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NARRATIVE REVIEW

Update on perioperative hypersensitivity reactions: joint document of the Brazilian Society of Anesthesiology (SBA) and Brazilian Association of Allergy and Immunology (ASBAI) – Part I: post-crisis guidelines and treatment☆

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KEYWORDS
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Abstract: Experts from the Brazilian Association of Allergy and Immunology (ASBAI) and the Brazilian Society of Anesthesiology (SBA) interested in the issue of perioperative anaphylaxis, and aiming to strengthen the collaboration between the two societies, combined efforts to study the topic and to prepare a joint document to guide specialists in both areas. The purpose of the present series of two articles was to report the most recent evidence based on the collaborative assessment between both societies. This first article will consider the updated definitions, treatment and guidelines after a perioperative crisis. The following article will discuss the major etiologic agents, how to proceed with the investigation, and the appropriate tests.

PALAVRAS-CHAVE
Alergia e imunologia;
Hipersensibilidade;
Anafilaxia;
Período perioperatório

Atualização sobre reações de hipersensibilidade perioperatória: documento conjunto da Sociedade Brasileira de Anestesiologia (SBA) e Associação Brasileira de Alergia e Imunologia (ASBAI) – Parte I: tratamento e orientação pós-crise

Resumo Especialistas da Associação Brasileira de Alergia e Imunologia (ASBAI) e da Sociedade Brasileira de Anestesiologia (SBA) interessados no tema anafilaxia perioperatória reuniram-se com o objetivo de intensificar a colaboração entre as duas sociedades no estudo desse tema e elaborar um documento conjunto que possa guiar os especialistas de ambas as áreas. O objetivo desta série de dois artigos foi mostrar as evidências mais recentes alicerçadas na visão colaborativa entre as sociedades. Este primeiro artigo versará sobre as definições mais atuais, formas de tratamento e as orientações após a crise no perioperatório. No próximo artigo serão discutidos os principais agentes causais e a condução da investigação com testes apropriados.

Introduction

Perioperative hypersensitivity reactions are of great concern to anesthesiologists. Daily, every time a procedure is performed under anesthesia several agents that are administered sequentially can trigger allergic reactions of lesser or greater severity. It is difficult to estimate the incidence of these events due to the heterogeneity of the studies and the variety of medications used worldwide. The incidence of perioperative hypersensitivity reactions is thought to vary between 1:353 and 1:18,600 procedures.[1,2]

Mortality is higher than in anaphylaxis from other causes and oscillates from 3% to 9%.[3] In Brazil, a cross-sectional study carried out by answering a questionnaire (although without further investigation) indicated the incidence of anaphylaxis as greater than 7:10,000 anesthesias, which is higher than the previously described figure in the literature.[4] The greatest risk factor for perioperative hypersensitivity reaction is an earlier reaction, without adequate investigation.[5,6] The collaboration among anesthesiologists, allergists and immunologists is fundamental to carry out the investigation.

Few countries have organized an approach to diagnose, treat and investigate suspected perioperative allergic reactions, with published joint guideline documents that can guide both specialties.[7,8]

Method

A search was performed in the PubMed database, in English, French, Spanish and Italian, for the past 20 years, with the combination of the terms ''perioperative'', ''anaphylaxis'', ''management'', ''treatment'', ''protocols'', ''anesthesia'', ''allergy'' and ''hypersensitivity''. The articles were selected according to their current and clinical relevance.

Nomenclature

Medical nomenclature changes over time, depending upon the acquisition of new scientific knowledge.[8] The question of using accurate nomenclature for research and planning of global health actions is highly important, especially for drug hypersensitivity reactions, an ever-growing global health problem.

As a consequence, the World Health Organization (WHO), in its International Classification of WHO Disease ICD-11, will already bring advances such as the pioneering subsection

of drug hypersensitivity.[9] This concern may translate into a better registry even for fatal cases.[10]

The nomenclature used in the present article complies with the revised allergy nomenclature.[11] Obsolete terms (such as, anaphylactoid) should be discontinued as they are not in accordance with the classification and new concepts of mechanisms.[12] Thus, concepts used in this article obey the definitions proposed by Johansson et al., 2004[11]:

Hypersensitivity: Reproducible signs or symptoms, initiated by exposure to a defined stimulus, in doses tolerated by normal individuals.

Allergy: Hypersensitivity reaction triggered by a specific immune mechanism.

Anaphylaxis: Severe, systemic or generalized, life-threatening hypersensitivity reaction.

The term allergy should only be used when there is a proven IgE- or IgG-mediated mechanism, or concrete evidence of complement-related immune complex. Although it may seem paradoxical, the expression non-allergic anaphylaxis can be used in cases where these mechanisms cannot be proven.[11]

Adults

Clinical aspects and classification of severity

The miscellany of clinical presentations of perioperative hypersensitivity is the result of different pathophysiological, immunological or non-immunological mechanisms involved combined with the comorbidities and diseases determining the surgery. The variability of these combinations challenges the anesthesiologist in care of the patient.

It is very difficult to specify the effects of each exact mediator because of the ethical concerns preventing anaphylaxis induction in humans, and the multiplicity of mediators of anaphylaxis that are simultaneously released.[7,12]

However, signs and symptoms of anaphylaxis can be expected as a result of some of the currently known effects of the major mediators of anaphylaxis. There is evidence that histamine, leukotrienes and Platelet Activating Factor (PAF) are involved in vasodilation, capillary leakage, and bronchospasm.[12]

Hypersensitivity reaction presumptive diagnosis is based on the development of clinical manifestations primarily affecting the cardiovascular, respiratory, and integumentary systems. The particular presentation will depend on the combination of the pharmacological action resulting from the various substances used in sequence, mediators released, and the previous clinical condition of the patient.

