Anaphylaxis

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Anaphylaxis occurs commonly in community settings. The rate of occurrence is increasing, especially in young people. Understanding potential triggers, mechanisms, and patient-specific risk factors for severity and fatality is the key to performing appropriate risk assessment in those who have previously experienced an acute anaphylactic episode. The diagnosis of anaphylaxis is based primarily on clinical criteria and is valid even if the results of laboratory tests, such as serum total tryptase levels, are within normal limits. Positive skin test results or increased serum specific IgE levels to potential triggering allergens confirm sensitization but do not confirm the diagnosis of anaphylaxis because asymptomatic sensitization is common in the general population. Important patient-related risk factors for severity and fatality include age, concomitant diseases, and concurrent medications, as well as other less well-defined factors, such as defects in mediator degradation pathways, fever, acute infection, menses, emotional stress, and disruption of routine. Prevention of anaphylaxis depends primarily on optimal management of patient-related risk factors, strict avoidance of confirmed relevant allergen or other triggers, and, where indicated, immunomodulation (eg, subcutaneous venom immunotherapy to prevent Hymenoptera sting–triggered anaphylaxis, an underused, potentially curative treatment). The benefits and risks of immunomodulation to prevent food-triggered anaphylaxis are still being defined. Epinephrine (adrenaline) is the medication of first choice in the treatment of anaphylaxis. All patients at risk for recurrence in the community should be equipped with 1 or more epinephrine autoinjectors; a written, personalized anaphylaxis emergency action plan; and up-to-date medical identification. Improvements in the design of epinephrine autoinjectors will help to optimize ease of use and safety. Randomized controlled trials of pharmacologic agents, such as antihistamines and glucocorticoids, are needed to strengthen the evidence base for treatment of acute anaphylactic episodes. (J Allergy Clin Immunol 2010;125:S161-81.)

Key words: *Anaphylaxis, allergic reaction, mast cell, basophil, IgE, Fc∈RI, histamine, tryptase, food allergy, medication allergy, venom allergy, epinephrine, adrenaline, H_1-antihistamine*

Abbreviations used
CNS: Central nervous system
COPD: Chronic obstructive pulmonary disease
CVD: Cardiovascular disease
NSAID: Nonsteroidal anti-inflammatory drug
OSCS: Oversulfated chondroitin sulfate
Siglec: Sialic acid-binding immunoglobulin-like lectin

This chapter focuses mainly on anaphylaxis in community settings. It provides an overview of epidemiology, pathogenesis, clinical diagnosis, confirmation of the triggers, and long-term management, including prevention of recurrences and emergency preparedness. It highlights recent advances published since the review of anaphylaxis published in the 2008 Mini-Primer.[1]

Anaphylaxis is currently defined as a serious allergic reaction that is rapid in onset and might cause death.[2] The diagnosis is considered to be highly likely when any one of 3 clinical criteria is fulfilled (Table I)[2]; the presence of reduced blood pressure or shock is not necessarily required. The terms anaphylactoid or pseudoanaphylaxis are no longer recommended for use.

EPIDEMIOLOGY

The lifetime prevalence of anaphylaxis from all triggers is estimated to be 0.05% to 2%.[3] The rate of occurrence appears to be increasing, especially in young people.[4-14] Accurate community-based population estimates are difficult to obtain because of underdiagnosis, underreporting, and miscoding, as well as use of different definitions of anaphylaxis and different methods of case ascertainment in the different populations studied.[15-17] Representative studies of anaphylaxis from all triggers in the general population are summarized in Table II.[3-12]

It is likely that anaphylaxis is underdiagnosed, especially if it is a patient's first episode, if there is a hidden or previously unrecognized trigger, or if symptoms are mild, transient, or both.[15] Patients might not be able to describe their symptoms if awareness, cognition, and judgment are impaired or if they are dyspneic or becoming unconscious. The presence of itching, flushing, hives, and/or angioedema is helpful in making the diagnosis; however, skin and mucosal symptoms and signs are absent or unrecognized in 10% to 20% of all anaphylactic episodes. Hypotension sometimes goes undocumented, especially in infants and young children.[15]

Underreporting and miscoding of anaphylaxis remain important issues.[15] Only 1% of emergency department visits for acute systemic allergic reactions receive the diagnosis of anaphylaxis; many are called acute allergic reactions, or acute hypersensitivity reactions.[16,17] In a recent nationally representative probability sample from hospital emergency departments in the United States, 57% of likely episodes of anaphylaxis to food did not receive an emergency department diagnosis of anaphylaxis.[13]

Death from anaphylaxis is considered rare[8,14,18-23]; however, underreporting of fatalities likely occurs for a variety of reasons.

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TABLE I. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, and swollen lips-tongue-uvula) AND at least 1 of the following:
A. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
B. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
A. Involvement of the skin–mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
B. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
C. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
D. Persistent gastrointestinal symptoms (eg, cramping abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
A. Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP*
B. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Adapted from reference 2.

