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**Review article**

# Anaphylaxis in children

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**Definition**

Anaphylaxis is an acute, potentially life-threatening hypersensitivity reaction, involving the release of mediators from mast cells, basophils and recruited inflammatory cells. Anaphylaxis is defined by a number of signs and symptoms, alone or in combination, which occur within minutes, or up to a few hours, after exposure to a provoking agent. It can be mild, moderate to severe, or severe. Most cases are mild but any anaphylaxis has the potential to become life-threatening.[1]

**Pathogenesis**

The term *anaphylaxis* is often used only for a severe allergic reaction affecting the whole body. A second term, *non-allergic anaphylaxis*, may be used to describe identical reactions that are not caused by allergy, but involve other mechanisms in the body.[1]

Mast cell activation in anaphylaxis results in the release of many mediators that include histamine, leukotrienes, tumor necrosis factor and various cytokines. The large numbers of mediators provide redundancy and positive feedback mechanisms whereby other effector cells are recruited to release more mediators, perpetuating the allergic response. This amplification and perpetuation, which has been referred to as a "mast cell leukocyte-cytokine cascade" underscores the importance of physiological antagonism with adrenaline and fluid resuscitation, rather than antagonism of a single mediator such as histamine.[2,3]

Clinical anaphylaxis also may be due to mechanisms other than Ig-E mediated reactions, sometimes termed anaphylactoid reactions (non allergic anaphylaxis), including direct release of mediators from mast cells by medications and physical factors (e.g. morphine, exercise, cold), disturbances of leukotriene metabolism (aspirin and non-steroidal anti-inflammatory drugs), immune aggregates and complement activation (e.g. radiocontrast dyes and dialysis membranes).[4]

**Pathophysiology**

Anaphylactic mediators cause vasodilatation, fluid extravasation, smooth muscle contraction and increased mucosal secretions. Death may occur from hypoxemia (due to upper airway angioedema, bronchospasm and mucus plugging) and/or shock (due to massive vasodilatation, fluid shift into the extravascular space and depressed myocardial function).[5] While compensatory tachycardia in response to hypotension is considered a characteristic feature, sudden bradycardia with cardiovascular collapse and cardiac arrest may occur before any skin features become apparent.[6] The cause of this phenomenon is unclear, but it is an important clinical feature to recognize in order to avoid making an initial misdiagnosis of a "panic attack" or "vasovagal reaction" in cases where dyspnea, nausea, anxiety, and bradycardia may occur just before cardiovascular collapse.[3]

**Etiology**

Food, insect venoms or medication trigger most cases of anaphylaxis, with a variable proportion of patients experiencing idiopathic anaphylaxis in which extensive evaluation fails to identify an underlying cause (Table 1). In emergency department studies, food allergy is the commonest cause in children - responsible for about 80% of anaphylactic reactions in which the cause has been identified.[7]

**Table 1. Etiology of anaphylaxis in children**

| |
|---|
| **Inside the hospital:** |
| Latex |
| Antibiotics (especially intravenous) |
| Intravenous immunoglobulin |
| Radiocontrast dye |
| **Outside the hospital:** |
| Food (e.g. peanut, tree nuts, shellfish, milk, egg) |
| Insect sting (Hymenoptera, fire ants) |
| Oral medications (e.g. penicillin) |
| Exercise (including food-associated) |
| Idiopathic |

*Quoted from Sampson and Leung*[4]

***1. IgE-mediated anaphylaxis (most common)***

*Food:*

Food is one of the most common responsible allergens in the outpatient setting. Food allergy, defined as an adverse immune response to food proteins, affects as many as 6% of young children and 3% to 4% of adults and the prevalence of food-induced anaphylaxis has been steadily rising.[8, 9]

In theory, any food protein is capable of causing an anaphylactic reaction. Foods most frequently implicated in anaphylaxis are:[1]

- Peanut
- Tree nuts (walnut, hazel nut/filbert, cashew, pistachio nut, Brazil nut, pine nut, almond)
- Fish
- Shellfish (shrimp, crab, lobster, oyster, scallops)
- Milk (cow, goat)
- Chicken eggs
- Seeds (cotton seed, sesame, mustard)
- Fruits, vegetables

