Guidelines

for

The Management of Anaphylaxis

By

Dr. Sinan Butrus
F.I.C.M.S
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Setting Clinical and Professional Excellence

Anaphylaxis is a serious life-threatening generalized or systemic hypersensitivity reaction that is rapid in onset and might cause death.

Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when ***any one of the following three criteria*** is fulfilled:

Criterion 1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (generalized urticaria, itching or flushing, swollen lips-tongue-uvula) *AND AT LEAST ONE OF THE FOLLOWING*:

A) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

B) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)

OR

Criterion 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 (e.g., generalized urticaria, itch-flush, swollen lips-tongue-uvula)

B) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow PEF, hypoxemia)

C) Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

D) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

OR

Criterion 3 Reduced blood pressure after exposure to *known allergen for that patient* (minutes to several hours)

A) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure

B) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as

less than 70 mm Hg from 1 month - 1 year,

less than 70 mm Hg +[2 × age]) from 1 - 10 years,

less than 90 mm Hg from 11 - 17 years.

Normal heart rate ranges is defined as

from 80-140 beats/min at age 1-2 years;

from 80-120 beats/min at age 3 years;

from 70-115 beats/min after age 3 years.

Infants are more likely to have respiratory compromise than hypotension or shock, and in this age group, shock is more likely to be manifest initially by tachycardia than by hypotension. Target organ involvement is variable. Typically, symptoms occur in 2 or more body systems: skin and mucous membranes, upper and lower respiratory tract, gastrointestinal tract, cardiovascular system and central nervous system. In certain circumstances, anaphylaxis can be diagnosed when only one body system is involved.

Skin, subcutaneous tissue and mucosa

Flushing, itching, urticaria (hives), angioedema, morbilliform rash, pilor erection.
Periorbital itching, erythema and edema, conjunctival erythema, tearing.
Itching of lips, tongue, palate, external auditory canals; and swelling of lips, tongue & uvula.
Itching of genitalia, palms and soles.

Respiratory

Nasal itching, congestion, rhinorrhea, sneezing
Throat itching and tightness, dysphonia, hoarseness, stridor, dry staccato cough
Lower airways: increased respiratory rate, shortness of breath, chest tightness, deep cough, wheezing/bronchospasm, decreased peak expiratory flow, cyanosis, respiratory arrest

Gastrointestinal

Abdominal pain, nausea, vomiting (stringy mucus), diarrhea, dysphagia

Cardiovascular system

Chest pain, tachycardia, bradycardia (less common), arrhythmias, palpitations
Hypotension, feeling faint, urinary or fecal incontinence, shock, cardiac arrest

Central nervous system

Aura of impending doom, uneasiness (in infants and children, sudden behavioral change, e.g. irritability, cessation of play, clinging to parent); throbbing headache (pre-epinephrine), altered mental status, dizziness, confusion, tunnel vision

Others

Metallic taste in the mouth. Cramps and bleeding due to uterine contractions in females

*Sudden onset of symptoms and signs is characteristic of anaphylaxis.

*The purpose of the above listing signs and symptoms is to aid in prompt recognition of the onset of anaphylaxis and to indicate the possibility of rapid progression to multi-organ system involvement, not to grade severity.

*Skin and mucosal symptoms are reported in 80-90% of patients with anaphylaxis, respiratory tract involvement in 70%, gastrointestinal tract involvement in 45%, cardiovascular system involvement in 45% & central nervous system involvement in 15%.

*Symptom patterns vary from one patient to another, and even in the same patient, from one anaphylactic episode to another. Only a few symptoms might be present.

*Anaphylaxis can sometimes be difficult to diagnose. Patients with concomitant impaired vision or hearing, neurologic disease, psychiatric illness, such as depression, substance abuse, autism spectrum disorder, attention deficit hyperactivity disorder or cognitive disorders might have diminished awareness of anaphylaxis triggers and symptoms.

*At any age, concurrent use of CNS-active medications such as sedatives, hypnotics, antidepressants, and first-generation sedating H1-antihistamines can interfere with recognition of anaphylaxis triggers and symptoms and with the ability to describe symptoms. In patients with concomitant medical conditions, for example, asthma, chronic obstructive pulmonary disease, or congestive heart failure, symptoms and signs of these diseases can also cause confusion in the differential diagnosis of anaphylaxis.

*Anaphylaxis can present as an acute coronary syndrome (ACS) (angina, myocardial infarction, arrhythmias) before, or in the absence of, epinephrine injection. This potentially occurs in patients with known coronary artery disease, those in whom subclinical coronary

artery disease is unmasked, and, due to transient vasospasm, those in whom no cardiovascular abnormalities can be detected after recovery from anaphylaxis

Risk Factors for Severe or Fatal Anaphylaxis

They include age-related factors, concomitant diseases such as asthma and other chronic respiratory diseases, cardiovascular diseases, mastocytosis or clonal mast cell disorders and severe atopic disease e.g, allergic rhinitis.

