-specific antigen) Inhalants, such as horse, hamster, and other animal danders and grass pollen (rare) Radiocontrast media Immunologic mechanisms (IgE independent, formerly classified as anaphylactoid reactions) Dextran, such as high-molecular-weight iron dextran Infliximab
Nonimmunologic mechanisms
Physical factors, such as exercise, cold, heat, and sunlight/UV radiation Ethanol Medications, such as opioids Idiopathic anaphylaxis Consider the possibility of hidden or previously unrecognized allergens Consider the possibility of mastocytosis/clonal mast cell disorder

Table 2. Mechanisms and triggers of anaphylaxis in the community (Simons, 2010 with permission)

5.2 Drugs

Many drugs may induce anaphylaxis as a consequence of drug allergy/hypersensitivity. The parenteral use of drugs increases the risk and severity of anaphylactic reactions, and most fatal reactions have occurred with intramuscular or intravenous administration (Chiu & Kelly, 2005). Although drug related anaphylaxis may occur at any age , it is particularly common in middle-aged and older adults. Atopy appears to be associated with a substantially increased risk of serious allergic reactions (including anaphylaxis) once an IgE antibody response to any drug has developed (Lieberman et al., 2010). Antibiotics, especially β-lactam antibiotics including penicillin, semi-synthetic penicillins (eg, amoxicillin), cephalosporins, carbapenems (eg, imipenem), monobactams (eg, aztreonam), and carbecephems, and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, and other agents, are the most often implicated drugs. In the retrospective review of pediatric cases of anaphylaxis, the incidence of drug-induced anaphylaxis was 11%, with nonsteroidal anti-inflammatory drugs causing 50%, antibiotics 40%, and muscle relaxants 10% of reactions (Novembre et al., 1998). In another study, the incidence of medications inducing anaphylaxis was 16%, with antibiotics causing 9%, and other drugs causing 7% of reactions (Dibs & Baker, 1997). In a review of fatal reactions, over four fifths of victims of fatal drug anaphylaxis had no previous awareness or indication of their drug allergy (Chiu and Kelly, 2005). Other common drugs that cause such reactions are insulin, enzymes (streptokinase and chymopapain), heterologous antisera (equine antitoxins and, antilymphocyte globulin), monoclonal antibodies (such as cetuximab, infliximab, and omalizumab), protamine, and heparin. However a great number of medications are known to cause anaphylactic reactions including chemotherapeutic agents, anesthetic agents, radioconrast media etc. Vaccines to prevent infectious diseases seldom trigger anaphylaxis (Simons, 2010). Allergic Type 1 reactions also have been reported after exposure to excipients such as eugenol, carmine, vegetable gums, paraben, thiomerosal, sodium metabisulfite, formaldehyde, and sulfonechloramide.

5.3 Venom

Hymenoptera stings can cause systemic and occasionally fatal anaphylaxis (Bilo & Bonifazi, 2009). Epidemiological population-based studies over the last decade show a prevalence of systemic reaction from hymenoptera stings ranging from 0.3% to 8.9%, with the lowest occurrence in children (Chiu & Kelly, 2005). Order Hymenoptera, family Apidae [honeybees]; family Vespidae [eg, yellow jackets, yellow hornets, white-faced hornets, and paper wasps]; and family Formicidae [eg, ants]) are well known causes. Factors determining the severity of reaction to hymenoptera sting include history of previous severe systemic reaction, insect type, older age, pre-existing cardiovascular and respiratory disease, and use of some medications. Mastocytosis and monoclonal mast cell activation syndrome are a risk factor for severe systemic reactions in allergic patients (Brockow & Ring, 2011).

5.4 Latex

Latex-induced anaphylaxis is due to IgE-mediated mechanisms and may occur in latex sensitive individuals due to direct contact with latex, usually gloves, or instruments, or with aerosolization of latex antigen adherent to the cornstarch powder of latex gloves (Lieberman et al., 2010). Anaphylaxis to natural rubber latex (NRL) became one of the most pervasive problems in medical and surgical care in the early 1990s in children with spina bifida (Chiu

& Kelly, 2005). Latex reactions may occur immediately with latex contact or may be delayed from 30 to 60 minutes. Latex has been reported to account for up to 17% of intraoperative anaphylaxis (Lieberman et al., 2010). Intraoperative latex anaphylaxis may be related to the administration of drug through a latex port prior to surgery, or during the surgical procedure itself. Latex reactions have also been reported to occur during dental procedures from latex gloves or dams, during obstetrical or gynecologic examinations and during latex condom use. Spina bifida patients are potentially at risk during each surgical procedure because of the number of procedures they undergo. Latex sensitization is due to IgE-mediated reactivity to any number of antigens from *Hevea brasiliensis*, the source of latex. Sensitization occurs in up to 12 percent of health care workers, up to 75 percent of patients with spina bifida and in patients undergoing multiple surgical procedures (Lieberman et al., 2010).

5.5 Perioperative anaphylaxis

The incidence of anaphylaxis during anesthesia has been reported to range from 1 in 4000 to 1 in 25,000 (Lieberman et al., 2005). The causes of anaphylaxis in this setting are varied, as are the mechanisms responsible for the reaction. The most common cause of anaphylaxis during general anesthesia or postoperatively is neuromuscular blocking agents (muscle relaxants), which are responsible for sixty to seventy percent of episodes of anaphylaxis occurring during this period. Most of the muscle relaxants cause direct release of mast cell histamine without the requirement for specific antibody. However, life-threatening reactions usually are IgE- mediated. The tertiary or quaternary ammonium group, common to all muscle relaxants, is likely the immunodominant determinant recognized by IgE. The antigenicity of the shared ammonium structures may be responsible for cross-reactivity among the muscle relaxants. Cross-reactivity occurs most consistently between pancuronium and vecuronium. Cross-reactions also may occur between muscle relaxants and other classes of pharmaceuticals, based upon in vitro inhibition of specific-IgE binding to the muscle relaxants. Agents that potentially cross-react with muscle relaxants include: acetylcholine, choline, morphine, neostigmine, and pentolinium. Cross-inhibition suggests that previous exposure to these non-anesthetic drugs may sensitize individuals to muscle-relaxing agents, resulting in reactions among patients without prior anesthesia (Lieberman et al., 2005).

5.6 Exercise anaphylaxis

In some individuals anaphylaxis can be triggered by exercise (exercise-induced anaphylaxis EIA); this phenomenon usually preceded by a causative food ingestion (food-dependent, exercise-induced anaphylaxis (FDEIA) (Barg et al., 2011) . Both are rare but potentially life-threatening clinical syndromes. The symptoms of FDEIA may vary in severity but, reassuringly, fatalities are rare. EIA occurs in all ages, in both sexes, and is more common in atopic individuals. Typical early signs and symptoms begin a few minutes into exercise, and include diffuse warmth, flushing, pruritus, urticaria, and fatigue. If exercise continues, there may be progression to angioedema of the face and extremities, gastrointestinal symptoms, laryngeal edema, hypotension, or collapse. Wheezing can occur, although it is less common than other symptoms. Some patients experience disabling headache that persists for several days after an episode. Attacks occur sporadically and unpredictably, even though most patients with this disorder exercise regularly. Vigorous exercises, such as jogging, racquet

sports, dancing, and aerobics, are most often implicated, although lower levels of exertion, such as brisk walking or yard work, are capable of triggering attacks in some patients. Cessation of exercise usually results in improvement or resolution of symptoms, although, patients often do not instinctively stop exercising when they first experience symptoms. Instead, many try to run for help or sprint home, and this precipitates a dramatic worsening of symptoms. Although wheat is the most commonly reported food allergen associated with FDEIA many other food allergens such as grains, nuts, and seafood, have also been reported (Barg et al., 2011).