Cow's milk is one of the first foreign proteins ingested by infants and is one of the most common and potent food allergens. The presence of cow's milk is widespread due also to its unlabelled inclusion as an ingredient, or to errors in cooking, processing and preparation, and in restaurant food. As several foods may contain cow's milk in a hidden form, foods for allergic babies should be prepared at home or with food items with all their ingredients listed on the label.[10] Contamination of probiotic preparations with milk allergens can cause anaphylaxis in children with cow's milk allergy.[11]

Food sensitivity can be so severe that a systemic reaction can occur to particle inhalation, such as the odors of cooked fish or the opening of a package of peanuts.[12,13] Contact with food may also cause systemic reactions.[14]

A severe allergy to pollen, for example, ragweed, grass or tree pollen, can indicate that an individual may be susceptible to anaphylaxis or to the oral allergy syndrome (manifested primarily by severe oropharyngeal itching, with or without facial angioedema) caused by eating certain plant-derived foods. This is due to homologous proteins found between pollens and foods. The main allergen of all grasses is profilin, which is a pan-allergen, found in many plants, pollens and fruits, and grass-sensitive individuals can sometimes react to many plant-derived foods. Typical allergen cross-reactivity associations are:[1]

– Birch pollen: apple, raw potato, carrot, celery and hazelnut
– Mugwort pollen: celery, apple, peanut and kiwifruit
– Ragweed pollen: melons (watermelon, cantaloupe, honeydew) and banana
– Latex: banana, avocado, kiwifruit, chestnut and papaya

*Antibiotics and other drugs*

Penicillin is the most common cause of anaphylaxis. Serious reactions to penicillin occur about twice as frequently following intramuscular or intravenous administration versus oral administration, but oral penicillin administration may also induce anaphylaxis. Muscle relaxants, e.g., suxamethonium, alcuronium, vecuronium, pancuronium and atracurium, which are widely used in general anesthesia, account for 70-80% of all allergic reactions occurring during general anesthesia. Reactions are caused by an immediate IgE-mediated hypersensitivity reaction.[1] Drugs that were reported to cause anaphylaxis[15] are listed in table 2.

**Table 2. Drugs frequently implicated in allergic drug reactions**

| |
|---|
| Aspirin (other analgesics-antipyretics) |
| Penicillins and cephalosporins |
| Sulfonamides |
| Antituberculous drugs |
| Nitrofurans |
| Antimalarials |
| Griseofulvin |
| Sedative hypnotics |
| Anticonvulsants |
| Anesthetics (local and general) |
| Phenolphthalein |
| Antipsychotic tranquilizers |
| Antihypertensive agents (hydralazine) |
| Antiarrhythmia agents (quinidine, procainamide) |
| Iodinated contrast media |
| Antisera and vaccines |
| Organ extracts (ACTH, insulin) |
| Heavy metals (gold) |
| Allopurinol |
| Penicillamine |
| Antithyroid drugs |

*Quoted from Thong et al [15]*

*Insects*

Hymenoptera venoms (bee, wasp, yellow-jacket, hornet, fire ant) contain enzymes such as phospholipases and hyaluronidases as well as other proteins which can elicit an IgE antibody response.[1]

*Latex*

Latex is a milky sap produced by the rubber tree *Hevea brasiliensis*. Latex-related allergic reactions can complicate medical procedures, e.g., internal examinations, surgery, and catheterization. Medical and dental staff may develop occupational allergy through use of latex gloves.[1]

*Foreign proteins*

Examples of foreign proteins which can cause anaphylaxis are insulin, seminal proteins, and horse-derived antitoxins, such as those used to neutralize venom in snake-bites.[1]

*Elective medical procedures*
Allergen immunotherapy is an example. Based on the literature, the risk of fatality due to skin prick tests (SPT) is extremely remote, and severe/anaphylactic reactions are rare.[1] Nevertheless, this risk cannot be completely excluded, especially in highly susceptible subjects. In general, the risk of systemic reactions is lower with SPT than with intradermal testing. Some patients (history of previous anaphylactic reactions, small children, pregnant women, uncontrolled asthma, and high degree of reactivity) should be considered at higher risk of systemic/anaphylactic reactions from SPT.[16]

