Diagnosis and management of anaphylaxis

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ABSTRACT

Anaphylaxis is a serious allergic reaction that is rapid in onset and may be life threatening. An informal review of the literature was performed in a nonsystematic way for this article. Key published work was identified and included. The incidence and prevalence of anaphylaxis have increased over time. Anaphylaxis is unpredictable and can be the result of various allergic triggers, including food, insect venom, and medication. In children, the most frequent trigger is food. The diagnosis is based on clinical criteria. After confirmation of the relevant allergen trigger, prevention occurs through strict avoidance of the allergen and optimal management of existing comorbidities. Patients with anaphylaxis require immediate assessment and treatment. The management of a patient with anaphylaxis should start with the removal of exposure to the known or suspected trigger, followed by the assessment of the patient's circulation, airway patency, breathing, and mental status. The administration of epinephrine at a dose of 0.01 mg/kg (1:1000) intramuscularly is the first-line treatment for anaphylaxis, and there are no absolute contraindications to this treatment. The maximum single dose of epinephrine is 0.5 mg and may be repeated after 5–10 minutes if needed. After administration of epinephrine, patients with anaphylaxis should be placed supine with their lower limbs elevated. They should not be placed in the upright position. Studies of fatal and near-fatal allergic reactions identified potential risk factors for fatalities such as asthma, peanuts and/or tree nuts, and delayed epinephrine use, and provided important information that may help minimize the future risk. Patients and their families need to be well educated on how to manage potential anaphylactic reactions with training in the use of epinephrine autoinjectors and personalized emergency management plans. Health care professionals must be familiar with this clinical emergency and able to respond to anaphylaxis in a timely and appropriate manner.

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Anaphylaxis is derived from the Greek words "ana" (against) and "phylaxis" (protection). It is defined as a serious allergic reaction that is rapid in onset and may cause death.[1] Analysis of research results indicates that the incidence of anaphylaxis has been increasing over time. The lifetime prevalence of anaphylaxis has been estimated to be between 0.5 and 2%.[2] In the United States, Rudders *et al.*[3] report that hospitalizations for food-induced anaphylaxis in children doubled between 2000 and 2009, from a rate of 0.60 per 1000 to a rate of 1.26 Food Induced Anaphylaxis (FIA) hospitalizations per 1000 total hospitalizations.

Common triggers for anaphylaxis include food, drugs, and insect venom. In terms of age distribution, food is the most frequent cause of anaphylaxis in children, whereas drug and Hymenoptera venom–triggered anaphylaxis are more common in adults.[4–6] Food anaphylaxis is reported to be more prevalent until the second decade of life, whereas drug and venom anaphylaxis are more frequently seen in older age groups. The European Anaphylaxis Registry[7] reports food as the trigger in 66% of cases, followed by insect venom in 19% of cases in children and adolescents. Different geographic areas (and dietary factors) as well as the age of patients are associated with different foods. In young children, ages 0–2 years, cow's milk and egg are the most commonly reported foods implicated in anaphylactic episodes,[8] followed by peanuts, sesame, and fish in areas where these foods are consumed regularly.

In certain European countries, especially in the Mediterranean area, peach is a common trigger; in the Middle East, sesame; and, in Asia, buckwheat, chickpea, rice, and bird's nest soup are all frequent triggers.[9] An Australian case study of children who presented with anaphylaxis in an emergency department in Melbourne over a 5-year period showed that peanut and cashew were the most common causes of anaphylaxis in 18% and 13% of patients, respectively.[10] In the United States, the top eight food allergens associated with anaphylaxis are peanuts, cow's milk, shellfish, tree nuts, eggs, fish, wheat, and soy. In the adult population, a recent survey study from the United States reported a food allergy

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prevalence of 10.8% with the most common allergens being shellfish (2.9%), milk (1.9%), peanut (1.8%), tree nut (1.2%), and fin fish (0.9%). Among adults with food allergy, 51.1% experienced a severe food allergy reaction, 45.3% were allergic to multiple foods, and 48.0% developed food allergies as an adult.[11]

An uncommon trigger for anaphylaxis is exercise. Exercise-induced anaphylaxis (EIA) is the occurrence of anaphylaxis after physical activity. The intensity able to elicit symptoms can vary, even in the same individual, from a low to high level. EIA is associated with cofactors such as food, warm or cold temperature, and medication (such as nonsteroidal anti-inflammatory drugs) in approximately a third of cases.[12] If food is the associated cofactor, then the correct term is food-dependent EIA, which indicates that both food and exercise are needed to elicit symptoms.[12] Wheat-dependent EIA is triggered by wheat ingestion combined with physical exercise. The major allergen seems to be ω 5-gliadin.[13]

A rare trigger for anaphylaxis is galactose-α-1,3-galactose (α-gal). The diagnosis of α-gal syndrome is based on a history of delayed allergic reactions to mammalian meat and the blood test for immunoglobulin E to the oligosaccharide α-gal.[14] The main approach to management is in avoiding mammalian meat and also dairy in some cases. In the United States, the lone star tick is the primary cause of this disease, but different ticks are responsible in other countries. A minority of cases may benefit from avoiding a wide range of products that are prepared with mammalian-derived constituents, *e.g.*, gelatin.[14,15]

