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Anaphylaxis: Pathophysiology, Risk Factors, and Clinical Management

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Abstract

Anaphylaxis is a syndrome characterized by broncho-constriction, vasodilatation, and hypovolemia, potentially fatal exposure to known or unknown antigens. It can be an immune-mediated (IgE & non-IgE) disease. Immunoglobulin G (IgG), complement related (C3a/C5a), bradykinin, leukotrienes, prostaglandin E2, and ligands of certain G-protein coupled receptors (GPCR) can directly activate mast cells, basophils, eosinophils, neutrophils, endothelial cells and smooth muscles. Serum tryptase level during episodes of anaphylaxis, skin test, and basophil activation test (BAT) improve the efficacy of IgE and non-IgE mediated diagnosis of anaphylaxis. Patients at high risk are more prone to experiencing anaphylaxis. However, there are no definitive contraindications against using intramuscular epinephrine to treat this condition. Self-management by the patient using an emergency action plan is an important key to administering EAI (EpiPen Auto Injector). This review will highlight the current recommendation, diagnosis, and management protocol of anaphylaxis.

Keywords: Anaphylaxis, mastocytosis, serum tryptase, Mast cells (MC), hereditary α-tryptasemia (HαT), Hereditary alpha tryptasemia syndrome (HATS), Mast cell activating syndrome (MCAS), wheat dependent exercise induced anaphylaxis (WDEIA).

INTRODUCTION

Anaphylaxis is a sudden and severe allergic reaction that can impact multiple organs throughout the body. It can progress rapidly, becoming life-threatening and potentially fatal. It affects 1–2% of the global population and 500–1000 deaths occur annually. The severity of anaphylaxis varies and depends on several risk factors, including both the triggering antigen (such as allergens, venom, or medications) and patient-specific factors (like immune response, behaviors, concurrent medications, and underlying conditions). Severe cases of anaphylaxis are marked by life-threatening respiratory or circulatory failure, often accompanied by low blood pressure and reduced oxygen levels. It is more common in older individuals, those with pre-existing heart or lung disease, and reactions triggered by drugs.

The risk of developing anaphylaxis is likely influenced by genetic factors. For instance, an increased copy number of the TPSAB1 gene has been linked to severe anaphylaxis in people with mastocytosis. In cases of food-induced anaphylaxis, the HLA DPB1*02:01:02 allele is associated with a higher risk of wheat-dependent exercise-induced anaphylaxis (WDEIA). The SERPINB gene cluster on chromosome 18q21.3 has been identified as a risk factor for developing food allergies. Mast cells (MCs) are key players in anaphylaxis, mediating the reaction through the cross-linking of IgE attached to their high-affinity receptors. Beyond IgE, other factors, such as Mas-related G protein-coupled receptors (MRGPRX2), the complement system,

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toll-like receptors, and non-IgE antibodies can also trigger mast cell degranulation.

WAO 2020 has defined anaphylaxis as a serious systemic hypersensitivity reaction, typically rapid in onset and potentially fatal. Severe anaphylaxis is life-threatening, affecting the airway, breathing, or circulation, and can occur even without the usual skin symptoms or signs of circulatory shock [1].

The Delphi study suggests classifying anaphylaxis outcomes by not only defining persistent, refractory, and bi-phasic anaphylaxis, but also addressing persistent and bi-phasic allergic reactions that do not meet the NIAID/FAAN criteria for anaphylaxis, as described below [2, 3]:

i. *Persistent anaphylaxis:* It is considered highly likely when anaphylaxis lasts for four hours without any period of resolution between the initial phase and the subsequent phase.
ii. *Refractory anaphylaxis:* It is considered highly likely when both of the following criteria are met:
   (1) anaphylaxis persists despite receiving appropriate doses of epinephrine and symptom-specific treatments, such as intravenous fluid for hypotension, and
   (2) the initial reaction was treated with three or more doses of epinephrine (or the initiation of an intravenous epinephrine infusion). This occurs in 0.5% of severe anaphylaxis cases, typically linked to drug-related causes, especially in perioperative or procedural settings.
iii. *Bi-phasic anaphylaxis:* It is more likely when all four of the following criteria are met:
   (1) new or returning symptoms and/or findings that meet the criteria for anaphylaxis,
   (2) the initial symptoms and findings have fully resolved before the appearance of new or recurrent symptoms or findings,
   (3) there is no re-exposure to the allergen or trigger, and
   (4) the new or recurrent symptoms or findings occur within 1 to 48 hours after the initial symptoms or findings have completely resolved.

RISK-FACTORS AND CONCOMITANT DISEASE OF ANAPHYLAXIS

The severity of anaphylactic reactions is influenced not only by risk factors but also by underlying health conditions. While food, drugs, and insect stings are the primary triggers across all age groups, differences exist between children and adults in terms of the specific triggers and the severity of the reaction. In children, common drugs that cause drug-induced anaphylaxis (DIA) include antibiotics, NSAIDs, neuromuscular blocking agents (NMBA), and monoclonal antibodies. The risk factors, along with any coexisting health conditions, are outlined in (Table 1)

Table 1. Risk factors for anaphylaxis.

