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Anaphylaxis: A Life-Threatening Hypersensitivity Reaction

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ABSTRACT

Anaphylaxis is an acute, life-threatening systemic hypersensitivity reaction, primarily mediated by immunoglobulin E. Food allergy is the most common trigger, followed by medications. Patients with anaphylaxis typically present with cutaneous or mucosal symptoms, often accompanied by respiratory and gastrointestinal manifestations. Epinephrine remains the first-line treatment for anaphylaxis. It is crucial to educate patients and caregivers on recognizing anaphylactic symptoms and the proper use of epinephrine autoinjectors.

Keywords: Anaphylaxis, children, immunology and allergy

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INTRODUCTION

Anaphylaxis is a rapidly developing, life-threatening systemic hypersensitivity reaction of varying clinical presentation and severity, resulting from the sudden release of mediators from mast cells and basophils.[1] It is the most severe clinical manifestation of allergy and can be fatal if left untreated. Prompt diagnosis and effective treatment are crucial for patient survival, making it an essential emergency condition that every physician should recognize and manage effectively.

DEFINITION

Anaphylaxis was first described in 1902 by Richet and Portier during vaccination studies in dogs, and they defined it as symptoms occurring in response to immunity.[2] The earliest recorded case of anaphylaxis is believed to be the death of Egyptian Pharaoh Menes in 2640 BC due to a bee sting. According to modern terminology, anaphylaxis mediated by immunological mechanisms such as immunoglobulin E (IgE), immunoglobulin G, and the complement system is classified as allergic (immunologic) anaphylaxis. In contrast, anaphylaxis resulting from non-immunological mechanisms, previously termed anaphylactoid reactions, is now referred to as non-allergic anaphylaxis. Anaphylaxis occurring without identifiable triggers is classified as idiopathic anaphylaxis (IA).

ETIOLOGY AND EPIDEMIOLOGY

The incidence of anaphylaxis remains uncertain; however, the estimated lifetime prevalence in the general population ranges from 0.05% to 2%.[3] The prevalence is higher in children. One study reported an overall incidence of anaphylaxis across all age groups as 49.8/100,000

person-years, while in the 0–19 years of age group, the incidence was 70/100,000 person-years.[4] Recent studies indicate an increasing prevalence of anaphylaxis, particularly among young individuals.[5] There has been a noticeable rise in hospital admissions due to food-related anaphylaxis among children.[6] This increase is particularly significant among children under the age of 10. A study by Lin et al. found that hospital admissions in this age group quadrupled between 1990 and 2006.[7]

Food, medications, and insect stings are the most common triggers of anaphylaxis across all age groups.[7] The most frequently implicated foods include cow's milk, eggs, soy, peanuts, tree nuts, fish, and shellfish. The most common medications causing anaphylaxis are antibiotics and nonsteroidal anti-inflammatory drugs. Other rare causes include latex, aeroallergens, and vaccines.

Food allergy is the leading cause of anaphylaxis in children, followed by medications.[8] In a retrospective study conducted in Turkey, foods accounted for 38.4% of anaphylaxis cases, followed by venom (37.5%) and medications (21%).[9]

PATHOPHYSIOLOGY

Anaphylaxis is classically mediated by IgE, leading to mast cell and basophil degranulation and the subsequent release of mediators.[10] These mediators can be classified into two groups: Preformed mediators (histamine, heparin, tryptase, chymase, carboxypeptidase A3, tumor necrosis factor-alpha [TNF-α], and cathepsin G) and newly synthesized mediators (platelet-activating factor [PAF], prostaglandin D2, leukotriene C4, cytokines such as interleukin [IL]-5, IL-6, IL-8, IL-13, IL-33, TNF-α, and granulocyte-macrophage colony-stimulating factor, as well as chemokines including MIP-1α, MIP-1β, and MCP-1).

In some cases, mast cells and basophils can be immunologically activated without IgE mediation.[11] Anaphylaxis can also occur through non-immunological mechanisms. Physical factors such as exercise, cold, heat, ultraviolet radiation, and certain drugs such as ethanol and opioids can directly induce mast cell degranulation, leading to anaphylaxis.

