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# Management of anaphylaxis

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# Background and Terminology

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- The human immune system is an assemblage of cellular and humoral components working together in a highly complex, coordinated, and elegant fashion to achieve the primary goal of protecting the human host (self) from harmful offenders (nonself).
- Exposure to offenders activates the various immune mechanisms to bring about immune responses aimed at neutralizing the dangerous nonself while preserving self.
- The immune system, however, can overreact to otherwise harmless nonself agents, producing inappropriate responses that are harmful to the host, thereby giving rise to allergy or allergic diseases.

# Important allergic syndromes

- **Urticaria** is a common allergic reaction to foods, drugs, or physical stimuli and is clinically characterized by an erythematous, raised, and pruritic rash.
- **Angioedemais** mediated by either an allergic (histaminergic) mechanism in response to exposure to foods, drugs, physical stimuli, or a nonallergic (non-histaminergic) mechanism (eg, hereditary angioedema [HAE], or angiotensin-converting enzyme [ACE] inhibitor). Angioedema is characterized by edema of the subcutaneous or submucosal tissues, which can cause airway compromise if the tongue or larynx is involved.
- **anaphylaxis** is a life-threatening systemic allergic reaction characterized by acute onset and multiorgan involvement. Mechanistically, anaphylaxis is a type I hypersensitivity reaction (allergic), mediated by IgE.





# Classification of Reactions

- **Type I reactions(immediate hypersensitivity)** are IgE mediated and account for most allergic and anaphylactic reactions observed in humans. Exposure to sensitizing allergens causes mediators from mast cells and basophils to be released through both IgE-dependent and IgE-independent (direct mast cell degranulation) mechanisms. Rhinitis caused by ragweed pollen and anaphylaxis caused by foods are examples of the IgE-dependent mechanism.
- **Type II reactions(cytotoxic)** denote antibody-mediated cytotoxic reactions. Complement-fixing IgG (or IgM) engages cell-bound antigen, activating the classic complement pathway and leading to the cell lysis. In the process, anaphylatoxins C<sup>3</sup>a and C<sup>5</sup>a cause mast cell mediators to be released, producing the same clinical syndrome seen in allergic anaphylaxis.

- **Type III reactions(immune complex)** are IgG or IgM complex mediated. Circulating soluble antigen-antibody immune complexes migrate from the circulation to be deposited in the perivascular interstitial space, thereby activating the complement system. Anaphylactic reactions to blood transfusions and blood component therapy, including serotherapy (immunoglobulin administration), are examples of the overlap of type II and type III reactivity. They have therefore been classified as complement-mediated or immune complex–mediated anaphylaxis.
- **Type IV reactions(delayed hypersensitivity)** are T-cell mediated and have no documented relationship to the pathogenesis of anaphylaxis.



# Risk factors for having anaphylaxis

- Age and sex: Pregnant women, infants, teenagers, elderly
- Route of administration: Parenteral >oral
- Higher social economic status
- Time of the year: Summer and fall (the outdoor seasons)
- History of atopy
- Emotional stress
- Acute infection
- Physical exertion
- History of mastocytosis

# Risk factors for increased anaphylaxis severity and mortality

- **Extremes of age:**

Very young (under-recognition) and Elderly

- **Comorbid conditions:**

Cardiovascular disease (heart failure, ischemic heart disease, hypertension) and Pulmonary disease (asthma, obstructive airway disease)

- **Others:**

Concurrent use of anti-hypertensive agents, specifically beta-blockers and angiotensin-converting enzyme (ACE) inhibitors

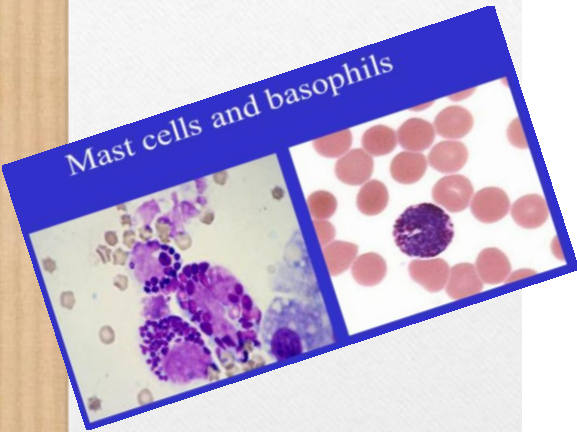
Concurrent use of cognition-impairing drugs (eg, alcohol, recreational drugs, sedatives, tranquilizers)