***2. Cytotoxic and immune complex-mediated reactions***
One of the mechanisms responsible for anaphylactic responses that follow the administration of whole blood or its products is the formation of antigen-antibody reactions on the red blood cell surface or from immune complexes resulting in the activation of complement. The active by-products generated by complement activation (anaphylatoxins C3a, C4a and C5a) cause mast cell (and basophil) degranulation, mediator release and generation, and anaphylaxis. In addition, complement products may directly increase vascular permeability and contract smooth muscle. Selective IgA deficient subjects (1:500 of the general population) can develop anaphylaxis when given blood products, because of their IgE anti-IgA antibodies. Cytotoxic reactions can also cause anaphylaxis, via complement activation. Antibodies (IgG and IgM) against red blood cells, as occurs in a mismatched blood transfusion reaction, activate complement. This reaction causes agglutination and lysis of red blood cells and perturbation of mast cells resulting in anaphylaxis.[1]

***3. Non-immunologic mast cell activators***
Hyperosmolar iodinated contrast media may cause mast cell degranulation by activation of the complement and coagulation systems. These reactions can still occur, but much less commonly, with the newer contrast media agents. Narcotics are mast cell activators capable of causing elevated plasma histamine levels and non-allergic anaphylaxis.[1]

***4. Modulators of arachidonic acid metabolism***
These can lead to non-IgE mediated systemic reactions due to overproduction of leukotrienes. IgE antibodies against aspirin and other NSAIDs (e.g. ibuprofen, indomethacin and others) have not been identified. Affected individuals tolerate choline or sodium salicylates, substances closely structurally related to aspirin but different in that they lack the acetyl group.[1]

***5. Sulfiting Agents***
Preservatives (e.g. Sodium and potassium sulfites, bisulfites, metabisulfites, and gaseous sulfur dioxides) are converted in the acid environment of the stomach to $SO_2$ and $H_2SO_3$, which are then inhaled. They can produce asthma and non-allergic hypersensitivity reactions in susceptible individuals.[1]

***6. Idiopathic Causes***
Exercise-induced anaphylaxis can occur during the pollinating season of plants to which the individual is allergic. Catamenial anaphylaxis is a syndrome of hypersensitivity induced by endogenous progesterone secretion. Patients may exhibit a cyclic pattern of attacks during the premenstrual part of the cycle. Moreover, flushing, tachycardia, angioedema, upper airway obstruction, urticaria and other signs and symptoms of anaphylaxis can occur without a recognizable cause.[1]

***Cofactor induced anaphylaxis***
Cofactors are sometimes required before an allergen will provoke a reaction. Factors associated with increased risk of anaphylaxis include intercurrent infection, concomitant medication/food (particularly α-blockers, β-blockers, angiotensin-converting enzyme [ACE] inhibitors, non-steroidal anti-inflammatory drugs [NSAIDS], alcohol or spicy food), high ambient temperature and exercise. So-called *"summation anaphylaxis"* may explain intermittent anaphylaxis despite frequent allergen exposure, and may account for some cases in which a cause has not been established. One of the most common cofactors, predominantly affecting young adults, is physical exercise. Some experience symptoms with exercise alone; others do so only if allergenic foods (most commonly wheat, celery, seafood, nuts, fruit or vegetables) are ingested within a few hours prior to exercise.[3] It may occur when individuals exercise within 2-4 hours after ingesting a specific food. The individual is, however, able to exercise without symptoms, as long as the incriminated food is not consumed before exercise. The patient is likewise able to ingest the incriminated food with impunity as long as no exercise occurs for several hours after eating the food.[1]

**Clinical Picture**

The onset of symptoms varies depending on the cause; reactions from ingested allergens are delayed in onset (minutes to 2 hours) compared with injected allergens and tend to have more gastrointestinal symptoms.[4] A few or all of the following symptoms, often developing in this order, may be experienced:[1]

- Itching of the lips, tongue and palate
- swelling of the lips, tongue and throat
- Swelling of the eyelids with itchy watery eyes
- Generalized itching, flushing, swelling of the skin, and hives (urticaria)
- Increased heart rate
- Abdominal cramps, nausea, vomiting, diarrhea
- Difficulty in breathing due to throat swelling, wheezing and asthma
- A sense of impending doom
- Collapse, loss of consciousness, weakness and faintness caused by a drop in blood pressure.

