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Guidelines in focus

Anaphylaxis: diagnosis

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Description of the method for collecting evidence

In order to elaborate this guideline, the following primary and secondary electronic databases were consulted: MEDLINE, Cochrane, Central Register of Controlled Trials – CENTRAL, Embase, and Lilacs. The search for evidence was based on real clinical settings, MeSH terms/descriptors and the following isolated terms were used: Anaphylaxis; Allergens; Anaphylatoxins; Mast Cells; Adult; Chymases; Serine Endopeptidases. The articles were selected after critical evaluation of scientific evidence strength by specialists from the participant societies, and the best publications were used for the recommendations. Recommendations were elaborated after a discussion within the group. The entire guideline was reviewed by an independent group specialized in evidence-based clinical guidelines.

Degrees of recommendation and strength of evidence

- **A:** Experimental or observational studies of higher consistency.
- **B:** Experimental or observational studies of lesser consistency.
- **C** Case reports (non-controlled studies).
- **D:** Opinions without critical evaluation, based on consensus, physiological studies, or animal models.

Objective

Anaphylaxis is a potentially fatal allergic reaction that can be triggered by various etiological agents. Clinical suspicion, along with the identification of etiology, is a fundamental point for safe and adequate approach of patients during an acute event. The etiology of anaphylaxis is varied according to age and especially to the area in which the reaction occurs. In this guideline, the main symptoms and clinical signs are discussed, in order to allow the diagnosis of an anaphylaxis event; its main etiological agents are also discussed.

Introduction

Anaphylaxis is known as a severe and acute allergic reaction presenting a sudden onset and rapid evolution, which is potentially fatal[1](D). The target organs involved include the skin and mucosae membranes (80% to 90% of episodes), respiratory system (70%), gastrointestinal tract (30% to 40%), cardiovascular system (10% to 45%), and central nervous system (10% to 15%)[1](D).

The cutaneous-mucosal manifestations consist of localized or diffused erythema, pruritus, rash, nettle-rash, and/or angioedema. Cutaneous manifestations are the most frequent, and usually arise early in anaphylaxis. In the respiratory system, pruritus and nasal congestion, sneezing, pruritus or tightening of the throat, disphony, hoarseness, stridor in the throat, coughing, wheezing, or dyspnea may occur. Manifestations in the gastrointestinal tract include nausea, vomiting, cramping, and diarrhea. The involvement of cardiovascular system may cause hypotension, whether or not presenting syncope; tachycardia; and cardiac arrhythmias. The neurological manifestations include cephalea, seizures, and changes in mental state. Other clinical manifestations can also occur, such as feeling of impending doom, uterine contractions, decrease in strength of sphincter muscles, loss of sight, and tinnitus[2](D).

There is an increasing attention concerning the importance of the heart as a target-organ in anaphylaxis. In the healthy human heart, mast cells are present in myocardium and in the intima of coronary arteries. In patients with coronary artery disease, mast cells are found in atherosclerotic lesions, and contribute to atherogenesis. Mast cells mediators, such as histamine, leukotriene C4, and prostaglandin D2 may lead to spasms of coronary arteries[3](D). Thus, anaphylaxis can "unmask" a subclinical coronary disease and may cause myocardial infarction and/or arrhythmia, regardless of adrenaline use.

The anaphylactic reaction usually occurs within seconds or minutes after exposure to a causative agent. However, some reactions can occur later. The episodes of anaphylaxis can have a sudden manifestation and be uniphasic; they may arise late (> 30 minutes), or be biphasic. In biphasic reactions, the immediate phase is followed by a period free of symptoms; posteriorly, the late reaction arises, and signs and symptoms upsurge, regardless of a new exposure to the triggering agent. The late phase occurs within eight to 12 hours after the immediate reaction, and it is present in approximately 20% of anaphylaxis cases. Biphasic reactions are more frequent in food-related anaphylaxis[4](D).

The diagnosis of anaphylaxis is based on defined clinical criteria[5](D). Anaphylaxis is highly likely when one of three criteria described in Box 1 is fulfilled.