Recent anaphylaxis episode



# Common Triggers for Anaphylaxis

- Virtually any agent that is capable of activating mast cells or basophils can potentially precipitate an anaphylactic reaction. However, in up to 60% of adults and 10% of children, an inciting agent cannot be identified, and these reactions are classified as idiopathic anaphylaxis.
- When a trigger can be determined, foods, insect stings, and medications are the most common causes

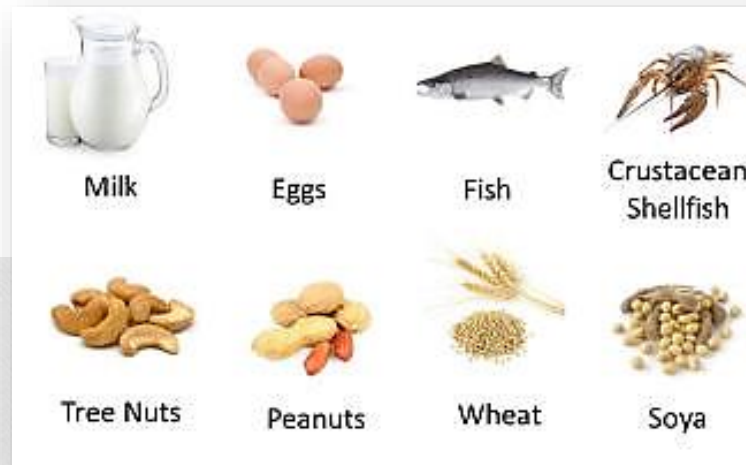


# Common Triggers for Anaphylaxis

- **Foods:**

Foods are the major identifiable causative agents, accounting for approximately one-third of the cases of anaphylaxis. The most commonly identified foods are tree nuts, peanuts, fish, shellfish, soy, cow's milk, and egg.

The majority of the severe and fatal reactions appear to be associated with peanut and tree nut exposure, especially if the patient has a history of asthma. The majority of these reactions occur after ingestion but may occur after inhalation of food particles or even after skin contact with vomit containing the instigating agent.



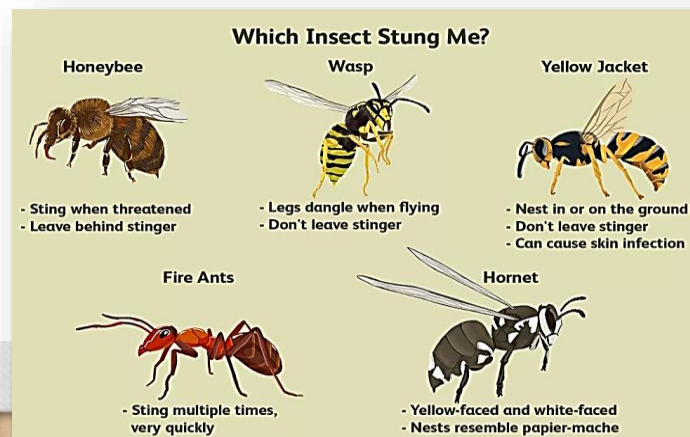


# Common Triggers for Anaphylaxis

- **Insect Stings**

Insect stings are the second most common cause of anaphylactic reactions, with the majority of them associated with hymenoptera venoms (wasps, bees, ants, and saw flies) and fire ant stings. These reactions typically require a sensitizing exposure, but there have been numerous reports of anaphylactic reactions following first known stings or bites.

Children tend to experience a more systemic cutaneous reaction, whereas adults are more likely to suffer hemodynamic collapse. Individuals displaying a large local reaction in the area of the sting or bite are less likely to suffer from a systemic reaction.