Cutaneous symptoms may be totally absent. The acute onset of severe bronchospasm in an asthmatic should suggest the diagnosis. Some degree of obstructive laryngeal edema is typically encountered with severe reactions.[4] Death may occur within minutes, but rarely has been reported to occur days to weeks after the initial anaphylactic event.[1]

Anaphylaxis can follow a biphasic course. Biphasic reactivity was reported with an incidence of 19.4%. The second-phase onset may be 8-10 hours on average, but it occurred as late as 38 hours. Biphasic anaphylaxis may be related, in part, to under treatment.[17] Protracted anaphylaxis may occur, with symptoms persisting for days.[1]

**Differential Diagnosis**

- Vasovagal reactions
- Globus hystericus
- Status asthmaticus
- Foreign body aspiration
- Pulmonary embolism
- Epiglottitis
- Myocardial infarction
- Carcinoid syndrome
- Hereditary angioedema
- Pheochromocytoma
- Hypoglycemia
- Seizures
- Overdose of medication
- Cold urticaria
- Cholinergic urticaria
- Sulfite or monosodium glutamate ingestion

Upper airway obstruction, bronchospasm, abdominal cramps, pruritus, urticaria and angioedema are absent in vasovagal reactions. Pallor, syncope, diaphoresis and nausea usually indicate a vasovagal reaction but may occur in either condition. If a reaction occurs during a medical procedure it is important to consider a possible reaction to latex or medication used for or during anesthesia.[1]

**Investigations**

- In-vitro testing for allergen-specific IgE is a useful initial screening test for a variety of allergens. It however lacks sensitivity and is limited by the range of allergens available.[3]
- Skin prick tests are more sensitive than in-vitro testing. As these carry a small risk of inducing anaphylaxis, they should only be carried out in an environment in which resources for treating anaphylaxis are available.[3]
- Some drug reactions (e.g. to NSAIDS, radiographic contrast agents) are independent of IgE, and there are numerous difficulties in assessing some cases of antibiotic allergy. To establish a diagnosis in cases in which the causative agent is in doubt, challenge testing under controlled conditions may sometimes be required, although a negative challenge test does not always exclude the diagnosis.[3]
- Plasma histamine is elevated for a brief period but is unstable and difficult to measure in a clinical setting.[4]
- Plasma beta-tryptase is more stable and remains elevated for several hours but is usually not elevated in food-induced anaphylactic reactions.[4]

**Treatment**

***Emergency management:***

The following steps are recommended: [6]

- Place the patient in the supine position (or left lateral position for vomiting patients);
- Give intramuscular adrenaline;
- Resuscitate with intravenous saline (20 ml/kg body weight, repeated up to a total of 50 ml/kg over the first half hour);
- Support the airway and ventilation; and
- Give supplementary oxygen.

Intramuscular 1: 1000 (1 mg/ml) adrenaline at a dose of 0.01 mg/kg (0.01 ml/kg) body weight up to a maximum dose of 0.5 mg (0.5 ml) injected into the lateral thigh (*vastus lateralis*) has the advantage

that it can be given without delay, is absorbed more reliably than injections into other locations or subcutaneously, is effective in most cases when given early, and avoids the potentially lethal effects of large intravenous bolus injections. The appropriate dose of epinephrine injector pen (EpiPen) can be used instead, if available. The intramuscular dose can be repeated after 3–5 minutes if required.[3]

The appropriate clinical use of epinephrine has been limited by misconceptions and by the reluctance of some patients and physicians to use this medication. Some of these misconceptions include: (1) a severe attack will always be preceded by an earlier and milder warning reaction; (2) there is always time to get medical attention so patients do not have to worry about administering epinephrine so quickly; and (3) medications, especially epinephrine, will always work when needed, even if use is delayed by patients who wait and see whether they will really need it. In fact, milder warning attacks will not necessarily precede a fatal or near-fatal reaction. It is also clear that some of these reactions progress so rapidly that there is not enough time to obtain medical attention.[18]