5.7 Idiopathic anaphylaxis

Idiopathic anaphylaxis is diagnosed when no triggers can be identified based on history, skin tests are negative, and serum specific IgE levels are absent or undetectable (Greenberger, 2007). Before this diagnosis is made, however, the possibility of a hidden or previously unrecognized trigger should be ruled out and the patients should be evaluated for mastocytosis and clonal mast cell disorders. Idiopathic anaphylaxis has been classified into two categories. When there is a sudden episode that includes urticaria and angioedema associated with acute bronchoconstriction, voice change or stridor, syncope or proven hypotension with or without abdominal pain and diarrrhea, it is then considered as idiopathic anaphylaxis generalized (IA-G). Anaphylaxis that is characterized by marked upper airway obstruction attributable to massive tongue enlargement or a severely edematous larynx or pharynx is categorized as anaphylaxis angioedema (IA-A) (Greenberger, 2007).

5.8 Mastocytocic and anaphylaxis

In adults with mastocytosis, the cumulative prevalence of anaphylaxis has been reported to be 22% to 49%, and in children 6% to 9%. Those with systemic disease have an increased risk of anaphylaxis as compared with patients with cutaneous disease only. As in patients without mastocytosis, the most frequently reported elicitors of anaphylaxis are insect venoms, drugs, and food. Severe and fatal reactions to hymenoptera venom have been described in patients with mastocytosis (Brockow & Ring, 2011).

A variety of drugs have been reported to elicit anaphylaxis in patients with mastocytosis. Every year, reports have been published regarding patients with mastocytosis in whom the diagnosis of systemic mastocytosis was made following anaphylaxis to muscle relaxants or other drugs used during general anesthesia. Other medications leading to reactions in patients with mastocytosis are opiates (including morphine and codeine), acetylsalicylic acid, other NSAIDs, antibiotics, and radiocontrast media. In some patients with mastocytosis, anaphylaxis remains idiopathic despite an extensive search for elicitors (Brockow & Ring, 2011).

The intensity of anaphylaxis in patients with mastocytosis has been described to be particularly severe. Among 55 patients with insect sting allergy and confirmed mastocytosis, 81% experienced severe anaphylaxis with shock or cardiopulmonary arrest (Brockow & Metcalfe, 2010). In another study in which the severity of anaphylaxis was rated, 60% of patients reported severe symptoms and 43% experienced loss of consciousness. Fatal reactions may occur. This is in agreement with the observation that baseline serum tryptase levels are the best known predictor of the severity of anaphylaxis in insect sting–allergic patients (Brockow & Ring, 2011) .

5.9 Rare causes of anaphylaxis

Although rare, anaphylaxis due to coital exposure to human seminal fluid is a known occurrence. Since the initial report in 1958, approximately 30 cases of seminal fluid induced anaphylaxis have been described. All reactions have occurred in female patients during or after sexual intercourse. The vast majority of such reactions are caused by IgE-mediated sensitization to human seminal plasma proteins with molecular weights ranging from 12-75 kD (Lieberman et al., 2010).

Subcutaneous allergen immunotherapy (AIT) injections may rarely cause systemic reactions. Its rate has been estimated at 0.25-1.3%. Fatal anaphylaxis to AIT injections occurs at an estimated rate of 1 in 2.5 million injections and near-fatal anaphylactic reactions at a rate of 1 in every 1 million injections. Patients with asthma, particularly poorly controlled asthma are at higher risk for serious systemic reactions to AIT injections (Lieberman et al., 2005).

In the patients having anaphylaxis attacks without any apparent trigger hydatid cyst ruptures must be kept in mind. Hydatid cysts can rupture as a result of trauma or sometimes spontaneously, and anaphylaxis can be a complication. However, several case reports indicate that anaphylaxis can also occur without macroscopic hydatid cyst rupture (Gelincik et al., 2007).

6. Clinical presentation

Although most definitions specify the need for more than one organ system involvement in the syndrome, it is more important to understand the systemic nature of the clinical symptoms. The first symptoms and signs of anaphylaxis often appear within seconds to minutes after exposure to an offending trigger, however sometimes they may develop later. Late phase or biphasic reactions could also arise 8-12 hours after the initial attack (Lieberman et al., 2010). Each exposure to antigen is unique, and past episodes of anaphylaxis do not predict future events (Boden & Burks, 2011). Among individuals recognized as having anaphylaxis, typical initial symptoms are palmar and/or plantar itch with or without urticaria and/or angioedema. Target organs include skin (90% of episodes), respiratory tract (70%), gastrointestinal tract (30% to 45%), cardiovascular system (10% to 45%), and central nervous system (CNS; 10% to 15%) (Simons, 2008). Accordingly, there may be nausea, abdominal pain, vomiting, or diarrhea. There may also be rhinoconjunctivitis, obstructive respiratory symptoms, tachycardia, arrhythmia, altered mental state, and fainting. Severe respiratory and cardiovascular signs and symptoms such as arterial hypotension and cardiovascular collapse may be the primary manifestations, particularly in perioperative reactions (Schnyder, 2009).

Urticaria and angioedema are the most common and usually the first manifestations of anaphylaxis (Greenberger, 2006). Angioedema was found in 40% and urticaria in 49.3% of 142 patients presenting to an ER with anaphylaxis (Brown et al., 2001). Laryngeal edema was present in 25% of such patients. In 67 patients referred to an outpatient service for evaluation of anaphylaxis, 44.8% of patients had experienced angioedema compared with 58.2% for urticaria. Dyspnea, which may have included oropharyngeal or laryngeal swelling, was noted in 59.7% of patients (Thong et al., 2005). In patients with idiopathic anaphylaxis, 335 patients, ages 5 to 83, were categorized based on whether the acute episode was generalized (urticaria or angioedema with bronchospasm, hypotension, syncope, or gastrointestinal symptoms with or without upper airway obstruction) or angioedema (urticaria or angioedema with upper airway compromise without other systemic symptoms

such as shock) (Ditto et al., 1996). From the 335 patients, 201 (60%) were classified as IA-G and 119 (35.5%) were designated as IA-A. In this series, urticaria or angioedema occurred in all 335 patients, but anaphylaxis, implying a life-threatening emergency, involved angioedema of the upper airway in over a third of patients. Indeed, these patients had experienced laryngeal or pharyngeal edema or ''massive tongue edema''. Perhaps, most persuasively, in this series of 335 patients, upper airway obstruction occurred in 210 (63%) patients (Ditto et al., 1996).

However, skin and mucosal symptoms and signs are absent or unrecognized in 10% to 20% of all anaphylactic episodes (Simons, 2010). These are rather more severe forms of anaphylaxis arising suddenly with either respiratory compromises or cardiovascular collapse. The lack of cutaneous signs reflects that anaphylaxis episode is likely to become fatal.

There are some differences in the presentation of anaphylaxis in the pediatric population compared with the adult population, including smaller numbers having cardiovascular signs and symptoms (21% compared with 41%). Other features noted in pediatric anaphylaxis include skin and respiratory signs appearing with an earlier onset compared with gastrointestinal and cardiovascular signs. Most children had a personal history of atopy (Dibbs & Baker, 1997).

The symptoms and signs of anaphylaxis are shown in Table 3.