1. What are the main triggers of anaphylaxis?

They are variable and dependent on patient's age. Medications, certain foods, and insect venoms (Hymenoptera: bees, wasps, and ants) are the main triggers of anaphylaxis. Other common agents are latex (contained in medical devices, air balloons, condoms, among others) and physical stimulations, such as exercise and cold. Exercise-induced anaphylaxis can occur isolated or associated with previous ingestion of certain foods or medications. In some crises it is not possible to identify the causative agent, thus characterizing idiopathic anaphylaxis[2,6](D) (Box 1).

Analgesic, non-hormonal anti-steroidal drugs and antibiotics are types of medication that frequently cause anaphylaxis. In hospitalized patients, allergic reactions to antibiotics are predominant. In the surgical environment, anaphylactic reactions can be caused by neuromuscular blockers, latex, antibiotics, opiates, and anti-inflammatory drugs[7](C) [2](D). In Brazil there is a prevalence of medication-triggered anaphylaxis, followed by certain types of food and insects[8](C).

The allergic sensitization towards food is dependent on genetic factors and eating habits. In childhood, the most important types of food in anaphylaxis are cow's milk and egg white; for adults, mollusks and crustaceans. Sensitivity to fruits and vegetables presents lower incidence, although it can also induce intense reactions[2,9](D).

The venom of bees, wasps, hornets, and ants can induce severe anaphylactic reactions. The sensitization arises after several contacts in which only local reactions are observed. Systemic reaction to insects is more common in beekeepers and their relatives, farmers and rural residents, rural professionals (veterinarians and agronomists), fruit growers, and outdoor recreationalists[5,10](D).

Latex proteins in medical devices, toys, and condoms can induce severe clinical pictures of anaphylaxis in susceptible people. Atopy is a risk factor for latex sensitization. The clinical picture is more frequent among health care professionals who usually work using gloves, such as surgeons, nurses, and nursing technicians; children bearing spina bifida; and patients who have undergone multiple surgeries[1,6](D). Latex allergens present antigenic determinants, which are found in numerous vegetables. In patients allergic to latex, it is common to observe an evolving sensitization to banana, kiwi, avocado, and cassava, among others[1,6](D).

Physical stimuli such as cold air and physical exercise can activate mast cells and as a result cause anaphylaxis. In recent years, clinical pictures of anaphylaxis were more frequently identified, as they were caused by the association between physical exercise and previous ingestion of certain types of food or medication. Those reactions may be specific for a given type of food or drug, or may arise associated with the ingestion of any type of food or drug.[2,10](D).

Recommendation

There are many etiologic factors that trigger the process of anaphylaxis. Some factors are associated with higher incidence, such as the nature of antigen and the history of atopy. Medicines are the agents that most frequently cause anaphylaxis, and the most common are analgesics, antipyretics, non-hormonal anti-inflammatory, and antibiotics.

2. How can the activation mechanisms of mast cells and basophils help to understand the phases of anaphylactic reactions?

The majority of triggering agents for anaphylaxis are related to the mechanism of immediate hypersensitivity mediated by immunoglobulin E (IgE), which results in the activation of mast cells and basophils[11](B). However, several other immunological and non-immunological mechanisms can also cause the activation of these cells, and trigger acute reactions clinically similar to classical anaphylaxis, mediated by IgE. These mechanisms include the antigen-immunoglobulin G(IgG) complex, activation of the complement system, activation of the coagulation system, direct activation of mast cells and basophils, cytotoxicity, changes in the arachidonic acid metabolism, release of neuropeptides, physical exercises, and cold air and cold water. In some patients, the anaphylactic reactions can simultaneously have more than one active mechanism[10](D).

Clinical experience and observational studies indicate that the main immunological mechanism in allergen-induced anaphylaxis is mediated by IgE. Therefore, based on studies with mice regarding experimental models of anaphylaxis to IgG-mediated penicillin, the possibility of activating basophils by complexes of IgG-allergens has been suggested, in patients with proven anaphylactic reaction to allergens (for instance, penicillin), who do not present evidence for specific IgE sensitization. It is still not clear whether the main effector cells from this way are the macrophages and/or basophils[12,13](D).

