

Anaphylaxis

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ABSTRACT

Anaphylaxis is a sudden onset, immediate reaction that implies a risk of death. Think of a “rule of 2s” for anaphylaxis, which implies that reactions usually begin within 2 minutes to 2 hours after injection, infusion, ingestion, contact, or inhalation. Fatalities can be from asphyxiation from laryngeal or oropharyngeal swelling, collapse from hypotensive shock, cardiac arrest, or acute severe bronchoconstriction that causes respiratory failure and arrest. When there is activation of mast cells and basophils in anaphylaxis, chemical mediators are detectable. The preformed mediators from mast cells include histamine, tryptase, carboxypeptidase A, and proteoglycans (heparin, chondroitin sulfates). Newly synthesized mediators include prostaglandin D₂, leukotriene D₄, and platelet activating factor. Crucial actions of the mediators include an abrupt increase in vascular permeability, vascular smooth muscle relaxation, and bronchial smooth muscle contraction. Anaphylaxis can be classified into immunologic, nonimmunologic, or idiopathic based on the associated mechanism. For example, immunologic causes of anaphylaxis are those mediated by immunoglobulin E (IgE) antibodies acting through the FcεR I (foods, insect venom, 32 β-lactam antibiotics), whereas non-IgE immunologic anaphylaxis is mediated without the presence of anti-allergen IgE antibodies or via FcεRI activation (radiographic contrast material). Nonimmunologic anaphylaxis involves mast cell mediator release such as occurs with exercise or with cold temperature exposure, or from medications such as opioids or vancomycin. Idiopathic anaphylaxis involves mast cell activation (acutely elevated urine histamine or serum tryptase) and activated lymphocytes. Because anaphylaxis is a medical emergency, the drug of choice is epinephrine, not H₁ antihistamines or H₂ receptor antagonists.

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Anaphylaxis is a sudden onset, immediate reaction that is potentially fatal.¹ Most patients do not succumb from anaphylaxis but when they do, in half the cases, death occurs within the first hour after onset of anaphylaxis.² From a pathophysiologic basis, fatalities can be from asphyxiation from laryngeal or oropharyngeal swelling, cardiovascular collapse from hypotensive shock, cardiac arrest, or acute severe bronchoconstriction that causes respiratory failure and arrest.² When any one of the following three criteria is present, the diagnosis of anaphylaxis is considered “highly likely”³:

1. Acute onset of an illness (over minutes to hours) that involves skin (generalized hives), mucosal tissue (swollen lips, tongue, uvula), or both, and at least one of the following: (1) respiratory compromise, or (2) reduced blood pressure or associated symptoms of end organ dysfunction (collapse, syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen (minutes to sev-

eral hours): (1) involvement of the skin mucosal tissue (generalized hives; swollen lips, tongue, or uvula), (2) respiratory compromise (acute dyspnea, wheezing, stridor, hypoxemia), (3) reduced blood pressure or associated symptoms (collapse, syncope), or (4) persistent gastrointestinal symptoms (abdominal cramping, vomiting).

3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours): for infants, age-specific declines or >30% decrease; for adults, systolic blood pressure < 90 mm Hg or >30% decrease from a patient’s baseline.

Anaphylaxis can be classified into immunologic, nonimmunologic, or idiopathic based on the associated mechanism.⁴ Immunologic causes of anaphylaxis are those mediated by IgE antibodies that act through the FcεR I on mast cells and/or basophils, whereas non-immunologic anaphylaxis is mediated without the presence of anti-allergen IgE antibodies or *via* FcεRI activation.⁴ Idiopathic anaphylaxis involves mast cell activation (acutely elevated urine histamine or serum tryptase) and activated lymphocytes.⁵ Use of the term “anaphylactoid,” which refers to the types of non-IgE-mediated anaphylaxis, such as with radiographic contrast materials, is not currently recommended. Such reactions are categorized as nonimmunologic anaphylaxis.⁴

Some examples of non-IgE immunologic anaphylaxis, besides radiographic contrast material (with few exceptions), are attributable to dextran and oversul-

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fated chondroitin sulfate (a contaminant in heparin), which caused activation of complement-derived anaphylatoxins, C3a and C5a, and bradykinin from the contact system.⁵ Nonimmunologic anaphylaxis involves mast cell mediator release such as occurs with exercise or with cold temperature exposure, or from medications such as opioids or vancomycin.