# Common Triggers for Anaphylaxis

- **Drugs:**
- **Antibiotics, chemotherapeutic agents, NSAIDs, and immunomodulators** are the most common reported triggers, and drugs as a class represent the third most frequent cause of anaphylactic reactions.
- **Penicillin** is the most common drug-induced cause of anaphylaxis. Although patients often report a history of penicillin allergy, this may not stand up to close scrutiny. Studies have shown that up to 90% of individuals with a reported history of penicillin allergy can safely use penicillin. These individuals are usually mislabeled as penicillin allergic or lose their allergy after years of avoidance. Parenterally administered penicillin is responsible for the majority of these anaphylactic reactions.



- **Cephalosporins** share the  $\beta$ -lactam ring structure and side chains of the penicillins, but allergic cross-reactivity appears to be low, somewhere between 1% to 8% of patients. Patients who have experienced urticaria or anaphylactic reactions after taking penicillin are more likely to have an adverse reaction to cephalosporins, but even in this setting, the risk of an anaphylactic reaction is very low. In patients with a history of penicillin allergy, a cephalosporin is considered safe if they have had a negative penicillin skin test. If penicillin skin testing is positive, they could undergo a graded challenge or rapid desensitization process.

**Aspirin** and other **NSAIDs** are believed to cause anaphylaxis through interruption of arachidonic acid metabolism, a non-IgE (non-immunologic) mediated process. The incidence of anaphylaxis to aspirin and NSAIDs varies widely, and these reactions appear to be drug specific and without cross-reactivity to other NSAIDs. Aspirin exacerbated respiratory distress (AERD) and NSAID-induced respiratory distress syndromes are unique in individuals with a history asthma or allergic rhinitis and are not considered anaphylactic reactions.



- Although **corticosteroids** are often used in the management of allergic syndromes and anaphylaxis, there have been reported anaphylactic reactions to these drugs. They appear to be rare, and the majority of them have been associated with the parenteral administration of methylprednisolone and hydrocortisone.

# Common Triggers for Anaphylaxis

- **Natural Rubber Latex:**

Natural rubber latex (NRL) allergy is the result of sensitivity to the proteins or chemicals contained in the latex products.

This sensitivity reaction can be delayed (type IV) contact dermatitis or an immediate hypersensitivity (type I) reaction

In addition to rubber gloves, NRL can be found in an array of other hospital supplies, including endo-tracheal tubes, blood pressure cuffs, stethoscope tubing, airway masks, tourniquets, and catheters. NRL is also found in balloons, condoms, pacifiers, sports equipment, and toys.



# Common Triggers for Anaphylaxis

- **Radiocontrast Media.:**

Radiocontrast media (RCM) represents an important class of agents that can cause an anaphylactic reaction. Anaphylactic reactions to RCM are largely idiosyncratic, occur within minutes of infusion, and are independent of the dose. The pathophysiologic mechanism of anaphylactic reactions to RCM is unknown, but it is believed to be non-immunologic (non-IgE). Risk factors for an anaphylactic reaction include a previous adverse reaction to RCM, a history of atopy or allergic disease, asthma, and certain medications. A history of an allergy to fish or shellfish is not a contraindication to the use of the currently used RCM, nor does it increase the risk of an adverse reaction to RCM. Clinically, the risk for severe adverse reaction with ionic and nonionic contrast materials is less than 1%. The death rate from RCM reactions is estimated at 1 to 3 per 100,000 administrations of contrast material.



# A Standard Treatment Protocol for Patients With a History of Radiocontrast-Induced Anaphylaxis

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- Prednisone 50 mg by mouth given 12 hours, 6 hours, and 1 hour before the procedure
- Diphenhydramine 50 mg PO given 1 hour before the procedure
- Consider ephedrine 25 mg by mouth given 1 hour before the procedure
- Consider an H<sub>2</sub> antagonist, such as ranitidine 150 mg by mouth given 2 hours before the procedure

# Common Triggers for Anaphylaxis

- **Exercise Induced Anaphylaxis:**

In certain settings, exercise has been recognized as an inciting event for an anaphylactic-like reaction. The mechanism is unclear, but the release of mediators from mast cells and basophils has been implicated. Patients with exercise-induced anaphylaxis are generally dedicated athletes who may have a personal or family history of atopy. In some individuals, anaphylaxis only occurs if specific co-triggers or cofactors are present during or prior to initiating exercise and typically do not cause symptoms without physical exertion. These may include certain foods, medications, or increased pollen levels in the area. Provocative foods, if identified, should be avoided.