Allergic Diseases	Higher Risk
IgE-mediated food allergy & Pollen food & lipid transfer protein syndrome	History of anaphylaxis or severe systemic foods.
Venom or insect bite/sting allergy (Honey bee allergy)	History of anaphylaxis (not treated with a complete course of VIT) Elevated basal tryptase level Frequent exposure.
Latex allergy & Drug allergy	Occupational exposure (e.g., compounding, mixing, or preparation of medications).
Exercise induced anaphylaxis & Physical urticarias	All cases & Cold induced.
Aeroallergen immunotherapy	History of prior systemic reaction(s) to AIT and/or relevant comorbidities (e.g., asthma).
Concomitant disease	Bronchial asthma, Cardiovascular Disease, Mastocytosis, Thyroid disease, Elevated BST level, old age.

Abbreviations: AIT, aeroallergen immunotherapy; VIT, venom immunotherapy.

CLINICAL PRESENTATION OF ANAPHYLAXIS

Common symptoms include flushing, itching, hives, swelling, difficulty breathing, wheezing, nausea, vomiting, diarrhea, low blood pressure, decreased oxygen levels, and cardiovascular collapse.

Two Clinical Presentations of Anaphylaxis

a. Type A Anaphylaxis

The cardinal signs/symptoms of urticaria, itching, angioedema, upper airway edema, dyspnea occurs within 5–15 minutes. Urticaria/angioedema is seen in 80% of the patients associated with either breathing difficulty or circulatory system involvement or severe abdominal pain or repeated vomiting.

- *Grade I:* If there is only skin involvement (itching, flushing, hives, swelling).
- *Grade II*
  - Skin + eye involvement (itching, tearing, redness, swelling around the eyes).
  - Skin + GIT involvement (nausea, vomiting, abdominal cramps, and diarrhea).
- *Grade III:* Skin + laryngeal edema.

b. Type B Anaphylaxis

- *Grade IV: 20*% of patients develop direct involvement of respiratory (breathlessness) & circulatory (collapse and shock) system.
  - Respiratory involvement (throat obstruction plus progression from acute breathlessness to respiratory failure).
  - Cardiac involvement: dizziness, weakness, fainting, tachycardia, hypotension progressing to cardiac failure.
  - Anxiety, confusion, sense of impending doom.

IMMUNOLOGICAL REACTIONS OF ANAPHYLAXIS (FOOD, VENOM, AND DRUG)

- **Food-Induced Anaphylaxis**

Oral tolerance leads to the generation of food-specific anergic T cells, which eventually develop into Treg cells that suppress other T effector cells. The microbiome influences the function of Tregs in relation to food. Clostridial species activate Tregs via the innate immune pathway, promoting food tolerance through the protective action of TGF-β. In food-induced anaphylaxis, the protective role of Treg cells is overridden by immunopathogenic cytokines like IL-4 and changes in the microbiota. Recent research on T cells involved in IgE production has shown that Tfh cells, rather than Th2 cells, are essential for allergen-specific IgE induction [4]. A subset of Tfh cells, identified by the expression of GATA3 and IL-13 (referred to as Tfh13), has been found to play a key role in the induction of high-affinity IgE, which triggers anaphylaxis. Alpha-gal syndrome is a recently identified type of food-induced anaphylaxis, characterized by symptoms that usually emerge 2 to 6 hours after consuming foods, like beef, pork, or lamb, which contain the polysaccharide galactose-alpha-1,3-galactose (alpha-gal) [5]. Delayed clinical symptoms are due to slow release of chylomicrons of alpha-gal in circulation. A comprehensive list of important hidden allergens and their sources are shown in (Table 2). If the ingredient list does not identify a known allergen, contamination or cross-contact with the allergen should be considered. If hidden allergens are suspected in an episode of anaphylaxis, the patient should be counselled to avoid the associated source of food [6]. An example of a "hidden" food allergen is anaphylaxis triggered by consuming food made with wheat flour that has been contaminated with house dust mites [7, 8].

Table 2. Important hidden food Allergens and their associated sources [6].