The clinical scale described in 1977 in the investigation on colloids[13] was adapted by the Société Française d'Anesthesie et Réanimation (SFAR) and remains a valuable guide for reaction severity classification based on the intensity of signs and symptoms (Table 1).[14–16]

In the perioperative period, cardiovascular and respiratory signs can progress rapidly.[17] Cardiovascular collapse may be the only manifestation and the initial event can be a cardiorespiratory arrest.[18] Absence of cutaneous signs, such as generalized erythema and urticaria, does not rule out the diagnosis[3] and may appear only when vascular perfusion is reestablished.[7] Hypersensitivity reaction should be suspected in the presence of hypotension or tachycardia as isolated and unexpected signs not responding to usual treatment. Patients with a pre-existing cardiac condition or using beta-blockers are more likely to develop severe hypotension or shock.[15] Bradycardia can also occur.[19] Its onset may be related to rapid vascular leakage, subsequent hypovolemia and Bezold-Jarish reflex.[20]

Associated with immediate hypersensitivity reactions, acute coronary events, known as allergic angina, or Kounis syndrome, may result from the release of mediators by cardiac mast cells.[21,22]

Although bronchospasm is more common in patients with underlying airway hyperreactivity, such as asthma, chronic obstructive pulmonary disease or obesity,[7] in a series of patients with a history of asthma and intraoperative anaphylaxis, based on the logistic regression results, we can suggest that bronchospasm during anesthesia should also be attributed to anaphylaxis, and not exclusively to the history of asthma of the patient. Additionally, it was found that it was not bronchospasm incidence that was increased, but the severity of the reactions.[23]

At hypersensitivity onset, it is very difficult to predict the speed of progression of reaction or its severity.[24] Thus, early presumptive diagnosis must be considered in the presence of hypotension and bronchospasm unresponsive to usual measures or subsequent unexpected cardiac arrest without a clinical or surgical rationale.[25,26] Next step is to start performing the differential diagnosis.

We can say IgE-mediated reactions are associated with greater severity, but it is impossible to define whether a reaction was IgE-mediated only based on initial severity.[24]

Grade III and IV multisystemic reactions meet the criteria for anaphylaxis, life-threatening and are most likely mediated by IgE.[15,27]

Differential diagnosis

Some clinical signs and symptoms of the hypersensitivity reaction may mirror patient response to anesthesia or surgery, such as inadequate level of anesthesia, hypovolemia and hemorrhage resulting from vascular injury, which may not be swiftly identified.

Differential diagnosis with conditions unrelated to hypersensitivity may be hindered by factors listed on Table 2.[28]

Among several conditions that can be confused with hypersensitivity, some are listed on Table 3. In addition, the temporal relationship may provide some clues (Table 4).

Immediate treatment (during anesthesia)

The foundations of the treatment of immediate reaction hypersensitivity are: early recognition; epinephrine in adequate doses; and correct replacement of intravascular volume.[7]

As mentioned above, the diagnosis is presumptive and based on clinical signs. Regardless of the mechanism, whether it is IgE dependent or not, at the onset of anaphylaxis, it is hard to predict the progression rate and the severity of the condition. Fatality can occur in minutes,[7,24]

Table 1 Classification of severity and clinical signs of anaphylaxis.[14–16]

Severity	Clinical signs
Grade I	Generalized cutaneous and mucosal signs: erythema, urticaria, with or without edema.
Grade II	Moderate multivisceral condition with cutaneomucosal signs, arterial hypotension (systolic drop > 30%), tachycardia (>30%), bronchial hyperreactivity (coughing, difficulty breathing).
Grade III	Severe multivisceral disease, life threatening, requiring specific therapy: cardiovascular collapse, tachycardia or bradycardia, arrhythmias, bronchospasm. Skin signs are absent or appear after blood pressure correction.
Grade IV	Cardiorespiratory arrest.

Table 2 Diagnosis of perioperative anaphylaxis.[28]

Factors that can contribute to delayed diagnosis	Anesthetized patient does not report malaise, dizziness or itching. Surgical drapes covering the patient make skin assessment difficult (erythema, macules/papules, angioedema). Tachycardia and increased AW resistance can be confused with superficial anesthesia Arterial hypotension (effect of neuraxial blockages, action of IV or inhalational anesthetics) Intrinsic conditions of the patient (asthmatic with bronchospasm, hemorrhagic shock in multiple trauma patients)

AW, airway; IV, intravenous.

Table 3 Differential diagnosis of intraoperative hypersensitivity. Adapted from [15,26,27]

Airways Upper • Traumatic orotracheal intubation • Angioedema caused by ACE inhibitors • Hereditary Angioedema (rare) Lower • Gastric content aspiration • Asthma with difficult management	Circulation Hypovolemia Sepsis Drugs • Anti-hypertensives • Tricyclic antidepressants • Serotonin uptake inhibitors Vasodilatation • Due to general anesthetics • Due to Neuraxial • Blockage Bone cement syndrome Embolus • Thrombotic • Amniotic Vasovagal	Cutaneous Skin-restricted signs • Histamine direct release Exacerbation of chronic urticaria • Due to COX-1 inhibitors • Mastocytosis? • Cold-induced urticaria?

ACE, angiotensin-converting enzyme; COX, cyclooxygenase.

Table 4 Possible triggers of hypersensitivity reaction in the intraoperative period, according to anesthesia timeline. Adapted from [29,30,31].

Anesthetic induction	Up to 30 minutes of induction	After 30 minutes of induction	End of surgery
Induction agents – neuromuscular blockers	Latex	Blood products	Non-steroidal anti-inflammatory drugs
	Colloids	Bone cement with antibiotic	Opioids
Antibiotics	Contrasts	Release of tourniquet	Anesthetic reversal agents
	Dyes (blue)		
Impregnated intravenous catheters	Chlorhexidine		
	Exposure routes other than intravenous		

Table 5 Management according to severity.[7,15,26]

Epinephrine must be administered IM – before solution preparation, monitoring or venous access is obtained.			
Grade I	Grade II	Grade III	Grade IV
Assess progress Facial angioedema? Laryngeal edema?	Epinephrine IM 200–300 μg IV 10–20 μg (*bolus*) Repeat every 2 min	Epinephrine IM 500 μg IV 100–200 μg (*bolus*) Repeat every 2 min	Epinephrine IV 1 mg (*bolus*) Current CPR protocol
	Crystalloid (not colloid) IV fluid therapy 20 $mg.kg^{-1}$ (bolus). Repeat.		