IA refers to cases where no specific trigger can be identified.[11] The exact incidence and prevalence of IA remain unknown. Its clinical presentation is similar to other forms of anaphylaxis, with an acute onset that may worsen within minutes to hours. Although the pathophysiology of IA is not yet fully understood, it is hypothesized that an IgE-mediated pathway triggered by unknown factors may be the underlying mechanism.

CLINICAL PRESENTATION

Anaphylaxis most commonly affects five organ systems, including the skin, mucosa, respiratory, cardiovascular, gastrointestinal, and neurological systems.[1,2,12] Symptoms typically appear within 5–30 min following parenteral exposure, but they may take up to an hour or more to develop. After oral exposure, symptoms usually manifest within the first 2 h but can be delayed for several hours. The faster the onset of symptoms, the more severe the anaphylaxis is likely to be. Early-onset reactions carry a higher risk of fatality. Initial symptoms include a sense of unease, fear of death, dizziness, and syncope.

At the onset of an anaphylactic reaction, "prodromal symptoms" such as mild itching, a burning sensation in the palms, soles, or anogenital region, metallic taste, anxiety, headache, and disorientation may occur.[3] The clinical manifestations of anaphylaxis are summarized in Table 1.

DIAGNOSIS

The diagnosis of anaphylaxis is primarily clinical.[1,13] A detailed history should be obtained promptly in patients presenting with anaphylactic symptoms; however, treatment should not be delayed. The clinician should inquire whether the patient was exposed to potential anaphylactic triggers before symptom onset and whether any underlying conditions could mimic anaphylaxis. Anaphylaxis is diagnosed if any of the three criteria summarized in Table 2.

Key history elements include the timing of symptom onset after exposure, treatments received during the attack, and attack duration.[2,12,14] A detailed history of potential triggers is crucial. Questions should cover food and medication intake in the preceding 6 h, insect stings, physical activity, and exposure to temperature extremes. In female patients, the association with the menstrual cycle should be explored.

In 2006, the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network developed a consensus definition of anaphylaxis, outlining diagnostic criteria.[15]

The most commonly affected systems in anaphylaxis are the skin, respiratory, and cardiovascular systems.[15] Although skin involvement is observed in 80%–90% of cases, anaphylaxis can occur without cutaneous manifestations, making diagnosis more challenging. Respiratory symptoms are more common in children, whereas cardiovascular symptoms predominate in adults.[16]

Table 1. Clinical manifestations of anaphylaxis

System	Symptoms
Skin and mucosa (80–90%)	• Urticaria, angioedema, morbilliform rash
	• Itching, tingling, hot flashes, flushing
	• Periorbital itching, swelling, erythema, conjunctival itching, tearing
	• Lip, tongue, uvula, and soft palate itching and swelling
	• Itching in the external ear canal, palms, soles, and genital area.
Respiratory system (40–70%)	• Nasal: Rhinorrhea, congestion, itching, sneezing
	• Laryngeal: Hoarseness, choking sensation, stridor, dysphonia, dysphagia
	• Pulmonary: Dyspnea, wheezing, bronchospasm, respiratory failure, cough, chest tightness
	• Cyanosis.
Cardiovascular system (10–45%)	• Hypotension
	• Tachycardia, bradycardia, arrhythmia
	• Chest pain, palpitations
	• Shock, syncope
	• Cardiac arrest.
Gastrointestinal system (30–45%)	• Nausea, vomiting
	• Abdominal pain, cramping
	• Diarrhea.
Neurological system (10–15%)	• Fear of death, restlessness
	• Altered consciousness, seizures
	• Confusion
	• Headache, blurred vision
	• Sudden behavioral changes
	• Irritability and clinging to caregivers (in infants and young children).
Other symptoms	• Sweating, incontinence
	• Metallic taste, dysphagia
	• Uterine contractions.