Concurrent medications such as β-adrenergic blockers and angiotensin-converting enzyme (ACE) inhibitors might also increase the risk

Severe or fatal anaphylactic episodes might be associated with defects in mediator degradation pathways resulting in elevated baseline levels of tryptase, histamine, bradykinin (because of low serum ACE activity) and platelet-activating factor (PAF) (because of low serum PAF acetylhydrolase activity).

Co-factors that amplify or augment anaphylaxis like exercise-induced anaphylaxis, concomitant ingestion of a specific food; ethanol or NSAID drugs that enhances intestinal permeability and allergen absorption. Amplifying co-factors also include upper respiratory tract infections or other acute intercurrent infections, fever, emotional stress, travel or other disruption of routine activity and premenstrual status in females.

Multiple factors and co-factors might contribute to some anaphylactic episode.

Idiopathic anaphylaxis is diagnosed when no trigger can be identified despite a detailed history of the episode, allergen skin tests, measurement of serum IgE levels to obvious and potentially hidden allergen triggers and, if indicated in selected patients, medically supervised, graded challenge/provocation tests. The diagnosis of idiopathic anaphylaxis provides an opportunity to identify previously unrecognized triggers; it also provides an opportunity to identify patients with mastocytosis and clonal mast cell disorders through clinical history, physical examination, elevated baseline serum tryptase levels and additional tests as indicated.

Biphasic anaphylaxis defined as a recurrence of symptoms that develops following the apparent resolution of the initial anaphylactic episode with no additional exposure to the causative agent. They typically occur within 12 hours after resolution of the initial symptoms, although recurrences up to 72 hours later have been reported.

Protracted anaphylaxis defined as an anaphylactic reaction that lasts for hours, days, or even weeks in extreme cases**.**

Delayed anaphylaxis rarely, the onset of anaphylaxis will be delayed, i.e., beginning hours rather than minutes after exposure to the causative agent

Diagnostic pitfalls: Anaphylaxis is not always easy to recognize clinically. The patterns of target organ involvement are variable and may differ among individuals, as well as among episodes in the same individual. Anaphylaxis is likely underdiagnosed & under-reported for:

• Some health care professionals remain reluctant to diagnose anaphylaxis in the absence of hypotension or shock, even though changes in blood pressure (BP) are not required for the diagnosis according to criterion 1 or criterion 2. In fact, it is important to recognize anaphylaxis in its earlier stages because once shock has developed, anaphylaxis may be much more difficult to treat.

• Hypotension may go undetected when measured very early in the course of the episode (when compensated by reflex tachycardia), when the initial BP measurement is obtained after epinephrine administration or when an inappropriately small BP cuff is used.
• Age-appropriate standards for normal BP must be used for children and infants.
• Many of the dramatic physical signs associated with hypoxia and hypotension in anaphylaxis are nonspecific, such as dyspnea, stridor, wheeze, confusion, collapse, unconsciousness, and incontinence.
• Skin symptoms and signs (such as hives, itching, flushing, and angioedema), which are helpful in making the diagnosis, are absent or unrecognized in up to 20% of all episodes especially if a patient has taken an H_1 antihistamine. They may also be missed if an individual cannot describe itching or is not undressed and fully examined during the episode or in patients who are draped during surgery.
• Anaphylaxis may be difficult to recognize or may not be considered in certain clinical situations as in dramatic physiologic shifts conditions (e.g., hemodialysis, surgery, childbirth) or inability of the patient to communicate the presence of early symptoms (e.g. if anesthetized, sedated, or unconscious) impedes prompt recognition of anaphylaxis.
• Anaphylaxis in a known asthmatic may be mistaken for an asthma exacerbation if accompanying skin symptoms and signs, such as itching or hives, mucosal, tongue, or lip edema, or dizziness suggestive of impending shock, are overlooked.
• Patients experiencing their first episode may not recognize the symptoms as anaphylaxis. As a result, they may not report symptoms fully or may focus on one prominent symptom (e.g., unless specifically asked, a patient presenting with vomiting may not report that the episode was preceded by diffuse itching).
• The above factors are further compounded in patients with neurologic & psychiatric problems or those who take medications (sedating H_1 antihistamine, ethanol, or antipsychotic medications).

Laboratory Tests

These tests are not universally available, not performed on an emergency basis and not specific for anaphylaxis.