The cellular episodes that occur during the anaphylactic reaction involve the activation of tyrosine-kinases and calcium inflow into mast cells and basophils, resulting in a quick release of pre-formed mediators such as histamine, tryptase, carboxypeptidase A3, chymase, and proteoglycans. Later, the activation of phospholipase A2, cyclooxygenase, and lipoxygenase occur, leading to the production of arachidonic

Box 1 – Criteria for diagnosing anaphylaxis.

1. Acute onset of disease (minutes or hours) with involvement of skin, mucosa, or both (for instance, generalized nettle-rash, pruritus or facial erythema, lips-tongue-uvula edema).

And at least one of the following items:

a) Respiratory impairment (dyspnea, wheezing-bronchospasm, stridor, decreased peak expiratory flow, hypoxia).

b) Low blood pressure or symptoms associated with organic dysfunction (for instance, hypotonia [collapse], syncope, incontinence).

2. Two or more of the following symptoms occurring shortly after exposure to a likely allergen for that patient (minutes to hours)

a) Involvement of skin-mucosa (for instance, generalized nettle-rash, pruritus or facial erythema, lips-tongue-uvula edema).

b) Respiratory impairment (dyspnea, wheezing-bronchospasm, stridor, decreased peak expiratory flow, hypoxia).

c) Drop in blood pressure or symptoms associated with organic dysfunction (for instance, hypotonia [collapse], syncope, incontinence).

d) Persistent gastrointestinal symptoms (for instance, persistent abdominal colic, vomiting).

3. Drop in blood pressure after exposure to a known allergen for that patient (minutes to hours):

a) infants and young children: low systolic arterial pressure (age-specific) or a drop in the systolic arterial pressure > 30%

b) Adults: systolic arterial pressure less than 90 mmHg or drop > 30% in basal systolic arterial pressure

acid metabolites, especially leukotrienes and prostaglandins, and a synthesis of platelet activating factor (PAF). In addition, several cytokines are released and synthesized, including IL-6, IL-33, and TNF-α, which take part in the late phase of anaphylaxis[14](D).

Histamine is the critical mediator of symptoms arising in the immediate phase of anaphylaxis. In extracellular medium, histamine is quickly metabolized, presenting a half-life of 30 minutes, which tends to limit its use as activating marker for mast cells and basophils. In anaphylaxis, histamine reaches plasmatic levels in 5 minutes, and remains high for 30 to 60 minutes. Urinary histamine metabolites, including methylhistamine, can be detected up to 24 hours after the initiation of anaphylaxis[15](D).

Tryptase is secreted as an active proteoglycans complex in a large size, limiting its diffusion of the activation site of mast cells to the circulation. Tryptase reaches serum peak levels in 60 to 90 minutes after the initiation of anaphylaxis and remains elevated for up to 5 hours. Tryptase can activate the kallikrein-kinin system, resulting in production of bradykinin and causing angioedema[11](B),[4](D).

Mast cells generate and release icosanoid lipid mediators from cellular membrane phospholipids due to multiple enzymatic stages. Arachidonic acid is cleaved from cellular membrane phospholipids by phospholipase A2, and is subsequently metabolized by cyclooxygenase and lipoxygenase-5, which generate leukotrienes and prostaglandins, respectively. These mediators are released in the immediate phase within 10 minutes; prostaglandin is also synthesized in the late phase, resulting in a new release in 2 to 10 hours after the initial activity. The biological activities of leukotrienes include smooth muscle contraction, increased vascular permeability, vasodilation, mucus secretion, recruitment of inflammatory cells, cytokine productionmodulation, and changes in neuronal transmission[14](D).

In anaphylaxis mediated by IgG, PAF appears to be the main mediator[12](D). PAF is a potent vasoactive amine released by a large variety of cells including mast cells, basophils, endothelial cells, monocytes, and macrophages. Basophils, when stimulated by IgG allergens complexes, release PAF in much higher amounts as compared to other cellular sources of this mediator[12](D). PAF stimulates endothelial cells, resulting in increased vascular permeability; acts on bronchial smooth muscle, causing bronchoconstriction; and takes part in chemotaxis and in eosinophils and neutrophils activation[14](D).