- IM Epinephrine: vastus lateralis muscle/middle third.[26]
- If airway edema is suspected, consider early OTI.[26]
- Start cardiac massage when SBP < 50 mmHg.[7]
- Consider cardiac massage when $EtCO_2$ < 20 mmHg (3 kPa).[7]
- Collect blood sample (dry tube) for tryptase dosing up to 1 h after onset of the condition. (1–4 h).
- If possible, collect a second sample 2–4 h after starting the picture.

IM, intramuscular; OTI, orotracheal intubation; SBP, systolic blood pressure; $EtCO_2$, end-tidal CO_2.

thus one should not wait for multisystemic impairment to start treatment (Table 5).[32]

Epinephrine

Epinephrine is the only medication that reduces hospitalization and death in the event of an anaphylactic reaction. One of epinephrine beta-adrenergic' effects, suppression of the release of mediators by mast cells and basophils, is thought to explain its precise indication.[32] As for the use of epinephrine in patients with cardiovascular disease, it is necessary to remember that the heart is a target organ in anaphylaxis. Mast cells are present in the myocardium and in the intima of coronary arteries. Releasing histamine, leukotrienes and prostaglandins can cause coronary spasm leading to myocardial infarction, arrhythmias or both,[33] even if epinephrine has not been administered.[34] Thus, there is no absolute contraindication to the use of epinephrine in anaphylaxis in any scenario.[35]

Cardiorespiratory arrest occurs within 5 minutes in cases of iatrogenic anaphylaxis,[36] therefore, one should not wait for the condition to worsen before starting treatment. Even though anesthesiologists are specialists familiar with the daily use of intravenous (IV) epinephrine and in infusion, the use of intramuscular (IM) epinephrine is recommended by consensus on perioperative anaphylaxis while waiting for the preparation of dilution, monitoring, or if venous access has been lost.[7,26]

It is important to remember that starting treatment with IM epinephrine joins speed and safety with a lower risk of overdose,[37] and these are important factors for outcome, since in a large series on anaphylaxis casualties, only 23% of deaths were in patients who received epinephrine before cardiac arrest.[38] and excessive dose or very fast IV administration can cause arrythmias. [39]The site for epinephrine injection is the thigh, in the middle third of the vastus lateralis muscle.[26]

Regardless of the route used, the dose of epinephrine must be expressed in micrograms, and not in a ratio (1:1000), a factor identified as a source of error of medication administration.[32,40] The treatment of perioperative immediate hypersensitivity reactions is summarized in Tables 6 and 7.

There are several methods for correctly diluting epinephrine and they should be taught during the training practices for perioperative anaphylaxis.[7] The only presentation available in Brazil for epinephrine contains 1,000 $\mu g.mL^{-1}$.

Several publications, from different countries[7,25,26,30,40]recommend an ''anaphylaxis kit'' containing leaflets/cards with, among others:

Simple treatment algorithms;

Differential diagnosis;

Tables with dosing, routes and dilution of epinephrine and other vasopressors;

Instructions for obtaining blood samples (type of sampling tube, instructions on how and where to send the sample);

Form for recording the medications administered and measures taken.

Some guidelines on this consensus have been developed along the lines of these recommendations above, and some of them should be emphasized:

1. In grade I SFAR there is no immediate indication for epinephrine. One must remain alert, because in the suspicion of worsening, prompt treatment should be instituted.[26]
2. The following are worsening signs in adults[26]:
   Systolic Blood Pressure (SBP) < 60 mmHg.[26] It is recommended to start cardiac compressions with SBP < 50 mmHg;
   Life-threatening tachy or bradyarrhythmias;
   Oxygen saturation < 90%;
   Great difficulty to ventilate the lungs;
   Inspiratory pressure > 40 cm H_2O;
   Low $EtCO_2$. It is considered an estimate of low cardiac output and has been used as a predictor of anaphylaxis severity.[41] It is suggested to start cardiac massage immediately[7];

Table 6 Immediate treatment of anaphylaxis. Adapted from [7,26,30,39].

Early diagnosis Alert signs	Epinephrine adequate dose Immediate general measures	Adequate volume and dose Consider
• Hypotension • Bronchospasm • Unpredicted heart rate change and unresponsive to usual measures	• Eliminate suspected agent • Maintain patent airways • O_2 100% • ABC resuscitation • Call for help • Communicate surgeon	• Pharmacological actions of general/local anesthetics • Effect of regional blockades • Surgical technique/surgery complications • Airway manipulation • Underlying Diseases

Absence of cutaneous signs does not rule out anaphylaxis.