Culprit Food Allergen Plus Associated Allergen	Sources
Pink peppercorns + cashew, pistachio, mango	• Pink peppercorns
Cow's milk	• Dry powder inhalers (DPI) • DTaP, Tdap, oral polio vaccine (DPT) • Medications (i.e., intravenous methylprednisolone sodium succinate, lactulose) • Cosmetics and personal care products (i.e., lotions, bath products, make-up, gingival gel)
Egg	• Yellow fever, influenza, MMR, and rabies vaccines

Wheat (hydrolyzed wheat protein)	• Beer • Cosmetics (i.e., hair care products, bath products, makeup)
Oat	• Cosmetics
Lupine + peanut	• Baked goods or pasta, often listed as gluten-free
Gelatin	• Medications (i.e., cetuximab, heparin, porcine/bovine valves, gelatin) • Influenza, MMR, Varicella spp, Varicella zoster, rabies, typhoid, and yellow fever vaccines • Medications (i.e., hemostatic agents, capsules, suppositories, erythropoietin, plasma volume expanders, sulfur colloid injection) • Candy, gelatin desserts
Spices + cross-reactive fruits and vegetables (celery-mugwort-birch syndrome)	• Foods and beverages • Topical and oral products (i.e., dental products, personal care products, cosmetics, perfume/cologne, air fresheners, scented candles, household cleaners)
Guar gum (i.e., guarana)	• Food additive in baked goods, dressings, beverages • Herbal supplements and medications

Abbreviations: DTaP, Diphtheria tetanus acellular pertussis; MMR, measles, mumps, rubella; Tdap, Tetanus diphtheria acellular pertussis.

- **Venom Induced Anaphyalxis**

Systemic venom reactions are more common in middle-aged and elderly individuals and are often linked to cardiovascular and mast cell disorders, in contrast to food-induced anaphylaxis. Conditions, such as systemic mastocytosis, clonal mast cell disorders, and hereditary alpha tryptasemia (Hαt) increase the risk of severe venom-induced anaphylaxis. Venom-specific IgE is found in nearly all individuals with a history of venom-induced anaphylaxis. However, the presence of venom-specific IgE alone does not lead to anaphylaxis in most cases. In bee venom, one of the key allergens is active phospholipase A2 (APLA2), which stimulates IL-33 release and the Th2 response without directly inducing specific IgE. Melittin, the primary component of bee venom, drives inflammation via the inflammasome/caspase-1/IL-1β pathway.

- **Drug-Induced Anaphylaxis**

The incidence of drug-induced anaphylaxis is between 50–112 episodes per 100,000 persons per year and drug allergy mortality is estimated at 0.05 to 0.51 per million person per year [9]. The most frequent cluprit drugs are antiobiotics (penicillin and cephalosporins), non steroidal anti inflammatory drugs (NSAIDs), injected radio-contrats agents (Iodinated contrast media and gadolinium), anti-neoplastic drugs, therapeutic antibodies and neuro-muscular blocking agents (NMBAs) used during surgery [10, 11]. The risk factors are old age, pre-existing cardiovascular disease, atopy and allergic diseases, mastocytosis, etc. Gell and Coomb's classification of Drug allergy into IgE-dependent (Type I), IgG dependent (Type II and Type III), MRGPRX2 dependent, Complement dependent, and Cytokine release reactions (CRRs) as mentioned in (Figure 1). Drug-induced anaphylaxis (DIA) is mainly a Type I IgE-mediated immune response that triggers mast cells and basophils to release pro-inflammatory substances like tryptase, histamine, leukotrienes, prostaglandins, and platelet-activating factor (PAF). However, there are also non-IgE-mediated drug reactions, including mast cell and basophil degranulation with cytokine release, as well as non-immunological mechanisms like cyclooxygenase (COX) inhibition. Certain mast cell-specific receptors, such as Mas-related G-protein-coupled receptor X2 (MRGPRX2), can be directly activated by neuromuscular blocking agents (NMBAs) like rocuronium, mivacurium, and atracurium, as well as quinolones like ciprofloxacin. G-protein-coupled receptors (GPCRs) are critical in modulating mast cell function, affecting both FcεRI-mediated activation and mediator release [10]. Receptors, such as those for the complement component C3a, are associated with specific G proteins, highlighting the intricate interplay between receptor signaling, G protein activation, and cellular responses. Mast cells can also be activated through complement receptors and the anaphylotoxins C3a and C5a, triggered by agents, like contrast media, drug excipients, iron infusions, and vaccines, which may lead to hypersensitivity reactions (HRs). Complement activation-related pseudo-allergy (CARPA) is a non-IgE-mediated reaction characterized by symptoms

like flushing, hives, hypoxia, vasodilation, hypotension, and anaphylaxis [12–14]. On the other hand, cytokine release reactions (CRRs), often caused by chemotherapeutic drugs and monoclonal antibodies (mAbs), are driven by T cells, monocytes, macrophages, natural killer cells, and endothelial cells. The excessive release of cytokines, including IL-6, IL-1β, and TNF-α, can produce symptoms ranging from mild flu-like effects to severe, potentially life-threatening conditions. Mild CRR symptoms include fever, fatigue, headache, rash, joint pain, and muscle aches, while severe cases can involve hypotension, high fever, systemic inflammation, shock, vascular leakage, disseminated intravascular coagulation, and multi-organ failure [15]. CRRs can occur after the first exposure or after repeated doses, with IL-6 serving as a key biomarker. Lastly, NSAIDs can trigger anaphylaxis through a pseudo-allergic mechanism by inhibiting cyclooxygenase-1 (COX-1), reducing prostaglandin production and increasing leukotriene production [16].

