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REVIEW ARTICLE

# Perioperative anaphylaxis

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**KEYWORDS**
Anaphylaxis;
Hypersensitivity;
Anesthesia;
Perioperative period;
Treatment

**Abstract**
*Background and objective:* Anaphylaxis remains one of the potential causes of perioperative death, being generally unanticipated and quickly progress to a life threatening situation. A narrative review of perioperative anaphylaxis is performed.
*Content:* The diagnostic tests are primarily to avoid further major events. The mainstays of treatment are adrenaline and intravenous fluids.
*Conclusion:* The anesthesiologist should be familiar with the proper diagnosis, management and monitoring of perioperative anaphylaxis.


**PALAVRAS CHAVE**
Anafilaxia;
Hipersensibilidade;
Anestesia;
Período perioperatório;
Terapêutica

**Anafilaxia perioperatória**

**Resumo**
*Antecedentes e objetivo:* A anafilaxia continua sendo uma das causas potenciais de morte perioperatória pois geralmente não é prevista e evolui rapidamente para uma situação ameaçadora da vida. Uma revisão da anafilaxia perioperatória é realizada.
*Conteúdo:* O exames diagnósticos são importantes principalmente para evitar eventos posteriores. Os pilares do tratamento são a adrenalina e os líquidos intravenosos.
*Conclusão:* O anestesiologista deve estar familiarizado com o diagnóstico oportuno, manejo e monitoramento da anafilaxia perioperatória.


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## Introduction

The immediate hypersensitivity reactions occur in 1 out of 5000–10,000 anesthesias.[1] The variability occurs because it is based on retrospective studies with a calculated incidence according to voluntary information and the number of previous anesthesias performed, which may lead to undercounts.[2] Sixty percent of perioperative hypersensitivity reactions are allergic, with a mortality rate of 3–9%.[3] In this review the etiology, symptomatology, diagnosis and treatment of perioperative anaphylaxis are assessed with some final recommendations. This review does not focus on latex allergy.

## Methodology

A literature search was performed in PubMed, LILACS and Google Scholar, with no restriction of dates or types of articles; in PubMed the following MeSH terms were used: anaphylaxis, hypersensitivity, anesthesia, perioperative and treatment. The snowball method was used.

## Definition

The European Academy of Allergy and Clinical Immunology defines anaphylaxis as a reaction of severe life-threatening generalized or systemic hypersensitivity.[4,5] Perioperative anaphylaxis is a systemic reaction that occurs during anesthesia induction minutes after intravenous (IV) induction.[6,7] However, the agents administered through other routes, such as chlorhexidine, latex or methylene blue may also cause the reaction after 15 min[6] during maintenance of anesthesia or during recovery due to absorption by the skin, mucosa or tourniquet removal.[8]

## Types

The World Allergy Organization (WAO) has proposed the classification of anaphylaxis in immune and non-immune.[4] The immune anaphylaxis includes immunoglobulin (Ig) E-mediated, IgG-mediated and immune complex/complement-mediated reactions.[4]

## Immunoglobulin E-mediated anaphylaxis Physiopathology

This type of anaphylaxis is an immediate IgE-mediated hypersensitivity systemic reaction with release of pro-inflammatory mediators from mast cells and basophiles.[9] The mediators are histamine, triptase, cytokines, mediators derived from phospholipids as prostaglandin $D_2$, leukotrienes, thromboxane $A_2$ and platelet activating factor involved in the clinical presentation.[1,10] Target organs are the skin, mucous membranes and the respiratory, cardiovascular and gastrointestinal systems.[1,10] In IgE-mediated drug anaphylaxis prior contact with the agent is not required and sensibility can occur through cross-reactivity.[1]

The non-immune anaphylaxis is clinically indistinguishable from IgE-mediated anaphylaxis.[11]

## Etiology

The risk of anaphylaxis increases with frequency, the parenteral route of administration and the specific antigen exposure time.[9] Table 1 presents risk factors for the development of anaphylaxis.[3] Also, there are comorbidities and drugs that enhance the severity of the symptoms and decrease the response to treatment, such as heart diseases, chronic lung disease, recent intracranial surgery, and hyperthyroidism.[4]