Mast cells and basophils release cytokines and chemokines, which mainly contribute to the late phase of biphasic anaphylactic reaction. The behavior of cytokines and chemokines results in recruitment and activation of cells involved in allergic inflammation, as well as in potentiation of the anaphylactic response. Activated mast cells release IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-16, IL-18, IL-22, IL-33, TNF-α, and GM-CSF. Basophils are the main source of IL-4, IL-13, and chemokines. In anaphylaxis, IL-4 increases the responsiveness of target cells to vasoactive mediator action by three to six times including histamine, PAF, and cysteinic leukotrienes [14](D).

Recommendation

Some studies indicate that the main immunological mechanism involved in induced anaphylaxis, as a consequence of allergenic sensitization, is mediated by production of IgE class specific antibodies, which results in the activation of mast cells and basophils and in a quick release of pre-formed mediators, such as histamine, tryptase, carboxypeptidase A3, chimase, and proteoglycans.

The dosage of mediators can be useful in establishing the diagnosis of anaphylaxis; the laboratory methods used are the dosage of serum tryptase levels, plasmatic histamine, and urinary methylhistamine. The best moment for tryptase dosage is within one or two hours after the initiation of anaphylactic reaction, while for histamine it is between ten minutes and one hour. Histamine urinary metabolites can remain high in urine for up to 24 hours.

3. Which factors increase the risk for anaphylaxis and severe anaphylactic reactions?

Diverse factors can increase the severity of an anaphylactic reaction or interfere in its treatment, thus making it potentially more severe[1,10](D). The quick intravenous infusion of an allergen is associated with risks of more severe reactions. Older age or the presence of pre-existing cardiovascular disease are also risk factors for severe anaphylaxis. The presence of asthma is associated with more severe episodes, especially in reactions caused by allergy to certain types of food[6,16](D).

The concomitant use of β-blocker agents by topic or oral pathways is associated with risks of most severe reactions due to the interference with the treatment of anaphylaxis. Epinephrine applied to individuals using β-blockers can theoretically lead to an isolated alpha-adrenergic effect, resulting in severe hypertension. However, these individuals, when receiving epinephrine for the hypotension caused by anaphylaxis, may experience severe reactions associated with paradoxical bradycardia, deep hypotension, and severe bronchospasm. The difficulty of recovery can occur with both antagonists β-1 and β-2[17](D). Despite this fact, the majority of patients using β-blockers do not have their receptors totally blocked, and epinephrine should not be avoided in these cases.

Other classes of drugs can also act as factors that increase the risk for severe anaphylactic reactions. Angiotensin-converting enzyme (ACE) inhibitors can interfere with the endogenous shock-compensatory mechanism (activation of the rennin-angiotensin-aldosterone system), causing pharynx and tongue edema, with risk of death[18](D). Monoamine-oxidase inhibitors can increase risks from epinephrine by interfering with its degradation.

Recommendation

Advanced age, presence of pre-existing cardiovascular disease, asthma, concomitant use of β-blockers, and use of ACE inhibitors are associated with risk of more severe reactions.

4. What are the features of fatal anaphylaxis clinical picture?

Generally, fatal anaphylactic reactions are characterized by symptoms usually limited to a system. Death can occur by shock or by cardiorespiratory arrest[19](C)[20](D).

Death by shock mainly occurs in young individuals with healthy hearts. Shock is caused by vasodilation with volume redistribution and a drop in venous blood return. Erect posture is favorable to fatal evolution[21](D).

In elderly individuals or in those pre-existing cardiovascular disease, death usually occurs by cardio-respiratory arrest caused by arrhythmia, due to the myocardial action of the soluble mediators released in the anaphylactic reaction. Electrocardiographic changes from myocardial ischemia are usually found in anaphylactic shock and may lead to diagnostic confusion[20](D).