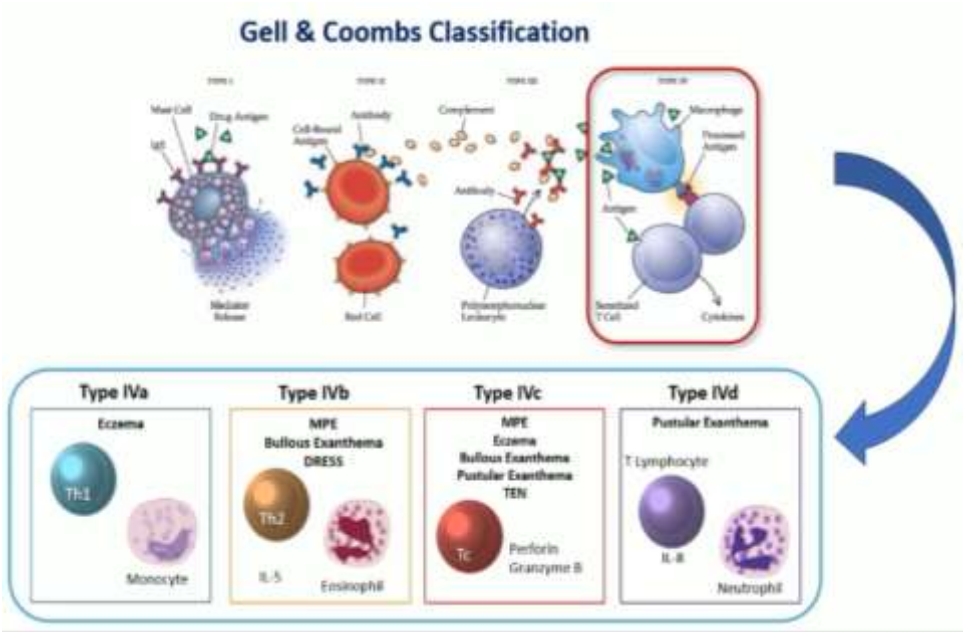

Figure 1. Gell & Coombs classification.

DIAGNOSTIC TESTS

Several diagnostic tests can help to differentiate MCAS, pheochromocytoma, carcinoid syndrome, mastocytosis, food and drug induced anaphylaxis, and others (Table 3).

1. *Skin Test & Specific IgE:* The positive predictive value (PPV) of cow milk (CM) specific IgE (> 15 KU/L) and CM Skin prick test (SPT) wheal size (>8 mm) along with Egg white (EW) specific IgE (7 KU/L) and EW SPT wheal size (>7 mm) is more than 95% (Table 4) and the recommended non-irritating concentration for drug skin test and intradermal test (IDT) are mentioned in (Table 5).
2. *Serum tryptase:* It does not distinguish between IgE and non-IgE mediated anaphylaxis. It is increased more in drug- and venom-induced anaphylaxis than food-induced. There is an increase in the level of serum tryptase within half an hour to two hours after an episode of anaphylaxis. bST should be done 24 hours after the complete resolution of symptoms (bST x 1.2 + 2 ug/L) [17]. Experts have agreed that an acute serum total tryptase level that is at least 20% higher, plus an additional 2 ng/mL above the patient's baseline serum tryptase (bST) level, indicates systemic mast cell activation, which can be linked to conditions, like clonal mast cell disease and hereditary α-tryptasemia (HαT), and is associated with more severe anaphylaxis. If the serum tryptase level exceeds 25 microg/L, it suggests an IgE-mediated reaction. The differential diagnosis for elevated bST levels is systemic mastocytosis, Hereditary alpha tryptasemia, Mast cell activatin syndrome, Myeloid neoplasm, etc. A bST level exceeding 42 ng/ml is linked to mastocytosis. Clinicians should consider testing for tryptase staining, CD25

immunohistochemistry or flow cytometry, and the KIT D816V mutation using a sensitive allele-specific PCR technique. If peripheral eosinophilia is present, FIP1L1-PDGFRA mutational analysis should be performed. A bone marrow biopsy showing at least 15 mast cells in clusters is a key diagnostic criterion for systemic mastocytosis [2]. The diagnostic algorithm for anaphylaxis and mast cell act activation syndrome is given in Figure 2.