Cutaneous/subcutaneous/mucosal tissue
Flushing, pruritus, hives (urticaria), swelling, morbilliform rash, pilor erection Periorbital pruritus, erythema and swelling, conjunctival erythema, tearing Pruritus and swelling of lips, tongue, uvula/palate Pruritus in the external auditory canals Pruritus of genitalia, palms, soles
Respiratory
Nose: pruritus, congestion, rhinorrhea, sneezing Larynx: pruritus and tightness in the throat, dysphonia and hoarseness, dry staccato cough, stridor, dysphagia Lung: shortness of breath, chest tightness, deep cough, wheezing/bronchospasm (decreased peak expiratory flow) Cyanosis
Gastrointestinal
Nausea, cramping abdominal pain, vomiting (stringy mucus), diarrhea
Cardiovascular
Chest pain, palpitations, tachycardia, bradycardia, or other dysrhythmia Feeling faint, altered mental status, hypotension, loss of sphincter control, shock, cardiac arrest
CNS
Aura of impending doom, uneasiness, throbbing headache, dizziness, confusion, tunnel vision; in infants and children, sudden behavioral changes, such as irritability, cessation of play, and clinging to parent
Other
Metallic taste in the mouth
Dysphagia
Uterine contractions in postpubertal female patients

Table 3. Symptoms and signs of anaphylaxis (Simons, 2010 with permission)

7. Laboratory tests

No optimal and readily available laboratory test can confirm the clinical diagnosis of an anaphylactic episode. Nevertheless, in some patients the clinical diagnosis of anaphylaxis can be confirmed by means of a blood test; for example, an increased plasma histamine level or serum total tryptase level (Simons, 2010). These tests are not specific for anaphylaxis. Plasma histamine levels should optimally be measured 15 to 60 minutes after onset of symptoms of anaphylaxis. Special handling of the blood sample is required. Histamine and its metabolite, N-methylhistamine, can also be measured in a 24-hour urine sample. Because tryptase is selectively and abundantly produced by mast cells, tryptase levels in biologic fluids should provide a more precise measure of local or systemic involvement of these cells than is possible to ascertain by clinical presentation or documentation of antigen-specific IgE. Basophils, the only other cell type that normally expresses tryptase, contain approximately 1/500th the amount mature β tryptase levels generally reflect the magnitude of mast cell activation and are elevated during most cases of systemic anaphylaxis, particularly with parenteral exposure to the inciting agent (Schwartz, 2006). Not all hypotensive reactions that clinically seem to be anaphylactic are associated with elevated levels of mature tryptase, however. For example, victims of fatal and near-fatal food-induced anaphylaxis often show no mature tryptase elevation, raising the possibility that some of these events may not be dependent on mast cell activation. Basophils have been suggested as an alternative effector cell, but direct evidence for this has not yet emerged. Other considerations might include overproduction through non-mast cell pathways of vasoactive mediators, such as complement anaphylatoxins, kinins, or lipids (Schwartz, 2006).

Serum total tryptase levels should optimally be measured from 15 minutes to 3 hours after onset of symptoms. No special handling of the blood sample is required. The total tryptase level is typically increased in patients with anaphylaxis triggered by an injected medication or an insect sting and in those with hypotension and shock but is less likely to be increased in those with anaphylaxis triggered by food or in those who are normotensive. Serial measurements of serum total tryptase and comparison with baseline levels obtained after the acute episode or available in stored serum might be more helpful than measurement at a single point in time. Other biomarkers reported to be useful in confirming an acute episode of anaphylaxis include serum mature β-tryptase; mast cell carboxypeptidase A3; chymase; platelet-activating factor; bradykinin; C-reactive protein; cytokines, such as IL-2, IL-6, IL-10, IL-33, and TNF-receptor I; and urinary cysteinyl leukotriene E4 and 9-a-11-b prostaglandin F2 (Simons, 2010).

It was shown that serum PAF levels were directly correlated and serum PAF acetylhydrolase activity was inversely correlated with the severity of anaphylaxis. PAF acetylhydrolase activity was significantly lower in patients with fatal anaphylactic reactions to peanuts than in patients in any of the control groups. Failure of PAF acetylhydrolase to inactivate PAF may contribute to the severity of anaphylaxis (Vadas et al., 2008).

8. Diagnosis

All individuals who have had a known or suspected anaphylactic episode require a careful and complete review of their clinical history. This history may elicit manifestations such as urticaria, angioedema, flushing, pruritus, upper airway obstruction, gastrointestinal symptoms, syncope, hypotension, lower airway obstruction, and/or other less common manifestations (Lieberman et al., 2010).

Other conditions that should be considered in the differential diagnosis include: (1) vasodepressor (vasovagal/neuro-cardiogenic) syncope; (2) syndromes that can be associated with flushing (e.g., metastatic carcinoid); (3) postprandial syndromes (e.g., scombroid poisoning); (4) systemic mastocytosis; (5) psychiatric disorders that can mimic anaphylaxis such as panic attacks or vocal cord dysfunction syndrome; (6) angioedema (e.g., hereditary angioedema); (7) other causes of shock (e.g., cardiogenic); and (8) other cardiovascular or respiratory events (Lieberman et al., 2005).

The history is the most important tool to establish the cause of anaphylaxis and takes precedence over diagnostic tests. A detailed history of all food consumed and drugs taken over the four to six hours prior to the episode should be obtained. In addition, the labels for all packaged foods ingested by the patient in this period of time should be reviewed since a substance added to the food could be responsible. A history of any preceding bite or sting should be obtained. The patient's activities (e.g., exercise, sexual activity) preceding the event should be reviewed. Patient diaries may be a useful adjunct in confirming or identifying the cause of anaphylaxis (Lieberman et al., 2010).

A detailed history of all potential causes should be obtained. This includes a list of ingestants consumed and/or medications taken within six hours of the event, any sting or bite occurring prior to the event, if the event occurred during exercise, location of the event (e.g., work versus home), and whether or not the event was related to exposure to heat, cold, or occurred during sexual activity. The patient's atopic status should be noted since food-induced, seminal fluid and idiopathic anaphylaxis are more common in atopic than non-atopic individuals. In women, the history should include any relationship between the attack and their menstrual cycle. A return of symptoms following a remission should be noted since this may indicate a late phase reaction, which might require a prolonged period of observation if subsequent events occur (Lieberman et al., 2010).

8.1 Confirmation of the triggers of anaphylaxis

The next step in the evaluation of a patient experienced anaphylaxis is confirmation of the trigger or triggers identified or suspected through the history (Simons, 2010). So that the relevant specific trigger or triggers can be avoided and recurrences of anaphylaxis can be prevented. Skin tests should be performed with validated instruments, techniques, and recording systems, preferably at least 3 to 4 weeks after the anaphylactic episode, to allow time for rearming of skin mast cells and recovery of mast cell releasability. When possible, standardized extracts for skin testing should be used, although occasionally fresh food extracts will be superior to available standardized extracts. If the skin testing extract has not been standardized (e.g., latex, protamine, or antibiotics other than penicillin), the clinical relevance of the results may be uncertain. Skin tests or in vitro tests can determine the presence of specific IgE antibodies to foods, medications (e.g., penicillin and insulin), and stinging insects as a cause of anaphylaxis (Lieberman et al., 2010). Measurement of allergen-specific IgE levels by using a quantitative method can be performed at any time during or after the acute anaphylactic episode; however, if the blood sample is obtained during or shortly after the episode from patients who have received intravenous fluid resuscitation, levels can be falsely undetectable or low because of the dilutional effect on circulating IgE. Negative tests for sensitization to a trigger in a patient with a convincing history of anaphylaxis from that trigger should be repeated weeks or months later. It is important to note that both positive skin tests and increased specific IgE levels indicate sensitization to the allergens tested but are not diagnostic of anaphylaxis or any other disease (Lieberman et

al., 2010). The clinical significance of skin testing or in vitro test depends on the ability to correlate the results of such testing with the patient's history. If tests for specific IgE antibodies (i.e., skin tests, in vitro tests, or both) do not provide conclusive evidence of the cause of anaphylaxis, challenge with the suspected agent can be considered. If indicated, incremental challenge/provocation tests should be conducted in appropriately equipped health care facilities by professionals trained and experienced in patient selection, timing of the challenge, use of challenge protocols, and diagnosing and treating anaphylaxis. Before a challenge is performed, the potential risks and benefits should be discussed with the patient (or, for children, the caregivers) and documented in the medical record. Challenge procedures may also be appropriate in patients who develop non-IgE-mediated reactions (e.g., reactions to aspirin (ASA) or other nonsteroidal anti-inflammatory drugs. Challenge with suspected agents must be done carefully by individuals knowledgeable in the challenge procedure and with expertise in managing reactions to the challenge agent if they should occur (Lieberman et al., 2010).

8.2 Assessment of patients with food-triggered anaphylaxis

Skin prick tests with foods that elicit a wheal of 3 mm larger than that caused by the negative control (eg. saline) are considered positive (Simons, 2010). Commercially available food allergen extracts do not contain standardized allergens. Some food allergens, such as fruits and vegetables, are labile and degrade in glycerinated extracts during manufacture and storage; therefore skin prick tests with these allergens are often performed with fresh foods.