Table 7 Epinephrine dilution methods.[26]

Bolus	Infusion
The only presentation available in Brazil for adrenaline contains 1,000 mg.mL^{-1} **Suggestion for preparation:** - Dilute 1 ml of epinephrine standard presentation (1 mg.mL^{-1}) in 9 ml of diluent (distilled water or 0.9% saline) = >100 mcg.mL^{-1} concentration - Dilute 1 ml of the solution with a concentration of 100 mcg.mL^{-1} in 9 ml of diluent (distilled water or 0.9% saline) = >final concentration of 10 mcg.mL^{-1} **Dose:** For Grade II: 10 to 20 mcg (1 to 2 ml) For Grade III: 100 to 200 mcg (10 to 20 ml)	Start after 3 boluses of intravenous adrenaline. Peripheral vein can be used **Suggestion for preparation:** - Dilute 3 ml of epinephrine standard presentation (1 mg.mL^{-1}) in 50 ml of 0.9% saline solution = >60 mcg.mL^{-1} concentration **Dose:** Start with 3 mL.h^{-1} = 3 mcg.min^{-1} Titrate up to 40 mL.h^{-1} = 40 mcg.min^{-1} Infusion rate = 0.05–0.5 mcg.kg.min^{-1}

Airway edema. If suspected, consider early tracheal intubation.[26]

3. Intravenous volume administration. Aggressive volume replacement is an essential step to ensure adequate blood flow to vital organs.[26] In severe anaphylaxis, poor distribution and hypovolemia lead to decrease in venous return and circulatory failure.[7] We recommend 20 mL.kg^{-1}, repeating if necessary.[20,26] The recommendation is fast infusion of 500 mL of crystalloid for Grade II reactions and 1,000 mL for Grade III, which should be repeated in case of inadequate response, as described by several authors.[7,15,25,26,30,39]
4. For Grade IV, follow the current resuscitation protocol.
5. It is important to observe positioning of patient, who should be placed in a supine position as soon as possible when resuscitation maneuvers are required,[26] with elevation of the lower limbs.[15]

Refractory anaphylaxis

There is no refractory anaphylaxis definition, but after 10 minutes of treatment with adequate doses of epinephrine and volume, reassessment and probable adjunct strategies are required.[42,43]

Besides the inclusion of other therapeutic management measures, reviewing the differential diagnosis and checking if the possible antigen has been discontinued are essential.[26,30] In some cases described agents, such as gelatin and chlorhexidine-impregnated central venous catheter, have not been removed, and in others, a second dose of the antigen has still been administered.[39]

One should be aware of the risk factors for fatal reactions. A significant finding was the association of increased age, physical status according to the American Society of Anesthesiology (ASA), morbid obesity, coronary artery disease, and use of beta-blockers or angiotensin-converting enzyme inhibitors.[39] Another study also found that age over 50 years and the presence of cardiovascular disease were factors of greater risk for fatal drug anaphylaxis.[43,44] Both groups of patients need higher levels of vigilance.

Table 8 shows other options for treatment in the case of refractory anaphylaxis.[7,26,30,47]

In cases of Refractory Anaphylaxis, other measures are indicated, in addition to drug therapy (Table 9):

1. Establish an arterial line, both to support monitoring and to enable blood sampling.[3,26]
2. Whenever possible, perform transthoracic or transesophageal ultrasound to obtain accurate ventricular function assessment.[26]
3. When available in the surgical environment, cardiopulmonary bypass can be used as part of the resuscitation process.[7,26,39,45]
4. Sugammadex, previously presented as an astonishing option for treatment of anaphylaxis, not only to rocuro-

Table 8 Refractory anaphylaxis management.[7,26,46,47]

Initially question whether all antigens have been removed (Chlorhexidine? Latex? Synthetic colloids?)
Tryptase sampling[7]
■ *Collect using a dry tube*
■ *First sample within one hour after starting*
■ *Second sample between two and four hours from start*
If persistent hypotension after 10 minutes (no response to epinephrine)[7,26]
• Norepinephrine
Dose = 0.05–0.1 mcg.kg.min^{-1}
• Glucagon (for patients using beta-blockers)
Dose = 1–2 mg ou 5–15 mcg.min^{-1}. Repeat after 5 minutes.
• Vasopressin
Bolus of 2–10 UI. Repeat if necessary
Alternatively: infusion of 0.2–0.4 UI.min^{-1} or 2 UI.h^{-1}.
If bronchospasm/high pressure in the airways (after 10 minutes or as an isolated signal)[7]
• Inhaled Salbutamol
• Consider volatile agents
• IV Bronchodilators
Ketamine
Salbutamol

Note: Sugammadex has no proven role in the treatment of suspected anaphylaxis reactions.[47]

Table 9 Suggested management for suspected anaphylaxis and perioperative allergy in children.[7,26]

	Epinephrine	IV Fluids
Grade 2	**- IM Epinephrine:** WHENEVER IV access is unavailable or while IV drug dilution has been prepared (which may be a lengthy process). Administer on the lateral side of the thigh according to age, in an insulin syringe (1: 1,000 = 1 mg.mL^{1}): age <6 years: 0.15 mL (150 μg); between 6 and 12 years: 0.3 mL (300 μg); >12 years: 0.5 mL (500 μg). Repeat every 5 to 15 min as necessary. **- IV Epinephrine:** 1 to 2 μg.kg^{-1} *bolus* If the response is inadequate in 2 min, increase the dose (maximum of 5 μg.kg^{-1}) Repeat every 2 min	**- Crystalloid:** Fast bolus infusion 20 mL.kg^{-1} Reassess response Repeat if needed
Grade 3	**- IV Epinephrine:** 4 to 10 μg.kg^{-1} *bolus* (repeat every 1 to 2 min) **- Epinephrine Infusion** 0.1 μg.kg^{-1} min^{-1} to 2 μg.kg^{-1}.min^{-1}. Start as soon as possible (consider in these cases administration in peripheral access).	**- Crystalloid:** Fast bolus infusion 20 mL.kg^{-1} Reassess response Repeat if needed
Grade 4	**- Epinephrine IV:** 10 μg.kg^{-1} *bolus* (0.1 mL.kg^{-1} from the dilution 1:10.000) (repeat every 1 to 4 min) Repeat according to recommendations of advanced pediatric life support for non-shockable rhythm. External cardiac massage when evidence of inadequate cardiac output **Epinephrine Infusion** 0.1 μg.kg^{-1}.min^{-1} to 2 μg.kg^{-1}.min^{-1}	

Table 9 (*Continued*)