3. *Prostaglandin D2 (PGD2):* Baseline measurement is most helpful about differentiation between the two conditions. Therefore, KIT D816V mutation analysis should be strongly considered in patients with anaphylaxis suspected of having mastocytosis.
4. *Chromogranin A* is a useful circulating marker for carcinoid tumors and is elevated in 90% of patients with neuroendocrine tumors. Chromogranin A is not elevated in mastocytosis [18].
5. *24-hour urinary 5-hydroxyindolacetic acid (HIAA):* It can be used to screen for neuro-endocrine tumors.
6. *Vasointestinal-polypeptide producing tumors, medullary thyroid tumors, and pheochromocytoma:* Vasointestinal-polypeptide, serum calcitonin, and catecholamines/metanephrines are useful biomarkers, respectively.

Table 3. Laboratory parameters and outcomes for probable mast cell activation or exclusionary diagnoses.

Laboratory Parameter	**Laboratory Outcome**
1. Mast cell activation	
Serum tryptase	Change from baseline 20% + 2.0 ng/mL
Urine histamine metabolites	Elevated from baseline
Urine 11β-PGF2α	Elevated from baseline
2. Pheochromocytoma	
24-hour urinary fractioned catecholamines	Norepinephrine >1005 nmol/d1 Epinephrine >191 nmol/d Dopamine >4571 nmol/d
24-hour urine metanephrines	>1.3 mg/24 h
Plasma fractionated metanephrines	Metanephrine 0.5 nmol/L Normetanephrine 0.9 nmol/L
3. Carcinoid syndrome	
Serum serotonin	>400 ng/mL
24-hour urinary 5-HIAA	>15 mg per 24 hours
4. Mastocytosis	
Urine prostaglandin D2	Elevated from baseline
KIT D816V mutation	Positive
5. Anaphylaxis (Food)	
Skin test/serum IgE levels	Positive
Alpha-gal	Positive
6. Neuroendocrine tumor	Serum chromogranin A: >36.4 ng/mL
7. Vasoactive intestinal peptide tumor	Vasoactive intestinal peptide: >200 pg/mL
8. Medullary carcinoma of the thyroid	Serum calcitonin >8 pg/mL in women >16 pg/mL in men

Table 4. Skin Test & Specific IgE in diagnosis of IgE-mediated Cow's milk and egg allergy.

	CM-sIgE	**OFC to Fresh Milk**	**EW-sIgE**	**OFC to Cooked Egg**
>95% PPV	>15 KU/L >5 KU/L if <1Y	Defer OFC	>7 KU/L if >2Y >2 KU/L if <2Y	Defer OFC
	CM SPT	**OFC to Fresh Milk**	**EW SPT**	**OFC to Cooked Egg**
>95% PPV	>8 mm	Defer OFC	>7 mm if >2 y >5 mm if 2 Y	Defer OFC

Note: CM – cow milk, EW – egg white, OFC – oral food challenge, sIgE – specific IgE, SPT – skin prick test, PPV – positive predictive value.

Table 5. Recommended concentration for skin tests: Skin Prick Tests and Intradermal Tests of Drugs.

Drug for Testing	SPT Concentration	IDT Concentration
NMBAs		
Cisatracurium	2 mg/mL	0.02 mg/mL
Mivacurum	0.2–1.0 mg/mL	0.002–0.01 mg/mL
Pancuronium	2–20 mg/mL	0.2–2 mg/mL
Rocuronium	10 mg/mL	0.05 mg/mL
B-lactams		
Pen G (10,000 U/mL)	20 mg/mL	20 mg/mL
Ampicillin	20 mg/mL	20 mg/mL
Cefazolin	20 mg/dL, 33 mg/dL	20 mg/dl, 33 mg/dl
Local anesthetics	Undiluted	1/10
Heparins	Undiluted	1/10
Tranexamic acid	Undiluted	1/10
Protamine	Undiluted	1/10
Hypnotics		
Etomidate	2 mg/mL	0.2 mg/mL
Ketamine	10 mg/Ml	1 mg/mL
Propofol	10 mg/mL	1 mg/mL
Thiopental	5 mg/mL	2.5 mg/mL
Midazolam		0.05 mg/mL
Opiods		
Fentanyl	0.05 mg/mL	0.005 mg/mL
Remifentanil	0.05 mg/mL	0.005 mg/mL
Morphine	1 mg/mL	0.01 mg/mL
Sugammadex	100 mg/mL	50 mg/mL