Intradermal tests to foods are contraindicated because of lack of specificity (false-positive tests) and their potential for triggering anaphylaxis (Lieberman et al., 2010). An exception to this might be use of intradermal tests to assess sensitization to fresh meat containing the carbohydrate galactose-alpha-1,3-galactose. In food-sensitized patients specific IgE levels have predictive values for positive (failed) or negative (passed) food challenge tests. Allergen-specific IgE levels with greater than 95% predictive risk values of a positive (failed) food challenge result have been identified by using the ImmunoCAP (Phadia, Uppsala, Sweden). These levels are defined for cow's milk (15 kU/L), egg (7 kU/L), peanut (14 kU/L), tree nuts (15 kU/L), and fish (20 kU/L); in infants lower values have been established for milk (5 kU/L) and egg (2 kU/L) (Boden & Burks, 2011). Predictive values for allergen-specific IgE levels potentially differ from one immunoassay to another, and this can affect management decisions.

A positive skin test, an increased serum IgE level, or both to a specific food document sensitization to that food. Such tests are not diagnostic of anaphylaxis because sensitization to 1 or more food allergens is common in the general population of healthy people who have no history of anaphylaxis. For example, 60% of young people have a positive skin prick test to 1 or more foods, yet most of those with positive tests have never experienced anaphylaxis from a food. In addition, although positive skin tests and increased allergen-specific IgE levels correlate with an increased probability of clinical reactivity to specific foods, the results of these tests do not necessarily correlate with the risk of future anaphylactic episodes or with the severity of such episodes (Simons, 2010).

Oral food challenge testing is accepted as a gold standard for detection of a food allergy/hypersensitivity (Sampson & Burks, 2009). Patients with a convincing history of anaphylaxis to a specific food and evidence of sensitization to that food should not undergo oral food challenge tests because of their high risk of anaphylaxis from such tests. Others, such as those with an equivocal history, low or moderate evidence of sensitization, or both,

might benefit from a physician-monitored incremental oral food challenge. A positive (failed) challenge provides a basis for continued avoidance of the food. A negative (passed) challenge allows introduction or reintroduction of the specific food into the patient's diet.

8.3 Assessment of medication- or biological agent –triggered anaphylaxis

Any medication or biological agent can potentially trigger anaphylaxis. In cases with severe anaphylactic reactions, it is advisable to first perform skin tests with the presumably causative drugs only by prick (Schnyder & Pichler, 2009). If responses are negative and the involved drug is available as a parenteral formulation, negative skin tests do not have sufficient sensitivity to exclude an immune-mediated hypersensitivity in the case of a suggestive history. For most agents, the antigenic determinants have not been characterized or validated; indeed, the relevant immunogenic prodrugs, haptens, metabolites, and unidentified degradation products or contaminants are often unknown. For most medications, with the exception of some β-lactam antibiotics, appropriate reagents are not commercially available for use in skin tests, measurement of medication-specific IgE levels, or other in vitro tests. In penicillin allergies, standardized preparations with penicilloylpolylysine and minor determinant mixture may be used (Lieberman et al., 2010). Penicillin allergy may also be evaluated by in vitro tests for specific IgEs; however, these tests have a low sensitivity. Additionally, assays for a few drugs such as suxamethonium, rocuronium, morphine, sulfamethoxazole, and chlorhexidine, are offered, some with potentially higher sensitivity (Schnyder, 2009). A further in vitro test to identify the relevant drug may be the basophil activation test. This test is based on flow cytometric quantification of drug-induced CD63 expression or CD203c up-regulation or measurement of sulfo-leukotriene release by ELISA. The sensitivity in IgE-mediated reactions appears to be superior to CAP-based IgE determinations and comparable with skin tests. Customized tests and physician-monitored challenge/provocation tests performed in specialized centers therefore play a central role in assessment of patients with a history of anaphylaxis triggered by a medication. A drug provocation test (DPT) is defined as controlled administration of a drug to diagnose immune-mediated and non–immune-mediated drug hypersensitivity. Its advantage is that it permits testing of a patient with his or her individual metabolism and immunogenetic background. A DPT reproduces not only symptoms of allergy but other adverse clinical manifestations, irrespective of their mechanism. A DPT is currently the ''gold standard,'' but its use is limited by the possibility of severe and uncontrollable relapse of the reaction (Aberer et al., 2010). Therefore, a DPT should be reserved for specific situations when a significant drug is suspected to have provoked an intolerance reaction and alternative test methods have failed to yield conclusive results. The patient being tested has to be in stable condition, and an anticipated positive reaction must be controllable by adequate measures. Because of these restrictions, only physicians experienced in drug allergy should perform this test. The two main indications for a DPT with the suspected drug are the following: to exclude hypersensitivity in the presence of unconvincing histories of drug hypersensitivity or in patients with nonspecific conditions, such as subjective symptoms under local anesthesia, or to establish a distinct diagnosis in suggestive histories of drug hypersensitivity with inconclusive, negative, or nonavailable allergy test results. A positive DPT result optimizes the avoidance of certain drugs, whereas a negative one permits the clinician to rule out a false diagnosis of drug hypersensitivity.

For assessment of anaphylaxis triggered by vaccines to prevent allergic diseases, skin prick tests should be performed not only with the immunizing agent but also with the relevant

excipients in the culprit vaccine, such as gelatin in measles vaccines or egg in some influenza vaccines and in yellow fever vaccine (Simons, 2010).

8.4 Assessment of stinging insect-triggered anaphylaxis

Standardized Hymenoptera venoms, such as honeybee, yellow jacket, yellow hornet, white-faced hornet, and Paper wasp, are available for skin testing. Skin prick tests, if negative, should be followed by intradermal tests (Bilo & Bonifazi, 2009). Use of dialyzed venoms in skin tests is reported to improve the identification of venom-sensitized patients (Golden et al., 2009). For fire ant-triggered anaphylaxis, whole-body extracts are used as skin test reagents. Measurements of venom-specific IgE levels are commercially available (Freeman, 2004). Some patients with a history of Hymenoptera sting–triggered anaphylaxis have negative skin test responses to insect venoms but increased specific IgE levels to venoms and vice versa (Simons, 2010). Positive intradermal tests to stinging insect venoms, increased venom-specific IgE levels, or both occur in up to 28.5% of the general adult population, most of whom do not have systemic symptoms after an insect sting (Simons, 2010). It is therefore critically important that the test results be interpreted in the context of the clinical history. In some centers additional tests used to assist in interpretation of positive test results include consideration of total IgE levels as well as venom-specific IgE levels, and measurement of basophil activation markers, such as CD63 or CD203c after incubation with different concentrations of venom (Simons, 2010). Conversely, venom skin tests might be negative and venom specific IgE levels might be absent or undetectable in patients with a convincing history of insect sting–triggered anaphylaxis (Simons, 2010).

8.5 Perioperative anaphylaxis

Skin testing may be useful to determine the safest alternative for subsequent anesthesia following a suspected reaction. Skin testing with neuromuscular blocking agents, hypnotics and opioids is used. Antibiotics frequently are administered before, during, or immediately after anesthesia and surgery. Allergic reactions to antibiotics, particularly anaphylaxis, may occur during the perioperative period. For this reason, following a suspected reaction during anesthesia, skin tests with antibiotics should also be done. It should be noted that nonimmunologic reactions are not identified by this diagnostic method. Skin testing is not recommended for preanesthetic screening of subjects without a history of suspected reactions (Lobera et al., 2008).

8.6 Assessment of anaphylaxis triggered by natural rubber latex

Skin prick tests should be performed with commercial latex allergens, where available, or with extracts of rubber products, such as natural rubber latex gloves, where commercial allergens are not available. In vitro tests have highly variable sensitivity and specificity characteristics (Lieberman et al., 2010). Consideration should be given to testing with foods that cross-react with latex, such as banana, kiwi, papaya, avocado, potato, and tomato. Latex-specific IgE antibodies can also be measured.

