Curr Allergy Asthma Rep (2014) 14:452
DOI 10.1007/s11882-014-0452-6

Perioperative Anaphylaxis

Violeta Régnier Galvão · Pedro Giavina-Bianchi · Mariana Castells

Published online: 21 June 2014

Abstract Perioperative anaphylaxis is a life-threatening condition with an estimated prevalence of 1:3,500 to 1:20,000 procedures and a mortality rate of up to 9 %. Clinical presentation involves signs such as skin rash, urticaria, angioedema, bronchospasm, tachycardia, bradycardia, and hypotension. Prompt recognition and treatment is of utmost importance to the patient's prognosis, since clinical deterioration can develop rapidly. Epinephrine is the main treatment drug, and its use should not be postponed, since delayed administration is associated with increased mortality. Elevated levels of serum tryptase help to confirm the diagnosis. The main agents involved in IgE-mediated perioperative anaphylaxis are neuromuscular blocking agents, latex, antibiotics, hypnotics, opioids, and colloids. Specific investigation should be conducted 4 to 6 weeks after the reaction and relies on skin tests, serum-specific IgE, and challenge procedures. This review aims to discuss the main aspects of perioperative anaphylaxis: risk factors, diagnosis, treatment, culprit agents, specific investigation, and preventive measures.

This article is part of the Topical Collection on *Anaphylaxis and Drug Allergy*

V. R. Galvão
Division of Clinical Immunology and Allergy, University of São Paulo Medical School, Rua Doutor Bacelar, 747 ap 81, Vila Clementino, 04026-001 São Paulo, SP, Brazil
e-mail: vgalvao@usp.br

P. Giavina-Bianchi (✉)
Division of Clinical Immunology and Allergy, University of São Paulo Medical School, Av. Dr. Enéas de Carvalho Aguiar, 255, 8° andar, Cerqueira César, 05403-900 São Paulo, SP, Brazil
e-mail: pbianchi@usp.br

M. Castells
Harvard Medical School, Division of Rheumatology, Allergy and Immunology, Department of Medicine, BWH, Boston, USA

Keywords Anaphylaxis · Perioperative · General anesthesia · Hypersensitivity · Immunoglobulin E (IgE) · Neuromuscular blocking agents · Hypnotics · Opioids · Antibiotics · Tryptase · Epinephrine · Skin test · Intradermal test · Prick test

Introduction

Perioperative anaphylaxis is an important entity in the context of surgery-related adverse events. Its estimated incidence varies from 1: 3,500 to 1: 20,000 surgeries, with a mortality rate ranging from 3 to 9 % [1, 2••, 3, 4].

Worldwide, perioperative anaphylaxis accounts for 9–19 % of all surgical complications and 5–7 % of all deaths during anesthesia [5]. The most important morbidity is brain damage secondary to anoxia and occurs in about 2 % of affected patients [1, 2••]. In France, cases of perioperative anaphylaxis have been reported since 1985, providing knowledge about these reactions and enabling the implementation of effective interventions to prevent them [5, 6]. After 8 years of monitoring such cases, the incidence of perioperative anaphylaxis was estimated to range from 0.5 to 2.9:10,000 [5–7].

The fact that several drugs are administered during general anesthesia makes the identification of the culprit agent more difficult and requires collaboration between allergists and anesthesiologists in order to conduct the investigation. The careful and detailed analysis of anesthetic records provides essential information regarding the event, such as clinical manifestations, drugs that might have been involved, and timing between the administration of each drug and the beginning of the reaction [8].

Anaphylaxis is defined as a serious, life-threatening systemic hypersensitivity reaction that is rapid in onset [9]. It can be considered a syndrome, and its diagnosis is based primarily on a detailed clinical history with recognition of patterns [10, 11]. Clinical criteria were developed in an attempt to make the

diagnosis more reliable, and their accuracy has been demonstrated [12, 13].

Anaphylaxis may be allergic or nonallergic [9]. Allergic reactions are those involving specific immunologic mechanisms, which may be IgE- or non-IgE-mediated (IgG and immune complex complement-related) [8–10]. Nonallergic anaphylaxis occurs without specific immune response and includes several mechanisms, such as activation of complement system with production of anaphylatoxins, dysfunction of arachidonic acid metabolism, and direct activation of mast cells [14].

In a study with 789 patients who had experienced an adverse reaction suspected of being allergic during anesthesia, an immune basis was confirmed in 66 % of the reactions [15]. It is estimated that around 60 to 70 % of the immediate hypersensitivity reactions that occur during anesthesia are IgE mediated [2••].

The main agents involved in IgE-mediated perioperative anaphylaxis are neuromuscular blocking agents (NMBAs), latex, and antibiotics, depending on the studied population [2••, 7, 15–17]. Other agents used during general anesthesia are also implied as anaphylaxis causatives, such as hypnotic agents, opioids, colloids, dyes, and antiseptics (chlorhexidine) [2••, 7, 15]. Nonsteroidal antiinflammatory drugs (NSAIDs) and iodinated contrast agents are common causes of nonallergic anaphylaxis, although recent evidences show that these agents can also induce IgE-mediated reactions [18–21].

In procedures under general anesthesia in which NMBAs were administered, the frequency of anaphylaxis was one in 6,500 and one in 5,200 in studies conducted in France and Norway, respectively [22, 23]. Data from an American study in 2011 showed a different proportion of agents involved in perioperative anaphylaxis. Evaluation of 38 patients revealed that 47.4 % experienced a likely IgE-mediated anaphylactic reaction, and the main agents involved were antibiotics. NMBDs were the causative agents in only two (11.1 %) IgE-mediated reactions [24, 25•]. The latter findings are similar to those obtained in a Spanish study, in which antibiotics were the most frequent causal drugs, followed by NMBAs [26]. Latex (22 %) and NMBAs (6 %) were the main agents accountable for perioperative anaphylaxis in a Brazilian study that evaluated 51 patients [27]. Table 1 shows the main agents implied according to different studies.