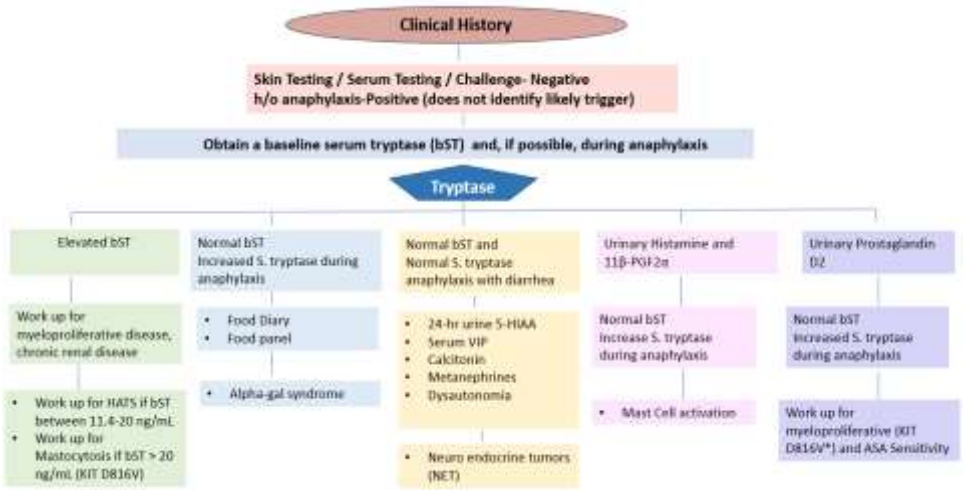

Figure 2. Diagnostic algorithms or anaphylaxis.
Note: bST, basal serum tryptase; ASA, acetylsalicylic acid; HATS, hereditary alpha tryptasemia; HIAA, hydroxyindolacetic acid; NET, neuroendocrine tumor; 11β-PGF2α-11 β prostaglandin F2a.

MANAGEMENT OF ANAPHYLAXIS

Prevention of Anaphylaxis

- *Drug elimination:* NSAIDs, beta-blocker, ACE inhibitor, systemic corticosteroids (succinate), etc.
- *Diet elimination:* Foods containing nsLTP (Tree nuts, peanuts, hazelnut, apricot, Rosaceae fruits including peach, apple, banana, strawberry, grapes, melon, kiwi, tomato, sesame. Wheat, lettuce, green beans, soy, rice, etc.)
- Fermented dairy products and fermented vegetables
- Avoid co-factors, such as alcohol, exercise, illness, anxiety, depression
- Adrenaline auto-injector and allergen immunotherapy.

EMERGENCY ACTION PLAN

1. Evaluate the patient's airway, breathing, circulation, and level of consciousness. If needed, secure the airway using the most effective yet least invasive method, such as a bag-valve-mask. Essential equipment includes a stethoscope, pulse oximeter, blood pressure cuff and cardiac monitoring tools, tourniquets, syringes (1 ml, 10 ml, and 20 ml), intravenous needles (gauge sizes 19, 20, 21, 23, and 25), intramuscular needles, and catheters (gauge sizes 14, 16, 18, 20, and 22). For intubation, materials needed include an Ambu bag/valve/mask (self-inflating with a reservoir), with volume capacities of 700–1,000 mL for adults and 100–700 mL for children, along with disposable face masks and oropharyngeal airways in sizes ranging from 6 cm to 10 cm. pocket masks and nasal cannula, laryngeal mask airways.
2. How should the patient be positioned?
   - Trendelenburg position: legs up for hemodynamic stability.
   - Half-sitting if dyspnea present.
   - Stable side position in case of impaired consciousness.
   - Avoid abrupt changes, sitting or standing up.
3. Begin chest compressions at a rate of 100 per minute if the patient experiences cardiovascular arrest at any point.
4. Insert an intravenous line for venous access and fluid replacement. Keep it open with 0.9% saline, administering fluids for hypotension or if the patient does not respond. Administer 5–10 mL/kg as quickly as possible, up to 30 mL/kg during the first hour for children, or 1–2 L for adults.
5. Provide high-flow oxygen at 10 liters per minute if there are signs of circulatory or severe respiratory distress. Administer a crystalloid bolus of 10 mL/kg for children weighing less than 25–30 kg, or 500 mL for children over 25–30 kg.
6. If there is no improvement after 5–10 minutes, administer another dose of adrenaline and continue giving intravenous fluids.
7. *Inj Adrenaline* is a vasoactive substance, acts by vasoconstriction, reduction of vascular permeability, broncho-dilator and reduction of edema and positive ionotropic agent of heart intramuscularly, oxygen inhalation, adrenaline inhalation / bronchodilator through nebulization. If treatment response is insufficient, then airway management should be done. Adrenaline should be given as intramuscular injection of 0.3–0.5 mg (10 ug/kg) or intravascular at a dose of 1ug/kg till the patient is stabilized Cardiac arrest/resuscitation: 10 ug/kg at 0.1 ml/kgbw up to 60 kgs (1mg per 10 ml) Respiratory: 1 mg/ml. Severe shock if im not possible titrate 1 ug/kg then continuous infusion of 0.05–1 ug /kg/min The EAACI Task Force recommends administering a dose of 0.01 mg/kg, with a maximum of 0.5 mg in healthcare environments. In community settings, the suggested doses are 0.15 mg for children weighing 7.5 kg to 25–30 kg, 0.3 mg for children weighing 25–30 kg, and 0.5 mg for adolescents who are overweight or have had a prior episode of severe, life-threatening anaphylaxis.
8. *Epinephrine autoinjector (EAI):* Epinephrine remains the preferred treatment for anaphylaxis in infants, just as it is for all age groups. A notable advancement in the management of anaphylaxis in infants and toddlers is the introduction of a 0.1 mg epinephrine auto-injector (EAI) for infants weighing between 7.5 and 15 kg, where previously only doses of 0.15 mg and 0.3 mg were

available. While older guidelines recommended a dosage of 0.01 mg/kg for epinephrine, this was based on expert consensus rather than clinical data.