LABORATORY

Anaphylaxis is primarily diagnosed clinically.[1] However, in some cases, laboratory tests such as serum tryptase and histamine levels can be utilized. Elevated serum histamine levels measured between 15 min and 1 h after the onset of symptoms may aid diagnosis. A serum tryptase level >11.4 mcg/L or an increase above baseline (>2 ng/mL+1.2×[baseline tryptase level]) measured between 15 min and 3 h after symptom onset supports the diagnosis of anaphylaxis.[12] However, normal levels do not exclude anaphylaxis.[2]

Additional markers of mast cell activation, such as carboxypeptidase A3, chymase, PAF, and cytokines (urinary leukotriene E4 and 9α, 11β prostaglandin F2), may also be used in diagnosing anaphylaxis.[2] In addition, the basophil activation test has recently been introduced as a diagnostic tool for anaphylaxis.

DIFFERENTIAL DIAGNOSIS

The most common condition mistaken for anaphylaxis is a vasovagal syncope episode.[12] In vasovagal syncope, sudden hypotension occurs due to vagal stimulation, often accompanied by bradycardia, whereas anaphylaxis typically presents with tachycardia. Vasovagal syncope is also characterized by pallor and sweating without urticaria or respiratory symptoms. Other conditions in the differential diagnosis of anaphylaxis include asthma attacks, urticaria, panic attacks, hyperventilation syndrome, and various forms of shock.

Table 2. Diagnostic criteria of anaphylaxis

1. Acute onset (within minutes to hours) involving skin and/or mucosal tissue (e.g., generalized urticaria, itching or flushing, swelling of lips, tongue, or uvula), plus at least one of the following:
2. a) Respiratory symptoms (dyspnea, wheezing, bronchospasm, stridor, reduced PEF, hypoxemia)
   b) Hypotension or signs of end-organ dysfunction (hypotonia, collapse, syncope, incontinence)
3. Exposure to a likely allergen with onset of at least two of the following within minutes to hours:
   a) Skin and/or mucosal involvement (e.g., generalized urticaria, itching, flushing, or angioedema)
   b) Respiratory symptoms (dyspnea, wheezing, bronchospasm, stridor, reduced PEF, hypoxemia)
   c) Hypotension or associated symptoms (hypotonia, collapse, syncope, incontinence)
   d) Persistent gastrointes-tinal symptoms (cramping, abdominal pain, vomiting)
4. Hypotension occurring within minutes to hours after exposure to a known allergen:
   a) In infants and children: Systolic blood pressure below age-specific thresholds or a >30% decrease from baseline
   b) In adults: Systolic blood pressure <90 mmHg or a >30% decrease from baseline

Hypotension thresholds: <70 mmHg for infants (1 month–1 year), (70+[2×age in years]) mmHg for children (1–10 years), and <90 mmHg for adolescents (11–17 years). PEF: Peak expiratory flow.

TREATMENT

The key to managing anaphylaxis is early recognition and rapid intervention.[17] At the onset of an anaphylactic episode, it is difficult to predict the severity, progression, or resolution, as the exact determinants of anaphylaxis remain unclear. Due to this uncertainty, early intramuscular (IM) epinephrine administration is crucial in preventing life-threatening symptoms. Epinephrine is the first-line medication and should never be delayed.

Epinephrine should be administered IM into the anterolateral thigh (vastus lateralis muscle).[18] The recommended dose is 0.01 mg/kg (0.01 mL/kg) of 1 mg/mL epinephrine, with a maximum dose of 0.3 mg (3 decigrams) in children and 0.5 mg (5 decigrams) in adults. The latest 2025 UpToDate guidelines recommend a uniform epinephrine dose of 0.01 mg/kg per injection, with a maximum dose of 0.5 mg, using a 1 mg/mL formulation and a 1 mL syringe. Epinephrine doses may be repeated every 5–10 min as necessary.[12] Treatment of anaphylaxis is summarized in Table 3.

Table 3. Treatment of anaphylaxis

Medication	Dose	Maximum dose	Route
Epinephrine (1 mg/mL)	0.01 mg/kg	0.3 mg	IM (lateral thigh)
Diphenhydramine	1 mg/kg	50 mg	IV
Ranitidine	1 mg/kg	50 mg	IV
Methylprednisolone	1–2 mg/kg	50 mg	IV
Salbutamol	2.5 mg	2.5 mg	Inhalation

IM: Intramuscular injection; IV: Intravenous injection.