The main etiological agents of perioperative anaphylaxis are the neuromuscular blocking agents, followed by latex and then the antibiotics.[12–16] Anaphylaxis to halogenated agents has never been reported.[14] Allergic reactions to local anesthetics are very rare.[17] Other substances that can cause immediate allergies at perioperative period are aprotinin, chlorhexidine, heparin, methylene blue and anti-inflammatory steroids.[17] Anaphylaxis to neuromuscular blockers can occur during the first exposure,[17,18] has a high incidence of cross-reactivity among the various neuromuscular blockers, and is more frequent in women (2:1–8:1);[18] the most involved is the suxamethonium.[17]

## Clinical features

The clinical presentation of anaphylaxis is characterized by its variability among patients and even in the same patient from one episode to another.[19] Clinical anaphylaxis during anesthesia can be masked or confused with hypovolemia, depth of anesthesia and extended regional block.[6,10,20] The increased vascular permeability by 35% within 10 min and the intrinsic compensatory response to endogenous catecholamines influence clinical manifestations.[21] The most common initial signs are no pulse, difficult ventilation and desaturation.[14,22] Another sign is the reduction of expired carbon dioxide[14,23] values.

There is a classification of the severity of symptoms in grades 1–5.[24] The perioperative cardiovascular collapse is the most common trait (88% of cases) and the worst

**Table 1** Factors that enhance anaphylaxis risk.

| Age range | Gender | Pathologies | Amplifiers | Severity |
|---|---|---|---|---|
| Nursing mothers<br>Elderly | Female | Asthma<br>Systemic mastocytosis | Fever<br>Active infection<br>Pre-menstrual state<br>Emotional state | Beta-blocker use<br>ACEI use<br>Spinal anesthesia |

ACEI, angiotensin-converting enzyme inhibitor.

sign.[7,22] Anaphylaxis can be fatal within the first 5–30 min of its presentation[25,26] with an incidence of cardiac arrest of 10%.[7,22] Myocardial ischemia, acute myocardial infarction, arrhythmias and myocardial depression may contribute to hemodynamic deterioration and cardiac arrest,[27] occurring even before administration of adrenalin.[28–31]

Skin symptoms, such as stiffness, hives and swelling, are recognized in 70% of cases[7,22] and during anesthesia may be hidden in the surgical fields.[10]

Ten to fourteen percentage of the reactions, especially the severe ones, affect only one system, fundamentally cardiovascular collapse and bronchospasm, which lead, in many cases, to other diagnoses.[14,32] Moreover, heart failure is the only sign present in the reaction, in 51.7% of cases;[33] therefore, when any of the previous signs take place, the protocol for allergic reactions should be conducted.[2]

Other signs and symptoms are swelling of the tongue, lips and uvula, stridor, hypoxemia, incontinence, abdominal pain, nausea, vomiting, rhinorrhea, among others.[4] It is necessary to consider that general anesthesia can mask many manifestations. In children, the skin signs and symptoms occur in most cases, bronchospasm is the most concerning manifestation, and hypotension and shock are not common at the onset of the problem.[8]

## Diagnostic tests

The diagnosis of anaphylaxis is mainly clinical.[4] The lack of experience, the lack of view of the patient's body, and the varied use of medication during anesthesia make it difficult to establish a proper diagnosis.[6] There are some tests such as measurement of triptase, histamine and IgE levels, but none has absolute accuracy.[8]

Skin tests can identify the causative agent but they are performed after the month in which anaphylaxis occurred, which restricts its use to prevent further cases.[10,34]

## Tryptase

Tryptase is a serine protease that has several main forms.[35] The serum tryptase concentration due to mast cell degranulation is 300–700 times higher than that released by basophiles.[2] An increase exceeding 25 $\mu g\,L^{-1}$ is considered an indicator of anaphylaxis.[2] Tryptase levels can be increased by other diseases such as systemic mastocytosis, mast cell activation syndrome or hematological diseases.[17] On the other hand, a normal level of tryptase does not rule out a diagnosis of anaphylaxis.[2,4]