If resuscitation using intramuscular adrenaline and volume expansion with intravenous saline is ineffective, an infusion of intravenous adrenaline may be required, but this should be done only by experienced hands. Intravenous boluses of adrenaline are potentially dangerous and should not be used unless cardiac arrest is imminent[5]. Controlled intravenous infusions of adrenaline were shown to be safe and effective in one prospective study.[6]

If the patient is still unresponsive after the treatments outlined above, there are several further options:[3]

- Persistent bronchospasm may respond to treatment with additional bronchodilators. If intubation is required, continuous puffs of salbutamol through an aerosol port directly into the ventilation circuit may help to "break" severe bronchospasm.
- Persistent stridor may respond to continuous nebulised adrenaline (5 mg in 5 ml [i.e. five 1 mg ampoules]) in addition to parenteral adrenaline. Surgical airway intervention (cricothyrotomy) may be required.
- Persistent hypotension may be due to either profound vasodilatation or cardiac failure. Anecdotally, vasodilatation may respond to vasopressors such as metaraminol or vasopressin. In patients who have pre-existing heart failure or are taking β-blockers, a phosphodiesterase inhibitor such as glucagon may be tried.[19,20]

The World Allergy Organization (WAO) recommends a simple ABC action plan1 for treatment of anaphylaxis displayed on its website (www. worldallergy. org) in the Allergic Diseases Resource Center (Table 3)

***Long-term management of individuals who have experienced anaphylaxis:*** [1,4,21-23]

- Agents causing anaphylaxis should be identified when possible and avoided. Patients and their care-givers should be instructed how to minimize exposure including reading food labels and early recognition of anaphylactic symptoms
- Beta-adrenergic antagonists, including those used to treat glaucoma, may exacerbate anaphylaxis and should be avoided, whenever possible.
- Individuals at high risk for anaphylaxis should be issued epinephrine syringes for self-administration and instructed in their use. Patients must be alerted to the clinical signs of impending anaphylaxis and the need to use epinephrine at the earliest onset of symptoms. Unused syringes should be replaced immediately when they reach their use-by/expiration date, as epinephrine content and bioavailability of the drug decreases in proportion to the number of months past the expiration date.
- Children and their care-givers should be offered a written emergency plan in case of accidental ingestion. They should be reminded that they cannot depend on an oral antihistamine or an asthma inhaler in anaphylaxis, and should be equipped with accurate medical identification and a practical anaphylaxis emergency action plan.
- Pre-treatment with glucocorticosteroids and H1 and H2 antihistamines is recommended to prevent or reduce the severity of a reaction where it is medically necessary to administer an agent known to cause anaphylaxis, e.g., radio-contrast media.
- Patients with egg allergy should be tested before receiving measles, influenza or yellow fever vaccines which contain egg protein.
- Children who experienced systemic anaphylactic reactions to an insect sting should be evaluated and treated with specific immunotherapy which is more than 90% protective.
- In cases of food-associated exercise-induced anaphylaxis, children must not exercise within 2-3 hours of ingesting the triggering food and should not exercise alone and should learn to

recognize the early signs of anaphylaxis (sensation of warmth and facial pruritis).
- Reactions to medications can be reduced and minimized by using oral medications in preference to injected forms.
- New hypo-osmolar radiocontrast dyes can be used in cases where previous reactions are suspected.
- The use of powder-free, low allergen gloves and materials should be used in children undergoing multiple surgeries.
- Verification of the trigger should be sought by obtaining a comprehensive history of the anaphylaxis episode and performing relevant investigations, as well as determining co-morbidities and concomitant medications.
- Anaphylaxis education should be provided for individuals at risk, their families and caregivers, healthcare professionals, and the general public.

**Table 3. ABC in the treatment of anaphylaxis**

**Emergency treatment of anaphylaxis**

**A = Airway**
- Ensure and establish a patent airway by repositioning the head and neck, endotracheal intubation or emergency cricothyrotomy.
- Place the patient in a supine position and elevate the lower extremities.
- Patients in severe respiratory distress may be more comfortable in the sitting position.