Fatal cases can also occur by cardiorespiratory arrest caused by severe bronchospasm (especially in asthmatic patients), or by edema in the upper airways, leading to suffocation. Fatal anaphylaxis in asthmatic patients is even more related to food allergy. Asphyxiation by edema in the upper airways is more common in reactions to insects stings and types of food than in reaction to drugs[22](D) [23](D).

Recommendation

Anaphylaxis is a severe acute allergic reaction and potentially fatal.

5. How to investigate the cause of anaphylaxis?

Anaphylaxis diagnosis is usually clinical. Generally, the history is characteristic. Sudden onset of signs and symptoms, such as hives, angioedema, diffuse erythema, pruritus, difficulty breathing, nausea, vomiting, abdominal colics, hypotension, bronchospasm, dizziness, or syncope must lead to the suspicion of anaphylactic reaction[10,24](D).

The levels of histamine, tryptase, and other mediators rise in the acute phase. Histamine is quickly degraded, while the levels of tryptase remains elevated for a prolonged time (4 to 6 hours). Determining serum tryptase levels can be used for confirming diagnosis of anaphylaxis[25](C)[2](D).

In a significant number of cases, the clinical history allows for the identification or suspicion of a triggering agent[26](D). The most common agents are medications, certain types of food, and venom of bees, wasps (hornets), and ants. It is important to identify cofactors such as infection, physical exercise, and alcohol consumption, among others[27](A)[2,4](D).

The medications most associated with anaphylaxis are analgesics, non-steroidal anti-inflammatory drugs, and antibiotics. In the surgical environment, neuromuscular relaxants, opiates, and other drugs should also be added to this list[2,26,28](D).

In Brazil, in infants and young children, cow's milk and white egg, followed by fruits and vegetables are the main

types of food causing anaphylaxis. In adolescence and adult life, hypersensitivity to mollusks and crustaceans is predominant[2](D) [8](C).

The venom delivered by insect stings can induce allergic sensitization and anaphylactic reactions. The main agents are bees, wasps (hornets), and ants. Generally, patients report having been stung moments before the onset of clinical manifestations[7,29](C).

Latex contained in gloves, medical products, toys, and condoms takes part in some reactions, especially in the medical-surgical environment. The triggering of anaphylaxis by physical exercise, whether or not associated with previous ingestion of certain types of food or medication, has been demonstrated. Physical stimuli such as cold weather, dialysis products, disinfection agents, and other products can be causative agents of anaphylaxis in a lower number of cases[2](D).

The identification of allergen-specific IgE antibodies can be made by skin prick testing (puncture) for immediate reading and by serum. These procedures are useful in evaluating allergies to food, to venom of insects, and to certain medications[8](C)[2,26](D). Cutaneous tests performed with standardized extracts present more sensitivity and are the preferential method of evaluation employed by specialists; they must be performed in the hospital environment[7](C)[2,26](D).

The presence of specific IgE antibodies for a given allergen indicates sensitization and it is not necessarily indicative of clinical participation[30,31](D).

Recommendation

Anaphylaxis diagnosis is usually clinical. Investigation is necessary to confirm the diagnostic suspicion, identify unknown etiological agents, and direct the prevention of new episodes. Complementary exams should be based on clinical history.

6. What is the diagnostic procedure in patients with anaphylactic reaction to insect sting?

In patients with anaphylactic reaction to insect sting, the identification of the insect is important . It is common that the patient is able to do so. Bees leave their stinger in the site, but wasps act differently. Ants cause a local lesion with erythema and blister formation. Usually, the stings cause pain and may or not have a reaction on the site[32](C)[26](D). Occasionally, the help of an entomologist can assist in the identification of species.

The allergic sensitivity diagnosis is performed by the characterization of the presence of specific IgE antibodies to the venom of insects. This can be performed by cutaneous tests or by determining specific IgE serum. The preferred diagnostic method is the skin test with venom, considering its high sensitivity and safety. Cutaneous tests are positive in 65% to 85% of patients with clinical history of systemic reaction to hymenoptera stings[33,34](D). It is recommendable to respect a period of 3 to 4 weeks after the acute episode in order to perform diagnostic exams.