BP, Blood pressure; *PEF*, peak expiratory flow.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. Normal heart rate ranges from 80 to 140 beats/min at age 1 to 2 years, from 80 to 120 beats/min at age 3 years, and from 70 to 115 beats/min after age 3 years. Infants and young children are more likely to have respiratory compromise than hypotension or shock.

These include incomplete clinical information, including lack of a history of concomitant diseases, concurrent medications, and drug or alcohol abuse, and absence of a detailed death scene investigation (eg, interview of witnesses).[22] Initial symptoms and signs in fatal episodes of anaphylaxis commonly include respiratory distress rather than circulatory collapse.[21] The autopsy findings might be nonspecific, and laboratory test results might be within normal limits; however, this cannot be used to exclude the diagnosis of anaphylaxis.[20-22]

PATHOGENESIS

Triggers of anaphylaxis

Triggers of anaphylaxis in the community are listed in Table III.[24-69] In many countries the most common food triggers are peanut, tree nuts, shellfish, fish, milk, egg, and sesame[24-26]; however, there are important geographic variations, and in some countries other foods, such as chestnut, rice, buckwheat, or chickpea, predominate.[27] Any food can potentially trigger anaphylaxis, including previously unrecognized triggers, such as quinoa,[28] dragon fruit,[29] or some fresh red meats containing carbohydrates.[30] Food triggers can be hidden (eg, substituted foods, cross-reacting foods, and cross-contacting foods).[26] Food triggers also include additives, such as spices, vegetable gums, and colorants (eg, carmine [cochineal])[31]; contaminants, such as dust mites[32]; and parasites, such as the live seafish nematode *Anisakis simplex*.[33]

Medication-triggered anaphylaxis can occur in patients of any age; however, it is particularly common in middle-aged and older adults. Antibiotics, especially β-lactam antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, and other agents, are often implicated, as are chemotherapeutic agents.[24,25,34-40] Newly recognized medication triggers include loperamide[37]; contaminants in medications, such as oversulfated chondroitin sulfate (OSCS)-contaminated heparin[38]; seemingly innocuous substances, such as vitamins and supplements containing folic acid[39]; and herbal treatments.[40] Perioperative medications,[41] iodinated contrast media[42] and medical dyes are becoming increasingly relevant triggers in community settings. Biological agents that trigger anaphylaxis include monoclonal antibodies (mAbs), such as cetuximab, infliximab, and omalizumab,[43-45] and allergens used in immunotherapy.[46,47] Vaccines to prevent infectious diseases seldom trigger anaphylaxis. If they do, the culprit is seldom the immunizing agent itself.[48-51] Rather, it is likely to be a protein excipient, such as gelatin or egg, or rarely another excipient, such as dextran.[48,51]

Venom from stinging insects (Order Hymenoptera, family Apidae [eg, honeybees]; family Vespidae [eg, yellow jackets, yellow hornets, white-faced hornets, and paper wasps]; and family Formicidae [eg, ants])[52-54] or, less commonly, saliva from biting insects (flies, mosquitoes, ticks, kissing bugs, and caterpillars) can trigger anaphylaxis.[54-57]

In health care settings ongoing efforts to prevent anaphylaxis from natural rubber latex have been relatively successful; however, in the community anaphylaxis is still occasionally reported after direct exposure to latex-containing gloves, condoms, rubber-handled racquets, balloons, latex-padded play pits, infant pacifiers, and bottle nipples. It also potentially occurs after ingestion of foods that cross-react with latex, such as banana, kiwi, papaya, avocado, potato, and tomato.[58]

Occupational allergens,[25] seminal fluid,[59] and, rarely, inhaled allergens, such as animal dander[60] or grass pollen, can also trigger anaphylaxis; some systemic absorption of these allergens likely occurs.

In addition, nonimmune perturbations of mast cells and basophils might lead to anaphylaxis. This potentially occurs after exercise[61,62] and/or exposure to cold air or water, heat, sunlight/UV radiation, insect venom constituents,[52,53] radiocontrast media,[34,42] ethanol, and some medications, including opioids, COX-1 inhibitors, and vancomycin.[24,25,34] In patients with exercise-induced anaphylaxis, food is a common cotrigger[61]; it is hypothesized that in these patients, food-sensitized immune cells are relatively innocuous until they are redistributed into the systemic circulation from gut-associated deposits during exertion.[62]

Idiopathic anaphylaxis is diagnosed when no triggers can be identified based on history, skin tests are negative, and serum specific IgE levels are absent or undetectable. Before this diagnosis is made, however, the possibility of a hidden or previously unrecognized trigger should be ruled out,[24,28-30,32,33,37-40,57] and the patients should be evaluated for mastocytosis and clonal mast cell disorders.[63-67]

Mechanisms

The underlying pathogenesis of human anaphylaxis commonly involves an immunologic mechanism in which IgE is synthesized