	Epinephrine	IV Fluids
Refractory anaphylaxis	- Consider arterial line - If inadequate response > 10 min after the onset of symptoms: double the dose of adrenaline - If inadequate response after more than three boluses of epinephrine: start infusion of epinephrine 0.1 to 2.0 $\mu g.kg^{-1}.min^{-1}$ - If hypotension: consider adding • Norepinephrine infusion: 0.1 to 2 $\mu g.kg^{-1}.min^{-1}$ • Vasopressin: 0.02 to 0.06 $IU.kg^{-1}.h^{-1}$ • Glucagon: 40 $\mu g.kg^{-1}$, IV, up to a maximum of 1 mg, if using beta-blockers NOTE: Continue infusion of epinephrine, add bolus of crystalloid IV, 20 to 40 $mL.kg^{-1}$. Add second vasopressor. Consider central venous access. - Suggest ECMO: when available - If bronchospasm: consider • Salbutamol: 100 $\mu g.puff^{-1}$ (6 puffs < 6 years and 12 puffs > 6 years) • Salbutamol IV according to institutional protocol • Mg Sulfate ++ 50%: 50 $mg.kg^{-1}$ up to a maximum of 2 g in 20 min • Aminophylline: 10 $mg.kg^{-1}$ in 1 hour, maximum 500 mg • Hydrocortisone: 2 to 4 $mg.kg^{-1}$, maximum 200 mg NOTE: Continue infusing epinephrine. Consider malfunction of the airway device or ventilatory circuit or hypertensive pneumothorax (consider pneumothorax relief)	

Note: Titrate epinephrine until response; if large doses are necessary, use IV infusion. Epinephrine dilution, 1: 10,000 for every 10 kg.[7]

nium, has no evidence so far to justify its use in the treatment of anaphylaxis.[7,39,46,47]

Specificities in pregnant women

Anaphylaxis is uncommon during pregnancy and shows a rate of approximately 3 for every 100,000 births in studies in the United States and the United Kingdom.[48] The main agents involved are beta-lactam antibiotics, latex and neuromuscular blockers.[39] It is important to underline that, in the obstetric scenario several other causes can cause profound hypotension and hinder the diagnosis. Early recognition and prompt initiation of treatment are critical.[49]

Main measures involve:

Manual left displacement of the uterus, to achieve aorta-cava decompression, is the fundamental measure. It must be maintained while cardiac massage is applied.[50]

Although phenylephrine is the recommended vasopressor for use in hypotension related to regional block,[51] in anaphylaxis, epinephrine is the recommended drug, in doses according to the severity scale.[14,26,39,48]

The impact on uteroplacental circulation will be short due to the short half-life of epinephrine,[52] and fetal survival is maximized by maternal resuscitation.[48]

Quickly start replacement with crystalloids; large volumes may be required.[48]

Establish an airway and ventilate the lungs with 100% FiO_2 to compensate for the increase in consumption.[48] Pay attention to airway particularities of the pregnant patient.[53]

Emergency cesarean section should be considered after 5 minutes of circulatory failure, despite efforts to resuscitate.[14]

Post-mortem cesarean section should be indicated after 4 minutes of maternal cardiorespiratory arrest.[48,54,55]

Specificities in children

The challenges for diagnosing perioperative anaphylaxis in children are similar to those in adults. Symptom onset can be delayed if the antigen is in a coated catheter or if the route of exposure is cutaneous, as reduced peripheral perfusion can make cutaneous manifestations absent, and surgical drapes can hinder physical examination and access to the airway.[56]

A recent retrospective study on perioperative anaphylaxis in children gathered 29 cases, which occurred during 10 years in the United Kingdom, France and the United States. Cardiovascular collapse was the first sign in 59% of cases, followed by tachycardia and bronchospasm. In 55% of cases there was involvement in multiple systems and in four cases, cardiorespiratory arrest.[57] In the pediatric cohort of the NAP6 of the Royal College of Anaesthetists,[58] a

study carried out to characterize the incidence, risk factors, treatment, clinical results and investigation of perioperative anaphylaxis, 11 cases of anaphylaxis were reported in children under 16 years. In these patients, bronchospasm and/or high airway pressure were the initial signs identified in 64% of cases.[39] These findings contrast with the study by Khaleva et al.,[57] in which the authors underline the fact that their findings (in a population with a mean age of 11 years) were analogous to those in adult patients in the NAP6 study regarding hypotension as the most frequent sign. The lowest blood pressure value recorded was <50 mmHg.[57,59] No cardiorespiratory arrest or death occurred in the pediatric cohort of NAP6.[59] Contrary to what was proposed for adults,[39] no blood pressure value was established below which cardiorespiratory resuscitation should be started before the occurrence of cardiac arrest.[59]

For the classification of severity of reactions, the modified Ring and Messner scale (used for adults)[14,15] has been used (Table 1).[57,60] For the pediatric cases reported in a French study,[61] the most severe manifestations, with cardiovascular symptoms and bronchospasm, occurred in the reactions mediated by IgE (Grade III), while the non-mediated by IgE were classified as Grade I, in the large majority. In the same study performed between 1997 and 2004,[61] latex ranked first amongst the agents involved. In two recently published studies, neuromuscular blockers occupy the top positions.[57,59]

Immediate treatment (during anesthesia)

The management of suspected perioperative allergic reactions involves three major steps: well-timed diagnosis, correct epinephrine dose and adequate intravascular volume replacement (Table 9). The perioperative allergy guidelines are consistent on the following recommendation: Grade 1 reactions do not require treatment with epinephrine.[7,26]

In all allergic reactions, the systematic approach (ABCD) is recommended: call for help; monitor, maintain a patent airway and perform early intubation when there is risk of glottis edema; check breathing, administer 100% oxygen and start controlled mechanical ventilation in the presence of respiratory failure; drug circulation support: do not delay epinephrine administration at the beginning, using IM route until venous access is secured and while the epinephrine solution is being diluted for IV administration. Perform the following important measures: stop surgery, remove possible triggers, reduce inhaled anesthetic concentration and raise lower limbs in case of arterial hypotension.[7,26]