Type I immediate or IgE-mediated reactions are discussed by Dispenza within this syllabus, and focus on the classification of hypersensitivity disorders.⁶ Causes of IgE-mediated immunologic anaphylaxis include foods such as eggs, milk, peanuts, soy, tree nuts, finned fish, and shellfish^{7,8}; stings or bites from insects⁹; medications such as penicillins and cephalosporins¹⁰; allergen immunotherapy injections and latex^{11,12}; some food additives (e.g., spices), bee pollen, and colorants (carmine)¹³; dust mites that contaminated wheat used for baked goods (beignets); and nematode (*Anisakis simplex*) contamination of mackerel.

Exercise-induced anaphylaxis (EIA) is a unique subset of anaphylactic reactions, of which there are three main types: (1) food specific, (2) postprandial, and (3) food independent. Patients with food-specific EIA have symptoms when exercising within 4 to 6 hours after ingestion of a particular food. These patients nearly always have positive skin test or *in vitro* test result to the specific food. The mechanism of this type of reaction is poorly understood but is thought to be IgE mediated and fairly reproducible, which means that ingestion of a particular food followed (or preceded) by exercise may result in anaphylaxis; however, consumption of the food independent of exercise does not produce symptoms nor does exercise alone. In postprandial and food-independent EIA, patients develop anaphylaxis after ingestion of food followed by exercise or after exercise alone. These reactions often are not reproducible, and varying degrees of exercise may precipitate a reaction. Treatment of patients with the food-specific or postprandial EIA entails avoidance of food within 6 hours of exercise. All patients with EIA should carry self-injectable epinephrine and exercise with a "buddy" who knows about the patient's condition and can administer epinephrine if needed.

When there is activation of mast cells and basophils in anaphylaxis, chemical mediators are detectable.¹⁴ The preformed mediators from mast cells include histamine, tryptase, carboxypeptidase A, and proteoglycans (heparin, chondroitin sulfates). Newly synthesized mediators include prostaglandin D₂, leukotriene D₄, and platelet activating factor. Crucial actions of the mediators include an abrupt increase in vascular permeability, vascular smooth muscle relaxation, and bronchial smooth muscle contraction.

A focused history is needed to diagnose anaphylaxis. The temporal relation of anaphylaxis after a specific

trigger, such as the ingestion of foods or medications, should be ascertained because the majority of these reactions occur within minutes to hours after exposure. Most reactions occur within 2 hours, although protracted and delayed anaphylaxis can occur, but both are rare. Think of a "rule of 2s" for anaphylaxis, which implies that reactions usually begin within 2 minutes to 2 hours after injection, infusion, ingestion, contact, or inhalation.

Laboratory tests can be considered according to the clinical status. In the acute setting, serum tryptase can be obtained in the first 6 hours but, ideally, from 15 minutes to 3 hours after onset. (A spot sample of urine might be obtained if there is access to an assay for histamine or a metabolite, N methyl histamine.) In the office setting, when the patient is asymptomatic, a serum tryptase can be obtained to exclude indolent systemic mastocytosis. Skin testing can be performed for any suspected foods, some medications, and stinging or biting insect venoms.¹⁵ For patients who have experienced angioedema, complement factor C4 is the critical screening test to exclude hereditary angioedema or acquired C1 inhibitor deficiency syndrome.¹⁶ A normal value excludes these two conditions. It remains uncertain how to diagnose type III hereditary angioedema because complement concentrations are normal and tests for activation of Factor XII are not widely available.

The differential diagnosis of anaphylaxis includes syncope (such as a fainting or vasovagal syncope immediately after an injection of a potential allergen); acute severe asthma with facial erythema and swelling just before a patient has a respiratory arrest from asthma¹⁷; cardiac arrhythmia or flash pulmonary edema after injection of radiographic contrast material; systemic capillary leak syndrome (extreme capillary hyperpermeability that occurs over several hours, with marked hypotension and hemoconcentration, often with monoclonal gammopathy); panic attack; neurologic-based seizure in the setting of an infusion of an antibiotic or radiographic contrast material; indolent systemic mastocytosis; urticaria pigmentosa; vocal cord dysfunction; a postprandial episode of poisoning from spoiled fish that harbored histamine-generating bacteria⁸; Munchausen's stridor (production of loud or terrifying sounds mimicking stridor but without organic cause); and undifferentiated somatoform, also known as somatic symptom idiopathic anaphylaxis (patient report of repeated symptoms consistent with anaphylaxis such as stridor, syncope, wheezing, dyspnea, generalized flushing, urticaria but with no objective data).¹⁸ These patients often are resistant to co-operating when asked for records and often do not respond to IA treatment. Munchausen anaphylaxis is true anaphylaxis that has been induced deliberately either by the subject (ingestion of aspirin or a food in a subject known to be allergic to

such) or by proxy (parent or caregiver to subject). The perpetrator-patient lies when queried about the ingestion of a known allergen.¹⁸