- 0.01 mg/kg, up to a maximum of 0.3 mg for children and teenagers, and 0.5 mg for adults.
- 0.1 mg SC/IM AUVI-Q for infants 7.5–15 kg
- 0.15 mg for children 15–30 kg.
- 0.5 mg for those weighing 30 kg or more.

9. Consider administering 2.5–5 mg of nebulized albuterol or salbutamol in 3 mL of saline for managing lower airway obstruction, repeating the dose every 15 minutes as needed.
10. For antihistamine treatment, consider 10 mg of chlorpheniramine intravenously for adults (2.5 mg for children), or diphenhydramine at 25–50 mg for adults (1 mg, with a maximum of 50 mg for children). Alternatively, administer 10 mg of cetirizine, fexofenadine, or bilastine as an oral antihistamine, or give 0.1 mg/kg of dimethadone intravenously, with dosing as follows: 1 mL for patients under 15 kg, 2–3 mL for 15–30 kg, 4 mL for 30–60 kg, and 8 mL for those over 60 kg.
11. Administer intravenous hydrocortisone (200 mg for adults, 100 mg maximum for children) or methylprednisolone (1–4 mg/kg up to 125 mg per dose), either intravenously or orally, or use an equivalent formulation.
12. For patients on beta-blockers who do not respond to epinephrine, administer 1.5 mg of glucagon intravenously over 5 minutes. Avoid rapid administration as it may induce vomiting.
13. If a patient does not respond adequately to intramuscular epinephrine and intravenous saline, a continuous epinephrine infusion should be considered. In an office setting, micro-drips can be used, while a hospital typically relies on an infusion pump. To prepare the infusion, mix 1 mg of epinephrine (1 mL of a 1:1,000 solution) with 1,000 mL of 0.9% saline. Start the infusion at a rate of 2 μg/min (2 mL/min or 120 mL/h) and adjust gradually up to 10 μg/min (10 mL/min or 600 mL/h), depending on the patient's blood pressure, heart rate, and oxygen levels.
14. If intravenous access is unavailable, consider obtaining intraosseous access to administer intravenous fluids and epinephrine infusion.
15. For significant stridor or severe laryngeal edema, or if bag-valve-mask ventilation is insufficient, use a supraglottic airway, endotracheal intubation, or cricothyroidotomy.
16. If the patient remains unresponsive to the treatments above, consider administering dopamine or noradrenaline, in addition to the epinephrine infusion. This is typically done in a hospital setting with cardiac monitoring and defibrillation available.
17. In cases where anaphylaxis presents primarily with abdominal symptoms:
    - Use anti-emetics like metoclopramide, dimenhydrinate, or serotonin antagonists (ondansetron).
    - For abdominal cramps, administer intravenous muscarinic antagonists like butyl scopolamine.
18. Call the emergency team, including critical care specialists, to provide advanced treatment, such as adrenaline infusion. If cardiac arrest occurs, follow standard guidelines. Keep a close watch on the patient's neurological status, oxygen levels, blood pressure, and ECG. After stabilization, measure serum tryptase 30 minutes to 2 hours post-reaction and assess if further treatment with antihistamines or corticosteroids is necessary.
19. Make sure all essential supplies are on hand, including extension tubing, T-connectors, 3-way stopcocks, arm boards, gloves, a written emergency protocol for treating anaphylaxis, and a flow chart for documenting events and timings.

CONCLUSIONS

Anaphylaxis is becoming more prevalent, but it is frequently unrecognized and untreated. Severe anaphylactic reactions are most triggered by foods, medications, and insect stings. Around 80% of patients first exhibit skin-related symptoms, such as hives or swelling, while 20% may skip these signs and experience severe symptoms like difficulty breathing or low blood pressure right away. While most anaphylactic reactions can be managed effectively with prompt treatment, fatalities still occur if intervention is delayed. It is important to disseminate knowledge to medical professionals, patients and other stake holders in schools, communities, flights of this potentially life-threatening reaction and familiarize them with the self-management-emergency action plan including the use of EpiPen Auto Injector (EAI).