Negative cutaneous tests in patients with positive clinical history may be caused by loss of sensitivity, if there was a long period of time between the event and the test. Negative tests can also occur if the reaction was recent, within a refractory period of allergy after the systemic reaction. In this situation, tests must be repeated at between 3 and 6 months[33,34](D).

In adults with negative tests, the chance for reaction to a new sting is small (5%) as compared to the risk from 25% to 70%, when cutaneous tests with venom are positive. Present guidelines do not properly approach the question of which would be the best treatment to patients with a convincing history of acute reaction to insect sting, but with negative results as to the research of venom sensitivity[35](C) [36](D). In complex cases with inconclusive results from diagnostic tests, the CD63 activation test is particularly useful and more sensitive as compared to intradermal tests, although it is still unavailable in this community[37](C).

Tryptase serum levels are related to severity of reaction, and safety and efficacy of venom immunotherapy . Thus, tryptase levels are risk factors to severe anaphylactic reactions by insect stings[38,39](B).

Patients with severe systemic reactions in which allergic sensitivity to venom has been demonstrated, and who are at risk of suffering a new sting, are candidates to receive specific immunotherapy with insect venom[26](D). Immunotherapy must not be employed in patients with negative tests to IgE antibodies, or with positive tests not correlated with the suspected triggering agents[40](D).

Recommendation

The preferred diagnostic method is the cutaneous test with venom.

7. What are the main agents of transoperative anaphylaxis?

Any of the drugs used during surgeries can induce anaphylactic reactions. Neuromuscular blockers, hypnotics, antibiotics, opiates, analgesics, anti-inflammatory drugs, plasma expanders, dyes, and products containing latex are the main triggering agents of anaphylaxis in the surgical environment[41](D).

The incidence of reactions is variable, from 1:3,500 to 1:20,000[42,43](D). Anaphylaxis diagnosis in the anesthetized patient is considered to be more difficult due to the low clinical expression in this situation. Thus, constant attention and knowledge on the part of the anesthesiologist are extremely important[42,43](D).

Evaluation by a specialist after an event of surgical anaphylaxis aims to identify the causative agent, to find a secure option in case of a new procedure, and to guide treatment in order to prevent a new episode[44,45](D). The investigation of surgical anaphylaxis is a delicate procedure that requires time and clinical experience. Simultaneous exposure to several potential triggering agents is one of the factors that make it difficult to identify the causative agent. Acute reactions caused by medication occur by mast cells and

basophils activation and consequent release of vasoactive mediators, such as histamines, leukotrienes, prostaglandins, and others. This type of activation can be mediated by an immune-specific mechanism, such as the connection between allergens and IgE antibodies, or by unspecified activation of mast cells and basophils[41,44](D).

From the information provided by the surgeon and anesthesiologist, a diagnostic conduct is established involving laboratory tests and performance of cutaneous tests. Diagnosis is based on skin test applications (puncture and intradermal), with the chemicals suspected, according to the routines defined by various centers[46,47](D). In addition, there are laboratory trials available for detecting IgE antibodies to certain medications and latex[41](D). techniques, which are used to identify activation of basophils, have been studied and applied to some specialized centers in Europe and in USA, even though they have not yet been standardized[41](D).

Recommendation

Based on the history of reaction and by using the available techniques, it is possible to efficiently evaluate anaphylactic reaction in the surgical environment.

The final diagnosis results from knowledge and clinical experience.

Conflict of interest

Pastorino AC received fees for preparing classes and reprints, sponsored by MSD.
Rizzo MC received fees from Laboratórios Takeda for preparing classes and reprints.
Rosário Filho N received a reimbursement for attending a symposium sponsored by the company Danone; received fees for presentation, conference, or lecture sponsored by the Ache, Danone, GSK, MSD, Nycomed, Sanofi-Aventis, and Support; received fees for consultancy sponsored by Ache, Danone, GSK, MSD, Nycomed, Sanofi-Aventis, and Support.

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