8.7 Assessment of exercise-triggered anaphylaxis

These should be done: meticulous clinical history, skin or in vitro testing for potential food allergen co triggers, and occasionally, documenting mast cell activation if this can be determined in the minutes or hours following an attack (Lieberman et al., 2010). The diagnosis of EIA can be confirmed by eliciting symptoms with treadmill testing. However,

symptoms are difficult to reproduce. The differential diagnosis includes arrhythmias and other cardiovascular events, but such events do not include pruritus, urticaria, angioedema, or upper airway obstruction. Exercise induced bronchoconstriction presents with symptoms that are limited to the airways. Exercise-associated gastroesophageal reflux could mimic mild symptoms of EIA, although, urticaria and/or pruritus are not observed (Feldweg & Sheffer, 2011).

8.8 Assessment of idiopathic anaphylaxis

When a meticulous history of antecedent exposures and events does not yield any clues about potential triggers and when allergen skin tests are negative and specific IgE measurements are absent or undetectable to selected common allergens, patients are said to have idiopathic anaphylaxis (Greenberger, 2007). The diagnosis of idiopathic anaphylaxis is based on exclusion. Before making this diagnosis, physicians should consider the possibility of a hidden or previously unrecognized trigger. Sensitization to a novel trigger for which there is no commercially available test material, can be identified through a history of the event and confirmed by objective tests.

Patients with idiopathic anaphylaxis should receive careful evaluation for possible causes, with emphasis on the history of events in the 3 hours prior to an episode. Selective skin testing with foods (and if indicated to fresh food extracts) may be of value. Indolent systemic mastocytosis must be excluded. Consistently elevated serum tryptase levels suggest the presence of indolent systemic mastocytosis since the serum tryptase will be elevated in the absence of episodes of anaphylaxis. In contrast, serum tryptase levels will be normal in quiescent idiopathic anaphylaxis. A bone marrow examination may be indicated in patients with a diagnosis of idiopathic anaphylaxis even in the absence or elevated tryptase levels if salmon colored, hyperpigmented macules and papules consistent with urticaria pigmentosa are found (Akın et al., 2007). The differential diagnosis of idiopathic anaphylaxis includes hereditary angioedema or acquired C1 inhibitor deficiency. Some patients with idiopathic anaphylaxis present with massive enlargement of the tongue and/or life-threatening upper airway obstruction due to pharyngeal or laryngeal angioedema, but their C4 concentration is not reduced.

9. Management

Anaphylaxis, as a potentially life-threatening condition must be diagnosed and managed promptly. Although the etiology may be various or indefinite and there is lack of rapid diagnostic tests, the diagnosis relies mostly on clinical symptoms, therefore requires a high index of suspicion. Irrespective of the trigger or mechanism of anaphylaxis, the initial management is the same and is based on basic therapeutic agents that all healthcare professionals should be able to provide, even in a low resource environment (Lee & Vadas, 2011; Simons et al., 2011). Prompt and definitive management can be life saving whereas the delay in the management may result in a fatal outcome (Lieberman et al., 2010).

Anaphylaxis can potentially affect cardiovascular and respiratory systems and be presented as a multisystem emergency. The trigger has to be removed, if possible and the patient's circulation, airway, breathing, level of consciousness, and skin should be rapidly assessed (Simons et al., 2011). According to the consensus of experts, in general the treatment in order of importance includes epinephrine (adrenaline), patient position, oxygen, intravenous

fluids, nebulized therapy, vasopressors, antihistamines, corticosteroids, and other agents (Lieberman et al., 2010).

In a series of over 200 anaphylaxis deaths the median time from onset of symptoms to fatal cardiopulmonary arrest was reported as <30 minutes (Pumphrey, 2000). In the same paper the median times to cardiopulmonary arrest were 5 minutes after administration of a diagnostic or therapeutic intervention, 15 minutes after an insect sting, and 30 minutes after food ingestion. As soon as the need is recognized, supplemental oxygen at a flow rate of 6-8 L/min, intravenous fluid resuscitation must be administered and the cardiopulmonary resuscitation with continuous chest compressions before giving rescue breathing must be initiated (Simons et al., 2011). Patients should be kept supine with legs raised to prevent death due to 'empty vena cava/ empty ventricle syndrome' with pulseless electrical activity (Pumphrey, 2003). In this syndrome patients in shock suddenly sit, stand, or are placed upright, the vena cava empties within seconds, and epinephrine is prevented from circulating the body (Pumphrey & Gowland, 2007). The patient must be kept in a comfortable position if vomiting or respiratory distress is present (Simons et al., 2011).

Supplemental oxygen should be given by face mask or oropharyngeal airway to all patients with concomitant asthma, other chronic respiratory disease, or cardiovascular disease and those having prolonged reactions or those who are receiving inhaled β-agonists as part of the treatment for anaphylaxis or repeated doses of epinephrine (Lieberman et al., 2010; Simons et al., 2011). Oxygen supplementation should be guided with continuous pulse oximetry and/or arterial blood gas determination (Lieberman et al., 2010).

The fluid management is critical as massive fluid shifts can occur due to increased vascular permeability within minutes (Brown et al., 2004). Saline stays in the intravascular space longer than dextrose and contains no lactate which may exacerbate metabolic acidosis. Therefore one to 2 L of 0.9% isotonic saline as a preferred solution should be commenced as 5-10 mL/kg in the first 5-10 minutes to an adult or 10 mL/kg to a child as soon as the need for it is recognized (Lieberman et al., 2010; Simons et al., 2011). The rate of administration should be titrated according to the blood pressure, cardiac rate and function and urine output. Caution should be undertaken for volume overload (Simons et al., 2011). In some cases fluid replacement may not be so effective when considered with other indications. It is possible that the replaced fluid during management can also shift from the vasculature to tissues. Therefore the cornerstone of management is a non-selective adrenergic agonist agent, epinephrine which acts on α-1, β-1 and β-2 adrenergic receptors and is highly effective to reverse the clinical symptoms mainly with vasoconstriction, cardiac stimulation and bronchodilatation (Lee & Vadas, 2011; Simons et al., 2009a). The World Health Organization (WHO) classifies epinephrine as an essential medication for the treatment of anaphylaxis (Simons et al., 2011). The evidence base for prompt epinephrine injection in the initial treatment of anaphylaxis is stronger than the evidence base for the use of antihistamines and glucocorticoids in anaphylaxis (Simons et al., 2011). Therefore overt signs of distributive shock or cardiovascular compromise should not be waited to administer epinephrine. It is recommended that epinephrine be given as soon as possible (Lee & Vadas, 2011). Although there is any doubt in recognition of the clinical situation as anaphylaxis, it is generally better to administer epinephrine (Lieberman et al., 2010).

Pharmacokinetic studies have shown that the intramuscular route of administration into the mid-anterolateral thigh (the vastus lateralis muscle) is preferable with a faster onset of action and more sustained levels as compared with the subcutaneous route (Lee & Vadas,

2011; Simons, 2009b). The rationale for intramuscular injection is that the striated muscle is well vascularized, facilitating rapid systemic absorption and prompt achievement of peak epinephrine pharmacologic effects. In contrast subcutaneous tissue consisting mostly of poorly vascularized adipose tissue provides the slow absorption of epinephrine with variable time intervals for peak pharmacologic effects (Simons, 2009b). Significantly faster peak plasma concentrations are achieved via the intramuscular route (8 ± 2 min) than the subcutaneous route of administration (34 ± 14 min) in children, and in adults (Frew, 2010). Intramuscular epinephrine injections into the thigh have been reported to provide more rapid absorption and higher plasma epinephrine levels in both children and adults than intramuscular or subcutaneous injections administered in the arm (Lieberman et al., 2010). Alternative routes of administration have been anecdotally tried. For example sublingual delivery of 40 mg epinephrine has been shown to lead to plasma concentrations that are not significantly different to those following intramuscular administration of 0.3 mg epinephrine (Frew, 2010).