# Common Triggers for Anaphylaxis

- **Idiopathic Anaphylaxis.:**

As previously mentioned, 30% to 60% of adults and up to 10% of children had no identifiable trigger for their anaphylactic reaction. The diagnosis of idiopathic anaphylaxis is often made after extensive evaluation by an allergist. In an attempt to prevent recurrent episodes, these patients are often treated with daily prophylactic medications, such as antihistamines and sometimes corticosteroids. Some women diagnosed with idiopathic anaphylaxis may actually represent “progesterone” anaphylaxis. Women suffering from this disorder experience recurrent episodes of anaphylaxis that are temporally related to their menstrual cycle.



# Clinical Features

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- Anaphylactic reactions vary in duration and severity, but they are typically rapid in onset and may result in death. They often present as a combination of clinical characteristics, commonly affecting an array of organ systems including the skin (80% to 90% of episodes), respiratory tract (70% of episodes), gastrointestinal tract (30% to 45% of episodes), cardiovascular (10% to 45%), and the central nervous system (10% to 15% of episodes).

# Clinical Criteria for Diagnosis of Anaphylaxis

- **Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:**
- 1. Sudden onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, itching or flushing, swollen lips-tongue-uvula) and at least one of the following:
  - a. Respiratory compromise (eg, shortness of breath, wheeze, cough, stridor, hypoxemia)
  - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

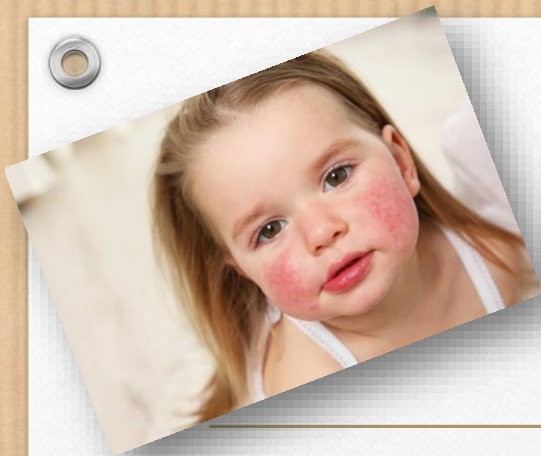
- ٢. Two or more of the following occurring rapidly (minutes to several hours) after exposure to a likely allergen or other trigger for that patient:
  - a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
  - b. Sudden respiratory compromise (eg, shortness of breath, wheeze, cough, stridor, hypoxemia)
  - c. Sudden reduced BP or symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
  - d. Sudden gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
  
- ٣. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
  - a. Infants and children: Low systolic BP (age specific) or greater than ٣٠% decrease in systolic BP\*
  - b. Adults: Systolic BP of less than ٩٠ mm Hg or greater than ٣٠% decrease from that person's baseline



# Diagnostic Testing

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- Anaphylaxis is primarily a clinical diagnosis. A good history and physical examination are the best tools for making an accurate and efficient diagnosis of anaphylaxis.
- Elevated serum histamine levels acquired within 1 hour and tryptase levels within 2 hours of the onset of symptoms have been shown to correlate with anaphylaxis. These laboratory tests are not helpful in the acute setting because the assays typically take over an hour to perform.
- Also, tryptase levels may not be elevated in food induced anaphylaxis.



# Management

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- In the setting of anaphylaxis, the key to avoiding adverse outcomes is prompt recognition and initiation of the appropriate interventions. Failure to immediately provide these measures, even by a few minutes, could lead to hypoxia and even death.



# Treatment Algorithm for Anaphylaxis

- **Emergency measures (taken simultaneously)**
- Remove any triggering agent.
- Place patient in supine position.
- Begin cardiac monitoring, pulse oximetry, and blood pressure autonomic monitoring.
- Begin supplemental oxygen if indicated.
- Establish large-bore IV lines (eg, 16 or 18 gauge).
- Establish a patent airway.
- Be prepared for endotracheal intubation with or without rapid sequence intubation.
- Be prepared to use adjunct airway technique (eg, awake fiberoptic intubation, surgical airway).