REFERENCES

1. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020 Oct 30;13(10):100472. https://doi.org/10.1016/j.waojou.2020.100472.
2. Golden DBK, Wang J, Waserman S, Akin C, Campbell RL, Ellis AK, et al. Joint Task Force on Practice Parameters Reviewers; Abrams EM, Bernstein JA, Chu DK, Ellis AK, Golden DBK, Greenhawt M, Horner CC, Ledford DK, Lieberman J, Rank MA, Shaker MS, Stukus DR, Wang J. Anaphylaxis: A 2023 practice parameter update. Ann Allergy Asthma Immunol. 2024 Feb;132(2):124–176. DOI: 10.1016/j.anai.2023.09.015.
3. Dribin TE, Sampson HA, Camargo CA Jr, Brousseau DC, Spergel JM, Neuman MI, et al. Persistent, refractory, and biphasic anaphylaxis: A multidisciplinary Delphi study. J Allergy Clin Immunol. 2020 Nov;146(5):1089–1096. https://doi.org/10.1016/j.jaci.2020.08.015.
4. Stevens WW, Kraft M, Eisenbarth SC. Recent insights into the mechanisms of anaphylaxis. Curr Opin Immunol. 2023 Apr;81:102288. https://doi.org/10.1016/j.coi.2023.102288.
5. Tripathi A, Commins SP, Heymann PW, Platts-Mills TA. Delayed anaphylaxis to red meat masquerading as idiopathic anaphylaxis. J Allergy Clin Immunol Pract. 2014;2:(3):259–65. https://doi.org/10.1016/j.jaip.2014.02.017.
6. Carter MC, Akin C, Castells MC, Scott EP, Lieberman P. Idiopathic anaphylaxis yardstick: Practical recommendations for clinical practice. Ann Allergy Asthma Immunol. 2020 Jan;124(1):16–27. https://doi.org/10.1016/j.anai.2019.08.024.
7. Sanchez-Borges M, Capriles-Hulett A, Fernandez-Caldas E, Suarez-Chacon R, Caballero F, Castillo S, Sotillo E. Mite-contaminated foods as a cause of anaphylaxis. J Allergy Clin Immunol. 1997 Jun;99(6 Pt 1):738–43. https://doi.org/10.1016/S0091-6749(97)80005-X.
8. Takahashi K, Fukutomi Y, Sekiya K, Taniguchi M, Akiyama K. 402 Oral Mite Anaphylaxis is Caused by Mite-contaminated Okonomiyaki Mix in Japan. World Allergy Organ J. 2012 Feb 17;5(Suppl 2):S145. https://doi.org/10.1016/S0091-6749(97)80005-X.
9. Bruhns P, Chollet-Martin S. Mechanisms of human drug-induced anaphylaxis. J Allergy Clin Immunol. 2021 Apr;147(4):1133–1142. https://doi.org/10.1016/j.jaci.2021.02.013.
10. Labella M, Garcia-Neuer M, Castells M. Application of precision medicine to the treatment of anaphylaxis. Curr. Opin. Allergy Clin. Immunol. 2018;18:190–197. doi: 10.1097/ACI.0000000000000435.
11. Kumar M, Duraisamy K, Chow BK. Unlocking the Non-IgE-Mediated Pseudo-Allergic Reaction Puzzle with Mas-Related G-Protein Coupled Receptor Member X2 (MRGPRX2). Cells. 2021;10:1033. https://doi.org/10.3390/cells10051033.
12. Kuehn HS, Gilfillan AM. G protein-coupled receptors and the modification of FcepsilonRI-mediated mast cell activation. Immunol Lett. 2007;113:59–69. https://doi.org/10.1016/j.imlet.2007.08.007.
13. Caimmi S, Crisafulli G, Franceschini F, Liotti L, Bianchi A, Bottau P, et al. Hypersensitivity to Intravenous Iron Preparations. Children. 2022;9:1473. https://doi.org/10.3390/children9101473.
14. Mori F, Saretta F, Bianchi A, Crisafulli G, Caimmi S, Liotti L. et al. Hypersensitivity Reactions to monoclonal Antibodies in Children. Medicina. 2020;56:232. https://doi.org/10.3390/medicina56050232 .
15. Shimabukuro-Vornhage A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, et al. Cytokine release syndrome. J Immunother Cancer. 2018;6:56. https://doi.org/10.1186/s40425-018-0343-9.
16. Doña I, Jurado-Escobar R, Perkins JR, Ayuso P, Plaza-Serón MC, Pérez-Sánchez N, et al. Eicosanoid mediator profiles in different phenotypes of nonsteroidal anti-inflammatory drug-induced urticaria. Allergy. 2019;74:1135–1144. https://doi.org/10.1111/all.13725.
17. Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes:a consensus proposal. Int Arch Allergy Immunol. 2012;157:215e225. https://doi.org/10.1159/000328760.

18. Di Giacinto P, Rota F, Rizza L, Campana D, Isidori A, Lania A, et al. Chromogranin A: From Laboratory to Clinical Aspects of Patients with Neuroendocrine Tumors. Int J Endocrinol. 2018 Jul 2;2018:8126087. https://doi.org/10.1155/2018/8126087.