The half-life of tryptase is 120 min[8] and the levels return to baseline in 24 h.[35] There may be false positives due to severe stress such as major trauma or hypoxemia.[8] The sample should be collected from 15 min to 3 h from the onset of symptoms,[4] and after 24 h.[36] A coagulated blood sample of 5–10 mL[36] is collected, along with clinical history data[37] and sample collection time at the onset of reaction.[10]

## Treatment

The early treatment is essential in anaphylaxis and could avoid hypoxic-ischemic encephalopathy or death.[38] The management is basically the same in all ages, considering the adjustment by weight in children.[4] The mainstays of treatment are adrenaline and IV liquids.[10]

**Table 2** First-line treatment.

| |
|---|
| Withhold all potential causes |
| Stop halogenated agents |
| 100% oxygen |
| Inform the surgeon. Postpone surgery |
| Ask for help |
| Intubate |
| Trendelenburg, if not contraindicated |
| IV Adrenalin or IM if IV not available |
| Crystalloids |
| Second IV access |
| Transfer to ICU/SCU |
| Inform family |

ICU, intensive care unit; SCU, semi intensive care unit.

Interventions in anaphylaxis are based on recommendations of experts as the realization of prospective, randomized, double-blind, placebo-controlled studies cannot be performed when there is an unpredictable condition.[19,39] During anesthesia, the patient is monitored and has venous access.[10] The team should be prepared to perform various tasks simultaneously;[36] investigate potential causes such as latex, chlorhexidine, blood products, and maintain anesthesia, if necessary, with only halogenated agents,[36] request help, take note of the time and inform the surgeon.[34,36] The advanced and fast airway management is critical to the development of laryngeal or oropharyngeal edema.[27] A hundred percent oxygen should be administered; if not contraindicated, lower limbs should be elevated,[7,40] and in adults 500–1000 mL of crystalloids[7] in 10–20 min should be given; in children bolus of 20 $mL\,kg^{-1}$, if they need more than 40 $mL\,kg^{-1}$ add support vasopressor,[41] titrate to maintain a systolic blood pressure above 90 mmHg in adults,[27] ideally with invasive monitoring of blood pressure.[41] WAO recommends the use of normal saline, rather than colloids.[38]

Adrenaline is the treatment of choice in anaphylaxis[5] for its alpha and beta-agonist properties, resulting in vasoconstriction, increased peripheral vascular resistance, decreased mucosal edema, inotropism, and chronotropism and bronchodilation.[28,42,43] The IV dose of adrenalin at 10–200 $\mu g$ varies depending on the patient's hemodynamic involvement and can be repeated every 1–2 min.[17] In children the dose is 1 $\mu g\,kg$.[17,36]

The intramuscular route can be used if there is no IV access.[36] The best application is in the anterolateral aspect of the middle muscle as it provides greater absorption, each 5 min, both in children and in adults;[44] doses of 0.5 mg in adults.[17]

In patients who require repeated bolus, continuous infusion of 0.05–0.1 $\mu g\,kg^{-1}\,min^{-1}$ should be started, an titrated.[10,45,46] Table 2 shows a checklist of the acute management of anaphylaxis.

Patients using beta blockers may require high doses of adrenaline when they have a poor response; in these cases norepinephrine should be added at a dose of 0.1 $\mu g\,kg^{-1}\,min^{-1}$.[17] IV glucagon[10] 1–2 mg IV can be used each 5 min,[34] followed by 5–15 $\mu g\,min^{-1}$,[17] vasopressin 2–0 UI IV

**Table 3** No response to adrenalin.

| |
|---|
| Norepinephrine |
| Vasopressin 2–10 U IV |
| Glucagon IV 1–2 mg IV each 5 min |
| Reports: methylene blue |
| Reports: sugammadex 16 mg $kg^{-1}$ IV in anaphylaxis to rocuronium |

according to response dose[6] as shown in Table 3. In children vasopressin[17] is not recommended. There are reports of cases of use of methylene blue in severe unresponsive anaphylactic shock.[18,47] In the case of anaphylaxis to rocuronium, the successful use of sugammadex 16 mg $kg^{-1}$ IV is described, at a dose according to the situation of cannot intubate, cannot ventilate.[18]