Epinephrine should be administered at the first suspicion of anaphylaxis, as there are no absolute contraindications for its use.[2] Even in elderly patients and those with cardiovascular disease, the benefits of epinephrine outweigh the risks.[1] If an epinephrine auto-injector is used, a dose of 0.15 mg is recommended for children weighing 7.5–25 kg, while 0.3 mg is used for those over 25 kg.[19] The dose may be repeated every 5 min if necessary. In cases of refractory anaphylaxis requiring repeated doses, an epinephrine infusion should be initiated.[12]

Second-line treatments include removing the triggering factor, proper patient positioning, oxygen and fluid support, and inhaled beta-2 agonist therapy.[18] However, these are supportive measures and are not life-saving interventions.

Patients should be placed in a supine position with their legs elevated to enhance venous return.[3] Those experiencing hypotension should remain in this position until symptoms resolve, as sudden repositioning can lead to fatal "empty ventricle syndrome."

High-flow oxygen (6–8 L/min) should be provided The latest 2025 UpToDate guidelines recommend administering oxygen at 15 L/min using a non-rebreather mask or high-flow oxygen masks capable of delivering at least 70–100% oxygen.[2]

For bronchospasm, 0.15 mg/kg salbutamol can be administered through inhalation every 15–20 min, up to a maximum of six doses.[12] If stridor due to laryngeal edema develops, nebulized epinephrine (2–5 mL, 1 mg/mL) may be administered in addition to IM epinephrine.

Intravenous (IV) access is essential in all anaphylaxis cases.[20] Due to increased vascular permeability, significant intravascular fluid loss can occur rapidly. Children should receive 20 mL/kg normal saline over 5–10 min, with repeat doses as needed. Up to 100 mL/kg may be required. If IV access is not feasible, intraosseous administration should be considered.

MONITORING AND DISCHARGE

Due to the risk of biphasic reactions, monitoring for at least 4–6 h is recommended.[20] Patients with respiratory symptoms should be observed for 6–8 h, while those with hypotension should be monitored for at least 12–24 h. Some authors recommend up to 24 h of observation, as reactions can occur within 72 h.[21]

Before discharge, risk factors should be evaluated, and patients should receive written action plans and prescriptions for epinephrine auto-injectors, along with proper usage instructions.[22] Referral to an allergy specialist for identifying triggers and preventive measures is essential.[23]

Indications for Epinephrine Auto-Injector Prescription[17]

1. Any patient with a history of anaphylaxis
2. Patients with a history of systemic allergic reactions
3. Patients with concurrent food allergies and asthma
4. Individuals allergic to peanuts, fish, or shellfish
5. Patients with IgE-mediated immediate food allergies should also be considered for an epinephrine auto-injector.

BIPHASIC REACTION

A biphasic reaction refers to the recurrence of anaphylactic symptoms after initial resolution without re-exposure to the allergen. It typically occurs within 12–72 h following the initial reaction.[20] Reported incidence rates vary from 1% to 20%.[17]

Severe initial anaphylaxis requiring multiple epinephrine doses may increase the risk of a biphasic reaction.[24] Although corticosteroids have been used to prevent prolonged anaphylaxis symptoms, a 2020 systematic review found no evidence supporting their efficacy in preventing biphasic reactions.

As anaphylaxis is unpredictable in its severity and course, early epinephrine administration is critical to prevent life-threatening complications.[25] A series of 164 fatal anaphylaxis cases found that the median time from symptom onset to respiratory or cardiac arrest was 5 min for iatrogenic anaphylaxis (e.g., anesthetics, IV drugs, and contrast agents), 15 min for insect stings, and 30 min for food-induced anaphylaxis.

Healthcare professionals must be well-trained in recognizing, managing, and preventing anaphylaxis.[26] Patients should be prescribed an epinephrine auto-injector, educated on its use, and referred to an allergist for further evaluation.

CONCLUSION

Many cases of anaphylaxis, and especially the potential for second-phase reaction, are underrecognized and undertreated, with potentially life-threatening consequences.[21] Immediate administration of epinephrine intramuscularly is often lifesaving, but repeated doses may be necessary in combination with other medications. Due to the risk of biphasic reactions, monitoring for at least 4–6 h is recommended. Patients with respiratory symptoms should be observed for 6–8 h, while those with hypotension should be monitored for at least 12–24 h.

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