- **Start rapid infusion of isotonic crystalloid (normal saline):**

Adults: 1000 mL IV in the first 5 minutes in the adult (several liters of normal saline may be required)

Pediatrics: 20 to 30 mL/kg IV increments



# Anaphylaxis treatment medications

- **First-Line Agent**

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Epinephrine is the first-line medication and should be given immediately at the first suspicion of an anaphylactic reaction.

- Adult: 0.3 to 0.5 mg IM (1 : 1000 concentration) in anterolateral thigh every 5 to 15 minutes as necessary
- Pediatric: 0.01 mg/kg IM (1 : 1000 concentration) in anterolateral thigh every 5 to 15 minutes as necessary
- Alternatively, epinephrine (EpiPen, 0.3 mL; or EpiPen Jr, 0.15 mL) can be administered into anterolateral thigh

# Anaphylaxis treatment medications

- **Second-Line Agents (Should Not Precede the Administration of Epinephrine)**

- Antihistamines

- Diphenhydramine: Adults: 50 mg IV or 50 mg oral , Pediatric: 1 mg/kg IV or oral

- Ranitidine: Adult: 50 mg IV (150 mg oral), Pediatric: 1 mg/kg IV or oral

- Aerosolized Beta-Agonists (if Bronchospasm Is Present) Adult:

- Albuterol: 2.5 mg, diluted to 3 mL of normal saline; may be given continuously

- Ipratropium: 0.5 mg in 3 mL of normal saline; repeat as necessary Pediatric:

Albuterol: 2.5 mg, diluted to 3 mL of normal saline; may be given continuously,

Ipratropium: 0.25 mg in 3 mL of normal saline; repeat as necessary

## Glucocorticoids (No Benefit in the Acute Management)

- Methylprednisolone: Adult: 125 to 250 mg IV, Pediatric: 1 to 2 mg/kg IV

- Prednisone/prednisolone: Adult: 40 to 60 mg oral, Pediatrics: 1 to 2 mg/kg oral

# Refractory hypotension

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- Consider continuous IV epinephrine drip (dilute 1 mg (1 mL 1:1000) in 100 mL of normal saline or D<sub>5</sub>W to yield a concentration of 1 µg/mL)
- Adults: 1 to 1.5 µg/minute IV (titrated to desired effect)
- Pediatrics: 0.1 to 1.5 µg/kg/minute IV (titrated to desired effect)



# Other vasopressors to consider

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- Dopamine:  $5$  to  $20$   $\mu\text{g}/\text{kg}$  per minute continuous IV infusion (titrated to desired effect)
- Norepinephrine:  $0.05$  to  $0.5$   $\mu\text{g}/\text{kg}$  per minute (titrated to desired effect)
- Phenylephrine:  $1$  to  $5$   $\mu\text{g}/\text{kg}$  per minute (titrated to desired effect)
- Vasopressin:  $0.01$  to  $0.4$  units/min (titrated to desired effect)

# Patients receiving beta-blockade

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- Glucagon: 1 to 5 mg IV over 5 minutes, followed by 5 to 15  $\mu\text{g}/\text{min}$
- continuous IV infusion

# Disposition

- Up to 20% of patients may experience a biphasic reaction defined as a reoccurrence of symptoms without reexposure to the triggering agent. Most of these reactions occur within 1 hours but have been reported as far out as 72 hours. The majority will again respond to the appropriate treatment, and recent literature suggests that clinically important biphasic reactions and fatalities are actually much rarer than previously reported.
- Biphasic reactions are more common in patients who have a history of asthma, ingest the allergen, or present with laryngeal edema, wheezing, or gastrointestinal symptoms.
- Consensus guidelines suggest that patients who respond to treatment and experience complete resolution of symptoms can be discharged home after an observation period of 4 to 6 hours. Consider extended observation or hospitalization for patients who (1) present with protracted anaphylaxis, hypotension or airway involvement; (2) receive IV epinephrine or more than two doses of IM epinephrine; or (3) have poor outpatient social support.
- Prior to discharge, the clinician should take an active role in educating the patient about their allergy and anaphylaxis. The patient should be discharged with a prescription for two auto-injectable epinephrine devices, one to remain at their home and the other to be carried with them at all times. It is also important to thoroughly explain and demonstrate how to use the device.