Programs implementing knowledge and training for correct epinephrine dose administration during management of pediatric anaphylaxis should be encouraged.[62]

As in adults, the management of pediatric perioperative anaphylaxis is guided by the clinical presentation. Crystalloid fluid therapy (20 mL.kg^{-1}), repeated as necessary, is recommended, if possible, warmed. The current recommendations are presented in Table 5.[7,26]

Epinephrine is the first line drug for treatment of anaphylaxis. Once anaphylaxis is diagnosed epinephrine can be lifesaving when administered as soon as possible. In addition to its vasoconstrictor effect, it prevents or reduces airway edema (laryngeal edema), hypotension and shock. It is an important bronchodilator and has inotropic and chronotropic effects.[63]

Children respond uniformly to epinephrine.[64] When administered IM, in the lateral part of the thigh, it can reduce hospitalization time, as well as morbidity and mortality, as the route enables rapid administration and does not require an existing access. In addition, the peak of action after administered intramuscularly is faster than after the subcutaneous route and it is not associated with serious adverse effects in children and is considered tenfold safer than when administered intravenously.[37] As in treatment for adults, several drugs such as, norepinephrine, vasopressin and glucagon are recommended for treatment of children presenting anaphylaxis refractory to epinephrine.[26]

When indicated, hydroxyethyl starch is the preferred colloid solution, as it is less likely to trigger allergic reactions. As recommended by NAP6[59] there is no evidence to administer gelatin-containing solutions.

Bronchospasm due to anaphylactic reaction should be treated with epinephrine following the criteria mentioned above (intramuscular initially and intravenous only after preparation of correct epinephrine dilution).

Secondary treatments for anaphylaxis have not been established in children. Although their role in anaphylaxis remains unclear, corticosteroids are beneficial in the management of other allergic diseases.[65] Corticosteroids can be useful in cases showing prolonged reaction (dexamethasone 0.1–0.4 mg.kg^{-1}, maximum 12 mg and hydrocortisone 2 to 4 mg.kg^{-1}, maximum 200 mg).[7,26]

There is no clear evidence that H1 or H2 blockers (diphenhydramine or ranitidine) alter anaphylactic outcomes in children. The use of IV or IM of these drugs is not recommended. Consider using them orally for symptomatic treatment of angioedema, urticaria and itching in children who are not sedated and able to ingest the drug.[7,26]

The decision to continue or interrupt the surgery will be determined by the urgency of the surgery, anaphylaxis reaction grade, response to treatment and the symptoms of underlying comorbidities.[26]

Post-crisis management

Administer corticosteroids and antihistamines;
Collect samples for tryptase analysis;
Consider continuing or interrupting the procedure;
Transfer the patient to the recommended unit;
At hospital discharge, provide written guidance;
Refer to an allergy service.

Post-crisis drugs do not replace first-line drugs, such as epinephrine, but can be used in mild reactions (Grade I).[30]

After patient stabilization, corticosteroid can be administered as part of secondary therapy[26,30] after adequate resuscitation.[7] Its major indication in anaphylaxis used to be for preventing late phase or biphasic reactions. However, because of corticosteroid potential adverse effects and the lack of compelling evidence of its role in reducing or preventing biphasic reaction, after recently performing a systematic review of 31 studies the authors have not recommended routine use of corticosteroid in anaphylaxis, although the existing anaphylaxis guidelines still recommend it.[66]

Antihistamines can be used, as no harm has been demonstrated with their use, although they do not modify the outcome.[7,39]

Sample collection for tryptase analysis

Tryptase is a serine protease, produced primarily by mast cells and, to a lesser extent, by basophils and myeloid progenitors. It exists in four isoforms, but only the alpha and beta types (the main) contribute to the total serum value of tryptase.[67]

Recent data from the NAP6 study show that the collection of samples for tryptase analysis as soon as possible – notably in the first 15 minutes after the reaction, just after stabilizing the patient – is associated with higher peak levels.[68] The most recent recommendation restated the importance of withdrawing the first sample within 1 hour after reaction onset. It is also recommended to collect a second sample 2–4 hours post-reaction. If it is not possible to obtain the two samples, a single sample should be obtained within 1–4 hours.[7] The baseline sample for comparison should be collected 24 hours after the reaction or, later, at the time of the skin tests.

An algorithm has recently been validated and it has been used for the interpretation of the results. It has international acceptance and also is the most effective tool. After the reaction, using the algorithm formula, the levels of tryptase must be higher than $[(1.2 \times \text{baseline tryptase}) + 2]\ \mu g.L^{-1}$, thus it enables us to distinguish an anaphylactic from and non- anaphylactic event, perioperatively.[69,70]

Post-mortem samples can be used due to the high stability of tryptase.[71]

Decision to continue the procedure

During an anaphylaxis episode, it can be difficult to predict the rate of progression, the severity and duration of the reaction, as well as its recurrence after its control.[24] However, when this reaction occurs at the beginning or during surgery, once the patient condition is stable after treatment, the critical dilemma is to choose to continue, abbreviate or stop the proposed procedure

The decision has to be individualized, based on the following factors[72]:

Physical status (ASA) of the patient;

Urgency of the procedure (cancer vs. cosmetic surgery);

Severity of the reaction;

Speed of the response to treatment.

It is also important to consider whether:

The stage of the surgery permits the interruption, or procedure conclusion will be less physiologically deleterious to the patient;

The surgical position allows resuscitation maneuvers;

The hypersensitivity reaction may exacerbate complications of the procedure (for example, occurrence of bowel wall edema in procedures involving intestinal anastomosis)[73] or if, in the case of surgery with anticipated major bleeding, blood loss may be increased by the activation of other pathways due to anaphylaxis.[74]

For those patients whose hypersensitivity reaction was difficult to control, requiring high doses of epinephrine and/or prolonged vasopressors infusion, the interruption of the surgery seems clear.