**B = Breathing**
- Assess adequacy of ventilation and provide the patient with sufficient oxygen with an oxygen saturation of at least 91% as determined by pulse oximetry.
- Treat bronchospasm as necessary.
- Equipment for endotracheal intubation should be available for immediate use in event of respiratory failure and is indicated for poor mentation, respiratory failure, or stridor not responding immediately to supplemental oxygen and epinephrine.

**C = Circulation**
- Minimize or eliminate continued exposure to the causative agent by discontinuing the infusion, as with radio-contrast media, or by placing a venous tourniquet proximal to the site of the injection or insect sting.
- Assess adequacy of perfusion by taking the pulse rate, blood pressure, mentation and capillary refill time.
- Establish IV access with large bore (16 to 18 gauges) catheter and administer an isotonic solution such as normal saline.
- If a vasopressor, such as dopamine becomes necessary, the patient requires immediate transfer to an intensive care setting.

**Pharmacologic management of anaphylaxis:**

**A = Adrenalin = epinephrine**
- Epinephrine is the drug of choice for anaphylaxis. It stimulates both the beta-and alpha-adrenergic receptors and inhibits further mediator release from mast cells and basophils.
- The dose for children is 0.01 mg/kg to a maximum of 0.3 mg intramuscularly every 5-30 minutes as necessary. Lower doses, e.g., 0.1 mg to 0.2 mg administered intramuscularly as necessary, are usually adequate to treat mild anaphylaxis, often associated with skin testing or immunotherapy.
- Epinephrine should be given early in the course of the reaction and the dose titrated to the clinical response.
- For a severe hypotension, 1 cc of a 1:10,000 w/v dilution of epinephrine given slowly intravenously is indicated. The patient's response determines the rate of infusion.

**B = Benadryl (diphenhydramine)**
- Antihistamines are not useful for the initial management of anaphylaxis but may be helpful once the patient stabilizes. Cimetidine offers the theoretical benefit of reducing both histamine-induced cardiac arrhythmias, which are mediated via H2 receptors, and anaphylaxis-associated vasodilatation, mediated by H1 and H2 receptors.

**C = Corticosteroids**
- Corticosteroids do not benefit acute anaphylaxis but may prevent relapse or protracted anaphylaxis. Hydrocortisone or its equivalent can be administered every 6 to 8 hours for the first 24 hours.

*Quoted from Lockey*[1]

**Table 4. Anaphylaxis avoidance strategies in schools and child-care settings**

**- Food avoidance**

- School or nursery staff should know the technical and scientific words for common foods.
- Ingredient statements should be carefully read before giving the child any food.
- Strict "no food or eating-utensil trading" rules should be implemented throughout the school to avoid peer pressure.
- Surfaces (e.g., tables and toys) should be washed clean of contaminating foods.
- The food used in lesson plans and cooking classes may need to be substituted depending on the allergies of the students.
- Hand washing after food handling should be encouraged in day care and preschool settings.
- Airborne food clinical reactions have been documented. Thus, preparing or cooking the food in the presence of the allergic student should be avoided.
- If a student is going to eat from the cafeteria menu, the child's parents should inform the staff in writing about foods to be avoided and suggest "safe" substitutions.
- Food service personnel should also be instructed about measures necessary to prevent cross contact during the handling, preparation, and serving of food. It should be stressed that minute amounts of certain foods, such as peanuts, can be life-threatening when ingested
- Foods brought in for special events should contain complete ingredient declarations.
- Education and supervision are paramount and guidelines for children should include the following: (1) no trading or sharing of foods, food utensils, and food containers, and (2) hand washing should be encouraged before and after eating.

**- Insect avoidance**:

- Insect nests should be removed from on or near school property
- Garbage should be properly placed in well-covered containers
- Eating areas should be restricted to inside school buildings for students and staff at risk.

**- Other allergies:**

- Anaphylaxis caused by drug and latex allergies is rare in the school setting. These should be dealt with on an individual basis.

*Adapted from an AAAAI Position Statement*[23]

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