<u>Total tryptase</u> (pro, pro', and mature forms of alpha/beta tryptases)

Obtain blood sample within 15 minutes to 3 hours of symptom onset,

If tryptase level is > 11.4 ng/mL in baseline serum, the diagnosis of mastocytosis or clonal mast cell disorder should be considered;

If tryptase level is higher during the acute anaphylactic episode than in baseline serum, the diagnosis of anaphylaxis is confirmed;

Increased serum tryptase levels often support the clinical diagnosis of anaphylaxis from insect stings or injected medications and in patients who are hypotensive; however, levels are often within normal limits in patients with anaphylaxis triggered by food and in those who are normotensive.

Serial measurement of tryptase levels during an anaphylactic episode, and measurement of a baseline level after recovery are reported to be more useful than measurement at only one point in time.

Normal levels of either tryptase or histamine do not rule out the clinical diagnosis of anaphylaxis.

Histamine

Obtain blood sample within 15 minutes to 1 hour of symptom onset

Measure histamine and its metabolite N-methylhistamine in a 24-hour urine sample

Others

Specific laboratory tests might be needed to rule out carcinoid syndrome, paradoxical response to a pheochromocytoma

Differential Diagnosis of Anaphylaxis

Common diagnostic dilemmas

Acute asthma. Syncope (faint). Anxiety/panic attack. Acute generalized urticaria. Aspiration of a foreign body. Cardiovascular (myocardial infarction, pulmonary embolus**)**

Flush syndromes

Peri-menopause. Carcinoid syndrome. Autonomic epilepsy. Thyroid Medullary carcinoma

Nonorganic Disease

Vocal cord dysfunction. Hyperventilation. Neurologic events (seizure, cerebrovascular event). Psychosomatic episode

Shock

Hypovolemic. Cardiogenic

Management of Anaphylaxis

1. Remove exposure to the trigger if possible; discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms
2. Assess circulation, airway, breathing, mental status, skin, and body weight (mass)
3. Inject epinephrine (adrenaline) intramuscularly in the mid-anterolateral aspect of the thigh, 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution, to a maximum of 0.5 mg in adult (0.3 mg in child); record the time of the dose and repeat it in 5-15 minutes, if needed; most patients respond to 1 or 2 doses
4. Place patient on the back or in a position of comfort if there is respiratory distress and/or vomiting; elevate the lower extremities; fatality can occur within seconds if a patient stands or sits suddenly
5. Give high flow supplemental oxygen (6-8 L/min) by face mask or oro-pharyngeal airway
6. Establish intravenous access using needles or catheters with wide-bore cannulae (14 or 16 gauge for adults). When indicated, give 1-2 litres of 0.9% isotonic saline rapidly (e.g. 5-10 mL/kg in the first 5-10 minutes to an adult; or 10 mL/kg to a child)
7. Second line medications

- H_1-antihistamine IV, chlorpheniramine 10 mg in adult), (2.5-5 mg in children) or diphenhydramine 25-50 mg in adult) (1 mg/kg, maximum 50 mg in children)
- ß2-adrenergic agonist, salbutamol (albuterol) solution, 2.5 mg/3 mL or 5 mg/3 mL in adult, (2.5 mg/3 mL in children) given by nebulizer and face mask
- Glucocorticoids IV, hydrocortisone 200 mg in adult), (maximum 100 mg in children); or methylprednisolone 50-100 mg in adult (1 mg/kg, maximum 50 mg in children)
- H_2-antihistamine IV, ranitidine 50 mg in adult (1 mg/kg, maximum 50 mg in children)

8. When indicated at any time, prepare to initiate cardiopulmonary resuscitation with continuous chest compressions which should be performed at a rate of 100-120/minute and a depth of 5-6 cm.

In children, the rate should be at least100 compressions/minute at a depth of 5 cm (4 cm in infants).

9. At frequent and regular intervals, monitor patient's blood pressure, cardiac rate and function, respiratory status and oxygenation and obtain electrocardiograms;

Recommendations at Time of Discharge

*Epinephrine/adrenaline auto-inject

*Anaphylaxis emergency action plan (personalized, written)

*Medical identification (e.g., bracelet, wallet card)

*Before discharge, consider assessing sensitization to allergens suggested in the history of the acute episode, by measuring serum IgE levels to relevant allergen(s),

*Confirm allergen sensitization using skin tests 3-4 weeks after the episode,

*Challenge/provocation tests might be needed in some patients in medically supervised, graded challenge/provocation test conducted in an appropriately equipped healthcare center in order to assess risk of future anaphylactic episodes

*Guidance about avoiding specific trigger allergin

*Idiopathic anaphylaxis: for frequent episodes, consider glucocorticoid and H_1-antihistamine prophylaxis for 2-3 months with/out relevant immunomodulation (prophylactic omalizumab)

*Optimal management of asthma and other concomitant diseases, evaluate the benefits and risks of medications such as beta-blockers or ACE inhibitors if needed.

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