References on the issue are scarce. Anaphylaxis protocols in general do not discuss this matter. In one of the NAP6 publications,[39] and in the most recent international consensus dealing with the management of suspected perioperative allergic reactions,[7] the authors raise the study by Sadleir et al.[73] Despite being an observational study and analyzing patients submitted to only three surgery specialties (vascular, ORL and neurosurgery), the authors classified as severity indexes the epinephrine dosing necessary for the resolution of the condition, ICU admission for mechanical ventilation and ICU length of stay, in addition to sequelae related to hypersensitivity, or unexpected sequelae from the same procedure without the hypersensitivity reaction.

This study by Sadleir et al.[73] reported that:

In low-risk SFAR I and II immediate hypersensitivity reactions, after reaction resolution the surgery was completed;

In Grade III, no significant differences were found regarding the sequelae related to hypersensitivity between the group in which the surgery was completed (after the reaction had resolved) and the group in which surgery was interrupted;

In Grade IV patients, the procedure was completed only when patients were undergoing emergency surgery. This guidance is endorsed by other authors.[7,39]

There are also risks when postponing the surgery, as the patient is not exempt from a new reaction[73] and the delay in performing a new surgery (the patient will be evaluated after 4–6 weeks of the event) can be harmful for oncological surgeries, for example.[73,75]

No matter what decision is to be made, it should be widely discussed between the surgical and anesthetic teams, assessing the risks and benefits for the patient.[75]

For genuinely urgent cases, which require surgery before the investigation is carried out, a comprehensive discussion between the anesthetic and surgical teams must be carried out again, balancing the risk-benefit and assessing a series of detailed guidelines aiming to minimize the risk (See Appendix).

Patient medical chart

Norm 2174/2017 enacted by the Brazilian Federal Council of Medicine,[76] which provides for the practice of the anesthetic act, aims to improve the safety of the anesthetic procedure and warrant patient safety. It states, in its first article, item III, the minimum documentation of anesthetic procedures, concerning prescription, clinical progress notes, and pre, intra and post-anesthetic treatment. In its Annexes II and III, the norm details the data to be recorded, including data on allergies to drugs and latex, to the numerical recording of vital sign values, the solutions and drugs administered, in addition to the brief description of complications and adverse events associated or not with anesthesia, and their respective management. These records also extend to the post-anesthetic recovery period.[76] As this norm is mandatory for anesthesia practice, it is crucial for the allergy specialist, who will be the patient's referral specialist, to be familiar with it and may request further details when assessing the patient.

Table 10 Follow-up after the anaphylactic reaction.[7,30,39,82,83]

Grade I	Grade II	Grade III	Grade IV
Medical discharge after clinical resolution	Monitoring at PACU Medical discharge after clinical resolution	Resuscitation/monitoring in PACU Medical discharge after clinical resolution	Resuscitation/ICU monitoring for 24 h

PACU, post-anesthetic recovery room.

Proper registration in the patient medical chart, not limited to the anesthesia record, is the first measure for further evaluation. The main data worth registering are:

Time interval between the last administered drugs and the onset of symptoms;

A comprehensive report of the signs of the reaction;

Treatment required to stabilize the reaction;

Time required for recovery;

Patient co-morbidities not reported in the anesthesia record.

Concerning the particular materials used in the various surgical specialties and which are not described in the anesthesia record, they must be listed in the surgery report, medical supplies expense sheet, for further analysis of an adverse event. Anesthetists from each surgical specialty can help being aware and registering substances such as antibiotics present in bone cement in the anesthesia record,[77] or even antibiotics for intracameral use.[78] Accurate recording of the administration of these substances, via different routes, is often neglected. However, these data are crucial when investigating a hypersensitivity reaction. The form suggested by Laguna et al.[30] is an approach to gathering data related to the reaction and consistently conveying it to the allergist. The form would be one of components of the ''anaphylaxis kit'' previously proposed.[7,26,39]

Post-treatment measures

After treatment and recording the measures taken on the medical chart, the next actions are:

1. Check the collection of biological samples for tests: As described before, investigation during the acute phase comprises collecting blood (in a dry tube) for tryptase test. Currently this is the only test to be requested during the crisis. Up to two samples can be withdrawn, within the first four hours from reaction onset.[18,79,80] On average, 4 mL are collected for adults, and 0.5 mL is sufficient for children. Ideally, samples should be centrifuged and frozen at −20 °C, before being sent to the reference laboratory.[81] Other tests (histamine, methylhistamine in urine) are not used in practice due to difficulties in sample collection and low sensitivity.[30]
2. Determine the unit the patient will be transferred to: Patients who had mild (Grade I) or moderate (Grade II) reactions that quickly resolve after treatment still require 6-hours observation at least.[26,82] Intensive Care Unit admission will be required in Grade IV patients and in the majority of Grade III patients, particularly those with prolonged resuscitation or requiring maintenance of vasopressor hemodynamic support.[7,8,39,83] Table 10 summarizes the follow-up after a reaction.
3. Provide written information to be handed to the patient and/or family: To avoid the recurrence of the adverse event, it is crucial to notify the patient when recovered, and the family members and/or guardians.[84] Harper et al.[39] found pitfalls in the communication with patients, as in 14% of the cases no information was given and in 27% the information was conveyed only orally. This situation has been commonly observed regarding patients referred to the Drug Reaction Assessment Center of the Federal University of Santa Catarina (NARTAD), where some of the authors of the present article carry out their activities.[28] The written report to be provided by the anesthetist who assisted the patient must describe the clinical presentation, drug therapies administered and their outcome and a list of substances to be avoided until further allergist assessment.[7,26,30,39,83] The investigation of the reaction occurring in a complex scenario such as the perioperative period, will require more than only the knowledge about negative and positive values for the tests, which may affect the safety of the ensuing recommendations.[85] Table 11 shows the management at the time of patient discharge.
4. Refer to an allergy service for evaluation after reaction: The assessment in specialized clinics is recommended, with the collaboration between anesthetists and allergists.[7,15,25,26] The evaluation by the allergist cannot be replaced by pharmacovigilance algorithms, since the latter are based mainly on history, and are not specific to hypersensitivity reactions.[85] The presumption of involvement of a particular drug is not a reliable way to exclude agents. Many patients are unduly exposed to risk by ruling out the wrong agent and, at the same time, being deprived of useful drugs. A study found that in 73% of the cases there was no correspondence between the substance blamed for the reaction and the agent actually involved.[86]