The recommended dose of epinephrine for children is 0.01 mg/kg body weight of a 1:1,000 (1 mg/mL) solution, to a maximum initial dose of 0.3 mg in a 30 kg child (Simons, 2009b). In the recent guideline of World Allergy Organization (WAO) the same dose of epinephrine in adults with a maximum initial dose of 0.5 mg is recommended (Simons et al., 2011). In the recent Practice Parameter on the Diagnosis and Management of Anaphylaxis, the dose is defined as 0.2-0.5 ml of aqueous epinephrine of a 1:1,000 dilution in adults and as 0.01mg/kg of the same dilution in children (Lieberman et al., 2010). The dose can be repeated every 5-15 minutes, as needed depending on the severity of the episode and the response to the initial injection (Lieberman et al., 2010; Simons et al., 2011). Approximately 20% of cases in the community require a second dose because of lack of response to the first dose, or development of a biphasic reaction (Simons, 2009b).

The patient has to be monitored with blood pressure, cardiac rate and function, respiratory status at regular intervals and oxygenation continuously, if possible (Simons et al., 2011). The duration of monitoring should be individualized. Patients with moderate respiratory or cardiovascular compromise should be monitored in a medically supervised setting for at least 4 hours and if indicated 8-10 hours or longer, and patients with severe or protracted anaphylaxis might require monitoring and interventions for days (Simons et al., 2011).

In patients who remain hypotensive and unresponsive to intramuscular epinephrine and fluid resuscitation, the ones who have progressed to shock or cardiac arrest intravenous epinephrine is recommended (Lee & Vadas, 2011; Simons et al., 2011). Ideally, this route should be administered only by trained, experienced physicians who are equipped to give vasopressors through an infusion pump and titrate the dose frequently according to noninvasive continuous monitoring of cardiac rate and function. A controlled infusion is safer than bolus administration (Soar et al., 2008). If cardiac arrest is imminent or has already occurred, an intravenous bolus dose of epinephrine is indicated according to Resuscitation Guidelines (Simons et al., 2011). An intravenous epinephrine infusion is prepared by adding 1 mg (1 mL) of 1:1,000 dilution of epinephrine to 250 mL of 5% dextrose to yield a concentration of 4.0 μg/mL. This 1:250,000 solution is infused at a rate of 1μg/mL, titrated to a maximum of 10.0μg/min for adults. In children, a dosage of 0.01 mg/kg (0.1 mL/kg of a 10,000 solution up to 10μg/min; maximum dose, 0.3 mg is administered (Lieberman et al., 2010). Other protocols for intravenous administration are also suggested (Lieberman et al., 2010).

Dopamine as a vasopressor agent is recommended when epinephrine and fluid resuscitation fail to alleviate hypotension in a dose of 2-20μg/kg/min, titrated to maintain systolic blood pressure greater than 90 mmHg. During cardiopulmonary resuscitation intravenous high-dose epinephrine is recommended. A common sequence is 1 to 3 mg (1:10,000 dilution) intravenous slowly administered over 3 min, 3 to 5 mg intravenous over 3 min, and then 4-10 μg/min infusion. For children, the recommended initial resuscitation dosage is 0.01 mg/kg (0.1 ml/kg of a 1:10,000 solution up to 10 μg/min rate of infusion), repeated every 3 to 5 min for ongoing arrest. Higher subsequent dosages (0.1-0.2 mg/kg: 0.1 ml/kg of a 1:1,000 solution) may be considered for unresponsive asystole or pulseless electrical activity (Lieberman et al., 2010).

The common adverse effects of epinephrine include anxiety, dizziness, restlessness, headache, palpitations, tremor, and pallor and indicate that a therapeutic dose has been given (Lee & Vadas, 2011; Simons, 2009b). Rare side effects of epinephrine more commonly related with high or rapid doses of intravenous administration include ventricular arrhythmias, angina, myocardial infarction, pulmonary edema, hypertensive emergency, and intracranial haemorrhage (Lee & Vadas, 2011; Simons et al., 2011). It was demonstrated that the heart is the target organ of anaphylaxis and acute coronary syndrome can occur in anaphylaxis in the absence of epinephrine administration in patients with known coronary artery disease, and those in whom subclinical coronary artery disease is unmasked by the anaphylactic episode (Simons et al., 2011). Concerns about adverse effects, especially potential myocardial infarction and cardiac arrhythmias, need to be weighed against the cardiac risks of untreated anaphylaxis (Simons, 2009b; Simons et al., 2011). As there is no controlled trials mainly because of ethical concerns, there is no way to estimate the risk in relation to benefit of epinephrine, but on the basis of current evidence, the benefit of using appropriate doses of intramuscular epinephrine is likely to far exceed the risk (Sheikh et al., 2009). According to the recent WAO guidelines epinephrine is not contraindicated in the treatment of anaphylaxis in patients with known or suspected cardiovascular disease, or in elderly patients without known coronary artery disease who are at risk of acute coronary syndrome only because of their age (Simons et al., 2011). However, careful monitoring and avoidance of an adrenaline overdose are necessary in these patients (Sheikh et al., 2009).

In a recent systematic Cochrane review, it was emphasized that there are no absolute contraindications to epinephrine use in anaphylaxis and in the absence of appropriate trials, and suboptimal evidence, epinephrine administration is recommended to be regarded as the first-line treatment for the management of anaphylaxis (Sheikh et al., 2009). Some relative contraindications include patients using mono-amine oxidase inhibitors, tricyclic anti-depressants, or stimulant medications or illicit substances, all of which are possibly increasing the risk of adverse effects of epinephrine (Lee & Vadas, 2011). Caution is needed in patients with recent intracranial surgery, aortic or cerebral aneurism(s), uncontrolled hyperthyroidism, or hypertensive emergencies (Lee & Vadas, 2011).

H1-antihistamines are frequently used in anaphylaxis, but they cannot be substituted for epinephrine as first line treatment (Sheikh et al., 2007). A Cochrane systematic review of the literature has found no high quality evidence either for or against the use of H1-antihistamines in anaphylaxis; therefore randomized controlled trials are needed (Sheikh et al., 2007). These agents do not prevent or reverse life-threatening upper and lower respiratory tract obstruction, hypotension or shock (Simons et al., 2009a), but they relieve itching, flushing, urticaria, angioedema and nasal and eye symptoms (Simons, 2009b;

Simons et al., 2011). As a second line medication, for example diphenhydramine 1 mg/kg, approximately 25-50 mg in adults, maximum 50 mg in children is recommended by slow intravenous infusion over 10-15 minutes. The route of administration depends on the severity of the attack. Only the first generation H1-antihistamines are available for intravenous use and they potentially increase vasodilation and hypotension if given rapidly (Simons et al., 2011). H2-antihistamines in combination with H1-antihistamines are sometimes used for anaphylaxis treatment in the US and Canada (Lieberman et al., 2010; Simons et al., 2011). When an oral H1-antihistamine is indicated, a low sedating medication such as cetirizine is preferable to a sedating H1-antihistamine (Simons et al., 2011).

Glucagon is preferred in patients who are already using β- blockers therefore experiencing a relative bradycardia and refractory hypotension and are not fully responding to epinephrine (Gallagher et al., 2011; Thomas & Crawford, 2005). It shows its effects independent of β-receptors by directly activating adenyl cyclase. The recommended dose is 1 to 5 mg in adults and 20-30 μg/kg (maximum of 1 mg) administered intravenously over 5 min as a bolus. The bolus dose can be repeated or followed by an infusion of 5-15μg/min, titrated to clinical response (Lieberman et al., 2010). The common side effect is emesis, particularly related with rapid infusion and therefore protection of the airways to prevent aspiration in severely drowsy patients is important (Lee & Vadas, 2011; Lieberman et al., 2010).