Anaphylaxis is a medical emergency, and the only accepted immediate first-line treatment is epinephrine, not H₁ antihistamines and H₂ receptor antagonists. Epinephrine dosing is 0.01 mg/kg (0.3 with a maximum of 0.5 mg for any patient. Epinephrine 1:1000 dilution (1 mg/ml) should be used for anaphylaxis administered intramuscularly in any patient suspected of having anaphylaxis and should be repeated if necessary, as frequently as every 5–15 minutes. In such a case, emergency assistance should be sought. There is evidence that, in 17% of cases of food anaphylaxis, a second dose of epinephrine may be necessary.¹⁹ An H₁ antihistamine and corticosteroid also should be administered because the former can relieve some symptoms and the latter may reduce or prevent a late biphasic reaction. Patients with anaphylaxis should be instructed on how and when to self administer epinephrine, such as in patients with peanut or tree nut anaphylaxis, EIA, or idiopathic anaphylaxis, and in patients with stinging or biting insect anaphylaxis. Self-injectable epinephrine devices contain autoinjectors with 0.10, 0.15, or 0.30 mg or a device with an autoinjector.

For idiopathic anaphylaxis^{18,20} or non-IgE immunologic anaphylaxis from radiographic contrast material,²¹ corticosteroid treatment has been found to be effective in reduction of either repeated episodes of idiopathic anaphylaxis or immediate reactions to radiographic contrast material. In the latter case, pretreatment of patients at risk with prednisone 50 mg orally at –13 hours, –7 hours, and –1 hour, along with diphenhydramine 50 mg at –1 hour before radiographic contrast material infusion has reduced the incidence of repeated anaphylactic reactions to approximately 0.5%.²¹

It is advisable that any patients who experience anaphylaxis be evaluated by an allergist/immunologist. Some specific areas of expertise include the confirmation of the diagnosis and determination of the level of risk of future episodes, advice on avoidance and cross-reacting allergens, reassurance about and teaching when to self-inject epinephrine, clarification if immunotherapy for stinging or biting insect anaphylaxis is indicated, recommending empiric treatment of patients with idiopathic anaphylaxis, and being a resource for patients who otherwise may live in fear of the next episode.

IMMUNOLOGY

- The preformed mediators of anaphylaxis include neutral proteases, some of which activate other inflammatory cascades, such as the kinin system, che-

motactic factors, histamine, and proteoglycans (heparin).

- Newly synthesized mediators include prostaglandin D₂, leukotriene D₄, and platelet activating factor. These are derived from lipids, *e.g.*, arachidonic acid. Cytokines that are newly generated include tumor necrosis factor (TNF) α .
- Susceptibility factors for anaphylaxis may include decreased levels of platelet activating factor acetylhydrolase, increased baseline histamine concentrations, and low serum angiotensin-converting enzyme activity.

CLINICAL PEARLS

- An anaphylactic reaction should be suspected, diagnosed, and treated with epinephrine (for adults, 0.3–0.5 mg; for children, at 0.01 mL/kg, up to 0.3 mg) intramuscularly in the vastus lateralis muscle to prevent further clinical deterioration. Let the patient “teach back” when and how to self administer epinephrine.
- A focused history is important in attempting to identify the cause of anaphylaxis. If a cause is found, then the agent should be avoided.
- An emergency regimen, including self-injectable epinephrine, prednisone, and cetirizine or levocetirizine, should be carried by patients with idiopathic anaphylaxis. In addition, an emergency action plan that outlines when to use the recommended treatment should be provided to the patient.
- An atopic history is associated with increased risk of anaphylaxis from latex, exercise, radiographic contrast media, and foods, and that which is idiopathic. (Note the absence of penicillin and stinging insects.)

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