Table 11 Procedures to be follow at hospital discharge of patient.[7,15,26,30,39]

- Make sure the complication was recorded on patient medical chart
- Provide the patient with a written report by the anesthesiologist with a complete list of drugs to avoid until further evaluation/Attach a copy of the report to the patient medical chart[15]
- Consultation with allergist within 4–6 weeks after hospital discharge[15]

As patients will be tested, the information about the drugs used during the reaction must be clear (name of the substance, trade name), thus preventing a patient who received a certain neuromuscular blocker (atracurium) from having skin tests performed with another drug (vecuronium, for example).[59]

A standard printed form for communication may be employed.[30]

Establishing an interaction between allergist and anesthesiologist for a joint investigation is crucial.

The resolution of an anaphylaxis reaction finishes only when the investigation is completed and safe alternatives to perform a future procedure are provided.[87,88]

In Brazil, the appointment of specialists in Perioperative Anaphylaxis by each Regional Office of both SBA and ASBAI societies is an objective to be pursued.

Appendix

In the ideal scenario, every patient after a hypersensitivity reaction would be properly investigated, with a multidisciplinary approach as suggested by NAP6, including discussing strategies for a future anesthesia.[89] This assessment should be performed 4–6 weeks after the event, under the penalty of a false negative result, however, situations other than the ideal may occur:

a) Urgent reoperation in a patient who experienced anaphylaxis and with data from the anesthesia record;
b) Urgent surgery in a patient with a history of perioperative hypersensitivity reaction not investigated and for which there is no documentation;
c) Patient who suffered a suspected reaction to previous perioperative hypersensitivity, of which there is no available documentation.

As general rules in situations of genuine urgency without investigation, one should:

Avoid agents administered or to which the patient was exposed up to 60 minutes before the event[7];

Avoid substances administered by all other routes, intramuscular, subcutaneous, spinal, epidural and other sites within 2 hours after the onset of the condition,[90] which should also be possible agents and be excluded;

Exclude latex (environment and medical devices). In Brazil, there is Collegiate Board Resolution RDC 37/2015 concerning medical devices and data about latex content and risk of allergy in medical supplies.[92] List all materials and equipment beforehand and check, removing from the room, those with latex. Maintain the precautions also in the postoperative period (post-anesthetic recovery room, inpatient and intensive care unit)[91];

Perform the surgery as the first one on the morning list[30,91];

All antibiotics belonging to the same class of that administered in the suspected event[39] should be excluded. Get advice from Hospital Infection Committee. Chosen agent should be administered in the operating room before anesthetic induction, with the patient awake and monitored to facilitate identifying the agent involved.[93] Cardiovascular resuscitation will also be easier without anesthesia drug effects upon the cardiovascular function[15];

Regarding general anesthesia induction agents, if propofol has been used and general anesthesia is necessary, the agents indicated are halogenated, thiopental, etomidate (non-lipid formulation) and ketamine.[39]

Tracheal intubation: if required to exclude neuromuscular blockers, remifentanil, magnesium sulfate and topical anesthesia will be valuable. Replace remifentanil with alfentanil if that was used previously.[39] Also consider dexmedetomidine for awake intubation,[89,94] including cases of allergy to local anesthetics[95];

If neuromuscular blockers have been administered during the event, they should be excluded due to high rate of cross-reactivity, unless its administration is absolutely mandatory. Remember that cross-reactivity is more frequent among amino steroid blockers than among benzylisoquinoline derivatives[96] and that pancuronium (which has an inflexible structure) appears to be less likely to have cross-reactivity with other amino-steroids. For patients who suffered anaphylaxis with rocuronium and vecuronium, cisatracurium was found to be the agent that had the lowest rate of cross-reactivity to them[97];

If chlorhexidine has been used previously, check for its presence in gel for urethral use, coated catheters for central venous puncture, ophthalmic solutions and antiseptic wipes[98];

Remember that some colloid solutions for volume replacement (IV) may contain alpha-gal[99] and are not allowed to be used in patients with alpha-gal syndrome[5];

Check for the use of radiological contrasts and dyes for lymphangiography;

Be aware of histamine-releasing drugs, such as phenanthrene morphine and codeine. These are different from phenylpiperidine derivatives, as they are not associated with histamine release.[100] Atracurium also releases histamine by direct action[31];

Remember that local anesthetics can cause an allergic reaction, that is, IgE-mediated. Reactions to local anesthetics correspond to less than 1% of reactions attributed to anesthetics[101];

Ethylene oxide is a gas used to sterilize most medical supplies. Although reactions are rare in the perioperative setting, there appears to be an increased risk of sensitization in patients with myelomeningocele and ventriculoperitoneal shunts,[90] and there are also reports in patients undergoing hemodialysis.[102] The diagnostic test is to search for specific IgE,[103] but the test is not available in Brazil. It is very hard to prevent using ethylene oxide. The replacement of medical supplies and the use of material that can be steam sterilized, and the adoption of measures to minimize ethylene oxide exposure have been recommended, whenever possible.[104,105] Pretreatment with omalizumab has been described.[106]

Conflicts of interest

The authors declare no conflicts of interest.

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