The $beta_2$-adrenergic agents relieve bronchospasm, but not upper airway obstruction and shock.[48] The patient should remain under observation during 24 h as the biphasic reactions[4] cannot be predicted. In case of cardiac arrest, the basic management and advanced pattern is followed, considering that it is preferable to continue the infusion of adrenaline during and after cardiac arrest.[27]

In the second line of anaphylaxis treatment line are glucocorticoids, the doses of which extrapolate asthma management and its onset of action takes several hours,[38] and there is no evidence of its use in the acute management.[5,49] A dose of 200 mg IV of hydrocortisone is recommended in over 12 years of age and 100 mg IV to those of 6–12 years of age.[36]

Antihistamines are also not recommended for the initial management; they are indicated to treat hives, pruritus[5] and rhinorrheia,[26] considering that some can cause hypotension and drowsiness.[26] Diphenhydramine 1–2 mg $kg^{-1}$ IV can be used, maximum 50 mg and can be associated with ranitidine 50 mg for adults or 1 mg $kg^{-1}$.[50]

## Referral to allergologist

The anesthesiologist responsible for the patient should make a referral to the allergologist if during general anesthesia there is an unexplained reaction of severe hypotension, bronchospasm or edema at recuperation.[14] This referral is performed in order to confirm the nature of the reaction, the offender drug, the possibility of cross-reactivity and recommendations for further studies.[1] The referral report should include a medical history of allergic reaction, the patient demographics, allergic and atopic history, the medical history and the medications they take, the administered drugs and the chronological sequence of administration, the detailed description of the reaction, the suspect drug, route of administration, the clinical features, the degree of severity, the treatment given, the evolution and the duration of reaction.[2] In addition, include information about exposure to latex, infusions and exposure time, interventions such as central line or urinary catheter and food allergies.[51] Also, all substance exposures should be noted in the anesthesia and referral record, including those used by the surgeon, even if they are not IV, such as local anesthetics, fluid irrigation, latex, disinfectants, methylene blue, among others.[10]

## To consider

There should be access to protocols for the management of anaphylaxis.[37,38]

There should be a habit of reporting the adverse reaction to drugs[52] and discussing the case for educational purposes. Additionally, the importance of referral to an allergologist should be emphasized to the patient.[38] In case of knowing the offender drug, it should be put on the electronic medical record, and a medical identification, such as a bracelet should be put on.[38]

In case of reaction to codeine or morphine, none of the two is to be administered, but there is no contraindication to other opioids.[17]

If allergic to seafood, iodinated media is not contraindicated.[17] There is one case of anaphylaxis to protamine in a patient with allergy to fish, but the literature does not warrant its prohibition.[17]

If there is any allergy to egg or soybean, propofol may be administered. There is a single case of hypersensitivity to propofol in a patient allergic to egg.[17]

## Recommendations

When the patient is submitted to anaphylaxis study with a positive test and requires anesthesia, one should avoid the identified agent and histamine-liberating substances, inject the drugs slowly, fractioned and separated, if possible, and be prepared to treat an anaphylactic reaction.[45]

When a patient who has a history of cardiovascular collapse in a previous anesthesia presents for urgent surgery, with no study of anaphylaxis, care should be provided in a latex-free environment, with the use of halogenated agents; in case of having previous record of anesthesia, avoid all medications used prior to collapse, except for halogenated agents, and avoid all neuromuscular blocking agents in the event of one being previously used.[18] If there is no record of anesthesia, all neuromuscular blockers should be avoided according to the risk-benefit balance, and regional or local anesthesia should be favored, avoiding chlorhexidine (allergy to iodine is less common) and avoid histamine-releasing drugs.[18] There is no evidence that prophylaxis, either with antihistamines or steroids, prevent or reduce the severity of reaction.[18,53]

Due to the potentially fatal feature of anaphylaxis, clinical suspicion and the knowledge of the management are fundamental to the impact of morbidity and mortality. It would also be perfect that a national network for reporting of cases and notification of allergies be provided among different health institutions.

## Conflict of interest

The author declares no conflicts of interest.

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