A recent Cochrane systematic review concluded that there is insufficient high-quality evidence to either support or not to support the use of glucocorticosteroids in the management of anaphylaxis (Choo et al., 2010). The existing evidence consists mainly of retrospective studies, case reports, and other descriptive literature. The recent WAO anaphylaxis guideline recommends glucocorticosteroid use in anaphylaxis management as a second line medication. It is used to prevent biphasic or protracted symptoms, although there is weak evidence for it (Simons et al., 2011). It doesn't provide rapid relief of upper or lower airway obstruction, shock, or other symptoms of anaphylaxis (Simons, 2009b). The route of administration depends on the severity of the attack (Simons et al., 2011). The recommended dose of methylprednisolone by WAO anaphylaxis guideline is 1-2mg/kg/day, approximately 50-100 mg or equivalent for 3-4 days in adults, at a maximum dose of 50 mg in children (Lee & Vadas, 2011; Simons et al., 2011). Other guidelines recommend hydrocortisone, triamcinolone, prednisone by intravenous, intramuscular, or oral routes using different doses and dose regimens (Soar, 2005, Brown et al., 2006, Alrasbi & Sheikh, 2007, Muraro et al., 2007, as cited in Choo et al., 2010). Short term glucocorticoid treatment is seldom associated with adverse effects (Choo et al., 2010).

Additionally short and rapid acting β2-adrenergic agonist, salbutamol is recommended in nebulised form in doses of 2.5 mg/3 mL in children or 5 mg/3 mL in adults to treat bronchoconstriction with combination of oxygen supplementation (Simons et al., 2011). Tremor, tachycardia dizziness are potential side effects in usual doses, where as headache, hypokalemia, vasodilation can be seen in overdoses (Simons et al., 2011). Vasopressors such as dopamine can be used to correct hypotension despite other interventions.

It should be pointed out that the time taken by draw up and administration of a second-line medication such as H1- antihistamines, corticosteroids, β2-adrenergic agonists should not cause a delay in the administration of the first line treatment of epinephrine, supplementation of oxygen or intravenous fluid resuscitation (Simons et al., 2011).

In refractory anaphylaxis methylene blue is used in a number of case reports. In anaphylactic shock endothelial nitric oxide synthase-derived NO appears to be the principal

vasodilator. Therefore methylene blue by inhibiting nitric oxide synthesis inhibition blocks nitric oxide (NO)-mediated vascular smooth muscle relaxation and seems to be effective in these cases (Lieberman et al., 2010). Tranexamic acid was used to treat anaphylactic episodes associated with disseminated intravascular coagulation (Lieberman et al., 2010).
The management of anaphylaxis in pregnancy is similar to the management of non-pregnant patients. The correct posture of the patient is also important. She has to be placed semi recumbent on her left side with the lower extremities elevated, to prevent positional hypotension resulting from compression of the inferior vena cava by gravid uterus (Simons et al., 2011).

10. Prevention

Long-term preventive measures to reduce the risk of fatality of anaphylaxis include avoidance of triggers, optimal management of relevant comorbidities such as asthma, cardiovascular diseases, mastocytosis and immunomodulation (Simons, 2009b).
When anaphylaxis has occurred because of exposure to a specific trigger, patients should be educated about agents or exposures that would place them at risk for future reactions and be counseled on avoidance measures that may be used to reduce risk for such exposures (Lieberman et al., 2010). Triggers should be identified with a detailed history, and the sensitization to the triggers should be confirmed by using allergen skin tests and/or measurement of allergen-specific IgE levels in serum or challenge tests especially for therapeutic agents or foods. Optimally the patients can be tested for IgE sensitizations approximately 3-4 weeks after an acute anaphylactic episode. The time interval has not been definitely identified for most of the allergens, preferably patients with a convincing history of anaphylaxis and a negative test result should be retested afterwards. Challenge tests should be conducted in an appropriately equipped healthcare setting staffed by trained and experienced healthcare professionals as a supervised, graded test in order to diagnose and to assess risk of future anaphylactic episodes further. Before a challenge is performed the potential risk versus the potential benefit should be discussed with the patient and documented in the medical record (Simons et al., 2011).
Absolute avoidance of triggers such as allergens like latex, foods, or a medication is life saving, but as an example lifelong avoidance of a food may disrupt daily life and may lead to anxiety or decrease the quality of life of the patients and their families or may lead to nutritional deficiencies, especially in children (Simons, 2009b). Additionally avoidance is difficult to perform in some situations. For example hidden, substituted, and cross-reacting foods, or foods that are contaminated and mislabeling or confusing labels on packaged foods are some of the reasons of difficulties in avoidance of triggers. So patients with food anaphylaxis should be informed about all of these possibilities, regularly provided personalized written instructions for avoidance of the confirmed specific triggers (Simons et al., 2011). Biphasic reactions appear to be more common in food-induced anaphylaxis when compared to other reasons of anaphylaxis and it is reported in up to 25% of fatal or near fatal reactions (Lieberman, 2005, as cited in Lieberman et al., 2010). Although it is rare for patients with oral allergy syndrome to develop anaphylaxis, they may be at increased risk. Therefore these patients may be prescribed epinephrine auto-injectors (Kleine-Tebbe et al., 2002, as cited in Lieberman et al., 2010). Another important trigger to which avoidance is difficult is the stinging insects. Beekeepers, gardeners, others with occupational exposure may find it difficult to follow this advice (Lieberman et al., 2010; Simons et al., 2011). In

patients with a history of anaphylaxis triggered by a medication should not be given the offending drug, and if available a safe, non-reacting alternative medication should be substituted. Patients should be informed about the offending drug, related and cross-reactive drug with written documents (Simons et al., 2011). During anesthesia patients are under drapes and are unconscious, so early cutaneous signs are often unrecognized (Brock-Utne, 2003). Therefore the staff has to be prepared and ready for unexpected anaphylaxis. Patients who experience anaphylaxis during the peri-operative period should be carefully evaluated to elucidate the responsible agent and be examined by an allergist prior future procedure. In the case of anaphylaxis due to radiocontrast agents, non-ionic radiocontrast agents should be considered as alternatives (Lieberman et al., 2010; Simons et al., 2011).

In exercise-induced anaphylaxis avoidance of relevant co-triggers such as foods, medications, cold or hot air exposure, or other concomitant factors should be considered (Simons, 2009b). Exercise under ambient conditions of high humidity, extreme heat or cold or high pollen counts should be avoided (Simons et al., 2011). These patients should never exercise alone, should stop exercise immediately with the first symptom of anaphylaxis, and should carry a mobile phone and an epinephrine auto-injector during every exercise (Lieberman et al., 2010; Simons et al., 2011).

In latex induced anaphylaxis avoidance of latex and if relevant, also the avoidance of cross-reactive fruits, vegetables is extremely important (Lieberman et al., 2010; Simons et al., 2011). Latex can enter the body through different routes including, mucous membranes, contact with the skin, parenteral exposure, and contact with internal organs as in surgery and with inhalation of latex powder. Therefore avoidance measures for latex allergy should be intensively applied to establish a latex-safe environment for the patients. Both latex-sensitive healthcare workers and their co-workers should wear non-latex or non-powdered gloves and all non-glove latex devices should be replaced by non-latex devices. The most important procedures during which latex avoidance should be instituted in latex-sensitive patients include surgical procedures, obstetrical or gynecologic examinations or dental care (Lieberman et al., 2010). The problem can also manifest itself when latex sensitive patients experience anaphylaxis with related foods. These patients should be informed about the possible foods known to be cross-reactive latex. For anaphylaxis induced by some nonimmune triggers such as cold, heat, sunlight or ethanol, avoidance of the trigger is the key to prevention of recurrence (Simons et al., 2011).

Anaphylaxis due to allergen specific immunotherapy is another important cause of anaphylaxis which can be strongly avoided when this treatment is administered by healthcare professionals trained in the recognition and treatment of anaphylaxis. In patients using β-blockers the beneficial therapeutic effects of epinephrine may be diminished. Therefore a cautious attitude should be adopted in patients receiving concomitant β-blockers and allergen specific immunotherapy (Lieberman et al., 2010).

Seminal fluid anaphylaxis is a rare condition, which can not be generally prevented with antihistamines or intravaginal cromolyn sodium taken as precoital medications, where as barrier condoms are successful options for prevention. When these therapies are not effective or unacceptable, immunotherapy with seminal plasma fractions can be instituted in specialized centers (Lieberman et al., 2010).