Despite the rise in prevalence, the majority of food-triggered anaphylactic reactions are not life threatening. Unfortunately, although not frequent, severe life-threatening reactions do occur and are unpredictable. A recent review examined factors that may be able to identify patients at risk of severe reactions to food.[16] Multiple factors may play a role, including (a) allergen-related factors (*e.g.*, type of food consumed, dose ingested, food processing and matrix, host immunoglobulin E levels and binding affinity, host cellular responses), (b) host behavior–related factors (*e.g.*, risk taking, alcohol, medication, exercise), and (c) other intrinsic and extrinsic factors (*e.g.*, sex, gender, age, asthma, allergic rhinitis, cardiovascular disease, immune activation).[16] In terms of specific food triggers, peanuts, and tree nuts are most commonly reported as causes of severe anaphylaxis and have been associated with fatalities.[17] Fatalities due to anaphylaxis are rare, with an overall case fatality rate of <0.001%.[4] Identified risk factors for fatal food-induced anaphylaxis in children include coexistent asthma, ages > 10 years (adolescents), peanut or tree nut allergy, and delayed access to adrenaline autoinjectors.[17,18]

Anaphylaxis is predominantly a clinical diagnosis and can present with symptoms from various organ systems, including the skin (*e.g.*, pruritus, urticaria, facial erythema and/or flushing, angioedema), the gastrointestinal system (*e.g.*, abdominal pain, vomiting, diarrhea), the upper and lower respiratory system (*e.g.*, rhinitis, hoarseness, laryngeal edema, stridor, dyspnea, cough, wheeze), and the cardiovascular system (*e.g.*, dizziness, hypotension, syncope, shock).[19] Anaphylaxis typically has a rapid onset; symptoms and signs may occur within minutes to a few hours of exposure to the trigger and involve two or more organ systems. Food-induced anaphylaxis usually presents within 30 minutes of exposure.[4,20]

A detailed clinical history is crucial in diagnosing anaphylaxis. Health care providers should aim to obtain information with regard to the circumstances of exposure and the events surrounding the onset of symptoms. There has been confusion about how to diagnose anaphylaxis, but the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network published diagnostic criteria to support health care providers.[1] Based on their report, the diagnosis is highly likely when any one of the following three criteria used by is fulfilled: (1) acute onset of an illness with involvement of the skin, mucosal tissue or both and at least one of the following: respiratory compromise and/or cardiovascular compromise; (2) two or more of the following that occur rapidly after exposure to a likely allergen: (a) involvement of the skin or mucosal tissue, (b) respiratory compromise, (c) cardiovascular compromise, (d) persistent gastrointestinal symptoms; or (3) hypotension after exposure to a known allergen. The use of these criteria to diagnose anaphylaxis was found to have a positive predictive value of 68.6% and a negative predictive value of 98.4%.[19] Laboratory tests that may support the diagnosis of anaphylaxis include mast cell mediators, such as tryptase, histamine, and platelet-activating factor, which are shown to be raised in episodes of anaphylaxis. However, these tests are not specific for anaphylaxis nor are they universally available and the diagnosis remains clinical.

In infants up to 2 years of age, the diagnosis of anaphylaxis may present some added challenges. Infants, who are nonverbal, may exhibit a symptomatic change in behavior, such as becoming lethargic or fussy, or crying inconsolably. Irritability and behavioral changes can be difficult to interpret because they may also occur in healthy infants. In addition, very young children are unable to describe certain symptoms, such as pruritus or throat tightness.[21] Anaphylaxis in infants typically involves the skin in 98%, the respiratory system in 59%, and the gastrointestinal system in 56%, whereas cardiovascular symptoms are rarely reported.[21]