The accompanying medications which can interfere with anaphylaxis and management such as β-blockers, angiotensin-converting enzyme inhibitors, NSAIDs, aspirin should be given weighing the risks and benefits of each medication (Lee & Vadas, 2011).

Oral desensitization to a specific food, subcutaneous anti-IgE injections, Food Allergy Herbal Formula-2, a well-characterized Chinese herbal formulation are investigational immunomodulator interventions being studied in humans for the prevention of anaphylaxis (Simons, 2009b). Desensitization strategies with the offending drug, where an alternative drug is not available are safe and effective immunomodulatory approaches particularly in patients with anaphylaxis due to β-lactam or other antibiotics, aspirin, or other nonsteroidal anti-inflammatory drugs, and chemotherapy agents. This procedure should be conducted by trained and experienced healthcare professionals in healthcare settings where all facilities for the management of anaphylaxis are available. This method provides protection only during the procedure as a temporary state of tolerance (Simons et al., 2011). Where as long-lasting protection against anaphylaxis can only be achieved with successful allergen specific immunotherapy which is mostly seen in subcutaneous venom immunotherapy (Simons, 2009b). It protects up to 80-90% of adults and 98% of children, in whom it lasts for decades (Simons et al., 2011). Latex sublingual immunotherapy has been shown to be an effective treatment in double blind placebo controlled studies both in children and adults, but according to our experience in the dose incremental phase precautions should be taken (Bernardini et al., 2008; Buyukozturk et al. , 2010).

In patients with frequent recurrent episodes of idiopathic anaphylaxis, empiric use of prednisone in a daily dose of 60-100 mg in combination with H1-antihistamines for 1-2 weeks followed by decreasing alternate day prednisone over 3 months as prophylaxis is recommended by the experts and has been demonstrated to reduce the frequency or severity of episodes (Lieberman et al., 2010). This treatment is considered in patients experiencing 6 or more episodes per year or 2 episodes in 2 months (Lieberman et al., 2010). Anti-IgE treatment is also promising (Simons, 2009b; Simons et al., 2011). These patients should carry their epinephrine auto-injectors at all times. Pretreatment strategies with antihistamines and corticosteroids have been used successfully to prevent anaphylaxis due to radiocontrast agents, cold-induced anaphylaxis and fluorescein (Lee & Vadas, 2011; Simons, et al., 2011).

Despite these preventive measures anaphylaxis sometimes recurs. Therefore, those at risk, should be prepared to recognize and treat unexpected episodes and be educated. Anaphylaxis education should begin before patients are discharged from the emergency department or other healthcare facility where the anaphylaxis was treated (Simons et al., 2011). Patients should be informed about the importance of the reactions that they have experienced. For this purpose, patients should carry medical identification prepared as a bracelet or a wallet card listing their diagnosis of anaphylaxis, confirmed trigger factors, relevant comorbidities, and concurrent medications (Simons, 2009b; Simons et al., 2011). They should be also advised that they are at increased risk for future episodes of anaphylaxis and therefore need follow-up, preferably by an allergy/immunology specialist (Simons et al., 2011) and prescribed for epinephrine auto-injectors and have their personalized written anaphylaxis emergency action plans (Simons 2009b; Liebermann et al., 2010). If epinephrine auto-injectors are not available or affordable, a substitute epinephrine formulation should be recommended, such as an ampoule of epinephrine, a 1 ml syringe, and written instructions about drawing up the correct dose. In emergency action plans, patients should be briefly informed about how to recognize anaphylaxis symptoms, instructed to inject epinephrine promptly and then admit to emergency to seek medical assistance (Simons et al., 2011).

Delayed injection or non-injection of epinephrine has been shown to be a risk factor for severe and biphasic reactions and fatal outcome (Gallagher et al., 2011; Lee & Vadas, 2011; Simons et al., 2010). Therefore patients are commonly prescribed at least two auto-injector devices for the administration of epinephrine in the community settings for this sudden, rapid, and usually unexpected clinical situation (Gallagher et al., 2011; Kemp et al., 2007). There is clear consensus in the research literature that these auto-injectors are under-used by patients of all-ages (Gallagher et al., 2011; Simons, 2009b, Simons et al., 2011). A recent paper suggested that auto-injector under-use is commonly due to patients preferring to take other medications most commonly antihistamines, not having auto-injector prescriptions, lack of severity of previous episodes or spontaneous recovery from previous episodes (Simons et al., 2009a). A recent study demonstrated that in addition to demonstrating injection technique, several other points must also be elucidated to the patients (Gallagher et al., 2011). They should be informed that auto-injectors should be used swiftly rather than waiting. They should be trained in recognizing anaphylaxis, taking into account the wide variability of symptoms and the side effects of epinephrine, offering reassurance about its safety if used unnecessarily (Gallagher et al., 2011). It should also be pointed out that an anaphylactic episode doesn't possess a predictive value for the severity of future episodes because of variable target organ involvement and the influence of comorbid illness and concurrently medications (Simons et al., 2009a).

The currently available epinephrine auto-injectors have some structural limitations (Frew, 2010). There are two types of delivery systems either as cartridge-based or a syringe delivery system used in the currently available auto-injectors (Frew, 2010). Evidence suggests there are several clear advantages of auto-injectors that utilize a cartridge system compared with a syringe system, but they are found in only 2 fixed doses as 0.15 mg which may be too high for infants and young children weighing less than 15 kg and 0.3 mg which can be a low dose for some children and adults, especially those who are overweight or obese (Frew, 2010; Simons, 2009b). Additionally the needle is 1.43 cm, not allowing optimal intramuscular injection in especially obese patients. New compact, lightweight, auto-injectors providing a 0.5 mg dose per injection, with a needle length of 2.54 cm are being designed and noninjectable epinephrine preparations for sublingual or transdermal administrations are also in development (Frew, 2010; Simons, 2009b).

The reasons for lack of response to epinephrine can be summarized as the error in the diagnosis, the wrong position of the patient after the injection, the rapid progression of anaphylaxis, the presence of a beta-adrenergic blocker or interfering drugs in the patient's medications, the low dose or the delayed injection of epinephrine, and the suboptimal route or injection site (Simons et al., 2011). Therefore the aim of every physician should be to teach their patients when and how to inject epinephrine and to educate them about anaphylaxis and save their lives.

11. Conclusion

Anaphylaxis is a serious acute allergic reaction and has to be recognized with signs and symptoms involving various organ systems and treated promptly. To diminish the risk for further attacks detailed history has to be taken carefully from the patients including the potential triggers or events, the clinical signs and symptoms. Laboratory tests most importantly an elevated serum tryptase level sometimes but not always support the diagnosis. The trigger has to be removed, if possible and the patient's circulation, airway,

breathing, level of consciousness, and skin should be rapidly assessed. Epinephrine is the cornerstone of the treatment. Patients should be kept in the correct position, oxygen and fluid supplementation should be given. Antihistamines, corticosteroids, and other agents are the second-line treatment agents. Patients should be informed about the potential risk for the future attacks and be educated and prepared. For this purpose, patients should carry medical identification and be prescribed for epinephrine auto-injectors and have their personalized written anaphylaxis emergency action plans.

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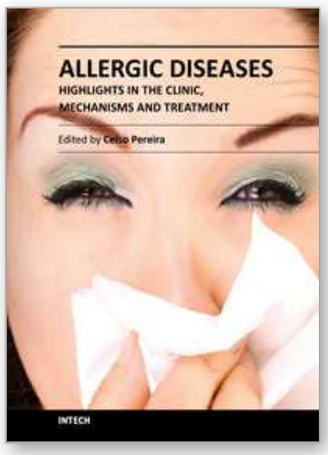

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The present Edition "Allergic diseases - highlights in the clinic, mechanisms and treatment" aims to present some recent aspects related to one of the most prevalent daily clinical expression disease. The effort of a group of outstanding experts from many countries reflects a set of scientific studies very promising for a better clinical care and also to the treatment and control of the allergy. This book provides a valuable reference text in several topics of the clinical allergy and basic issues related to the immune system response. The inflammatory reaction understanding in allergic disease is clearly evidenced, as well as new strategies for further researches.

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