Table 1 **Anaphylaxis management***

1. Immediate measures	
Allergen	Remove the inciting allergen, if possible
Airway	Assess airway, breathing, circulation, and orientation; if needed, support the airway by using the least invasive but effective method (*e.g.,* bag-valve mask)
Cardiopulmonary resuscitation	Start chest compressions (100/min) if cardiovascular arrest occurs at any time
Epinephrine intramuscular	Inject epinephrine 0.01 mg/kg (maximum single dose, 0.5 mg) intramuscularly in the vastus lateralis (lateral thigh); repeat intramuscular epinephrine every 5–10 min for up to three injections if the patient is not responding
Get help	Call for help
Position	Place adults and adolescents in the recumbent position; place young children in a position of comfort; place a pregnant patient on her left side
Oxygen	Give 8–10 L/min through a face mask or up to 100% oxygen as needed; monitor by pulse oximetry if available
EMS	Activate EMS (call 911 or local rescue squad) if no immediate response to the first dose of intramuscular epinephrine or if anaphylaxis is moderate to severe (grade 2 on World Allergy Organization grading scale)
Intravenous fluids	Establish intravenous line for venous access and fluid replacement; keep open with 0.9 nL saline solution, push fluids for hypotension or failure to respond to epinephrine by using 5–10 mg/kg as quickly as possible and up to 30 mL/kg in the first hour for children and 1–2 L for adults
Albuterol	Consider administration of 2.5–5 mg of nebulized albuterol in 3 mL of saline solution for lower airway obstruction; repeat as necessary every 15 min
2. Optional treatment	
H_1-antihistamines	Consider giving 25–50 mg of diphenhydramine intravenously for adults and 1 mg/kg (maximum 50 mg) for children; use 10 mg of cetirizine if an oral antihistamine is administered; once there is full recovery, there is no evidence that this medication needs to be continued
Corticosteroids	Administer 1–2 mg/kg up to 125 mg per dose, intravenously or orally, of methylprednisolone or an equivalent formulation; once there is full recovery, there is no evidence that this medication needs to be continued
3. Observation and monitoring	
Observation in hospital	Transport to emergency department by EMS for further treatment and observation for 4–8 hr; consider longer time intervals, depending on symptoms and response to treatment
Observation in office	Observe the patient in the office until full recovery plus an additional 30–60 min for all patients who are not candidates for EMS transport to the emergency department
4. Discharge management	
Education	Educate the patient and family on how to recognize and treat anaphylaxis
Autoinjectable epinephrine	Prescribe two doses of autoinjectable epinephrine for patients who have experienced an anaphylactic reaction and for those at risk for severe anaphylaxis; train the patient, patient provider, and family on how to use the autoinjector
Anaphylaxis action plan	Provide patients with an action plan, instructing them on how and when to administer epinephrine

EMS = Emergency medical services.
**Modified from Ref. 19.*

Patients with anaphylaxis require immediate assessment and treatment. The management of a patient with anaphylaxis should start with the removal of exposure to the known or suspected trigger, followed by the assessment of the patient's circulation, airway patency, breathing, and mental status (Table 1). The administration of epinephrine at a dose of 0.01 mg/kg (1:1000) intramuscularly (maximum single dose, 0.5

mg) is the first-line treatment for anaphylaxis.[22] There are no absolute contraindications to this treatment.

After administration of epinephrine, patients with anaphylaxis should be placed supine with their lower limbs elevated. They should not be placed in the upright position. In cases of vomiting or dyspnea, the patient should be placed in a comfortable position with the lower limbs elevated. This should prevent distributive shock and empty vena cava/empty ventricle syndrome.[23] Continuous monitoring of vital signs is recommended. Supplemental oxygen and intravenous fluid should be administered as needed.[4,19] Epinephrine is the medication of choice for the immediate treatment of anaphylaxis and is the only drug that exerts a vasoconstrictor effect, thus reverting airway mucosal edema and hypotension.[23] The epinephrine dose can be repeated after a 5-minute interval.[4,19] There is evidence that delayed injection of epinephrine is associated with higher hospitalization and mortality rates.[4,24]

Inhaled short-acting β_2-agonists can be given to patients who experience breathing difficulties, including bronchoconstriction during the anaphylactic episode. Antihistamines (both anti-H_1 and anti-H_2) and corticosteroids are second-line medications for the treatment of anaphylaxis because they are not life saving and, therefore, should not be used as the initial or only treatment. H_1-antihistamines relieve itching, flushing, and urticaria, but they do not act on airway obstruction or hypotension. Their onset of action is slower than that of epinephrine.[4,19,23]

After treatment of the acute episode and presenting symptoms, monitoring of patients in an appropriately equipped health care facility is essential. Patients who present with respiratory compromise should be closely monitored for at least 6–8 hours; if the presenting symptom is hypotension, then monitoring should increase to at least 12–24 hours. Management at discharge should include advice on allergen avoidance (when possible), a prescription for an epinephrine autoinjector device, education on how and when to use the autoinjector device, and follow up with an allergy specialist.[4,19] An individualized written management plan should be provided; this should include an emergency action plan with likely presenting symptoms and how to manage them, avoidance advice, and contact details for further advice if needed.[4,19,25] In addition, information on relevant support groups may be beneficial to patients.

In summary, anaphylaxis is a severe life-threatening systemic allergic reaction, which constitutes a clinical emergency. It is primarily a clinical diagnosis, and health care providers should be appropriately trained to recognize and treat patients in a timely manner. Prompt administration of epinephrine is key for the successful management of anaphylaxis. Severe, unstable asthma has been highlighted as a risk factor for severe anaphylaxis, including fatalities; therefore, optimal control is key to manage risk. Regular education of patients and families on how to identify symptoms and respond appropriately is very important and should form part of the routine management.

CLINICAL PEARLS

- The diagnosis of anaphylaxis is based on clinical criteria; use of laboratory tests, *e.g.*, for tryptase, may only be used to support the clinical diagnosis because they are not specific for anaphylaxis.
- Epinephrine is the first-line treatment for anaphylaxis, and there are no absolute contraindications to its use.
- Potential risk factors for life-threatening allergic reactions include asthma, peanuts and/or tree nuts, and delayed epinephrine use.
- After treatment of patients with anaphylaxis, they should be observed until full symptom resolution; all patients must be educated on avoiding their triggers, identifying symptoms of anaphylaxis, and treating their allergic reactions appropriately.

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