Drug-induced anaphylaxis was shown to be the leading cause among 112 anaphylaxis fatalities in an Australian study, which also showed a rising tendency in drug-induced anaphylaxis mortality [28]. If anaphylaxis is not promptly recognized and treated, cardiac arrest may follow initial symptoms, but it can also be a sole feature in up to 1.9 % of the cases [15].

The present review will discuss the main aspects of perioperative anaphylaxis, including risk factors, main causal agents, diagnosis, treatment, and preventive measures.

Risk Factors and Special Populations at Risk

Clinical history and previous medical records can reveal important factors associated with perioperative anaphylaxis. It was established that patients in the following categories are at increased risk [2••, 29]:

- Patients who report signs and symptoms of allergic reactions in previous anesthesia
- Patients with a diagnosed allergy to one of the drugs, or products, likely to be used during the current procedure
- Patients who have undergone several operations, especially children with spina bifida, due to the high latex exposure
- Patients reporting signs and symptoms suggestive of latex allergy, regardless of the exposure
- Patients who experience allergic clinical manifestations after ingestion of avocado, kiwi, banana, pineapple, papaya, chestnut, passion fruit, or buckwheat, because of the high frequency of cross-reactivity between those foods and latex

In one study, 34 % of patients who had experienced latex anaphylaxis had previous medical records showing evidence of latex sensitization, such as allergic manifestations after fruit ingestion (latex-fruit syndrome) and after exposure to rubber latex [15]. Atopy is a condition associated with increased risk of latex-induced anaphylaxis, but not to other agents [7, 15, 22, 23, 30].

A special population at risk of anaphylaxis consists of systemic mastocytosis patients. Recently, two cases of

Table 1 Main agents implied as causatives of IgE-mediated perioperative anaphylaxis, according to different studies

	Number of IgE-mediated reactions	NMBA (%)	Latex (%)	Antibiotics (%)	Others (%)
Mertes et al. 2011 [7]	**1,816**	**58.08**	19.65	12.85	10.19
Harboe et al. 2005 [23]	**59**	**93.2**	5	NR	NR
Lobera et al. 2008 [26]	**27**	37	7.4	**44**	11.1
Gurrieri et al. 2011 [25•]	**18**	11.1	16.6	**50**	44.4

The entries in bold are the total number of IgE-mediated reactions and the percentage of the main agent involved

NR not reported

perioperative cardiovascular collapse were reported, and subsequent investigation identified persistently elevated baseline tryptase levels. Bone marrow biopsy and genetic testing confirmed the diagnosis of mastocytosis [31].

Hereditary angioedema is a rare autosomal dominant condition caused by C1 inhibitor deficiency that mimics anaphylaxis, being one of its differential diagnosis. The disease manifests with angioedema of the face, larynx, oropharynx, extremities, abdomen, and genitalia, and its common triggers include surgery, intubation, and anesthesia. A recent study estimated a risk of perioperative angioedema ranging from 5.7 to 30.5 % in hereditary angioedema types I and II not undergoing prophylaxis [32]. Since sole angioedema is not a common feature in perioperative anaphylaxis [15], its observance should remind the possibility of hereditary angioedema or angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker)-induced angioedema.

Clinical Features

Signs and symptoms of perioperative anaphylaxis include rapid-onset skin rash, urticaria, flushing, erythema, angioedema, gastrointestinal manifestations (nausea, vomiting, diarrhea), respiratory manifestations (rhinoconjunctivitis, bronchospasm), tachycardia, and hypotension [8, 15]. Skin involvement that is observed in over 90 % of patients with anaphylaxis may be less frequent in perioperative reactions, making the diagnosis more difficult. In addition to less frequent, skin manifestations are also not easily recognized because the patient is covered and sedated, being unable to report pruritus. Laryngeal angioedema leading to asphyxia and cardiocirculatory collapse are the main causes of death in anaphylaxis. Hoarseness, dysphagia, dizziness, and blurred vision, which are warning signs of severe anaphylactic reactions, will not be present in a sedated patient.

Graduating the severity of anaphylaxis is important and will guide the treatment [6]. However, there is not a uniform system for classifying the reactions, which makes it more difficult to compare data between studies [6, 33, 34].

Clinical presentation and degree of severity of the reaction do not set apart allergic and nonallergic anaphylaxis, but studies show that clinical manifestations secondary to IgE-mediated anaphylaxis tend to be more severe [2••, 7]. A French study showed that skin manifestations were observed in 95.34 and 70.24 % of non-IgE-mediated and IgE-mediated reactions, respectively [7]. Cardiovascular collapse was present in 54.90 % of IgE-mediated reactions versus 10.57 % of non-IgE-mediated reactions.

Perioperative Anaphylaxis: Diagnosis

Quick recognition of anaphylactic signs and symptoms is of utmost importance to the patient prognosis. Perioperative anaphylaxis manifestations usually occur within a few minutes of the exposure of the culprit agent, but it should be pointed out that some triggers are linked to late reactions, such as latex, antibiotics, colloids, dyes, and antiseptics (chlorhexidine) [8, 17]. This could be due to late skin or mucosal absorption, administration of drugs at the end of the surgical procedure, or even deflation of a surgical tourniquet causing allergen circulation [8, 17].

The occurrence of hypotension and bronchospasm during surgery always has to lead to anaphylaxis suspicion, unless another cause can be clearly identified. Since decrease in arterial pressure, difficulty to ventilate, and heart rate variations also occur as a result of different and more common factors during anesthesia, the diagnosis of anaphylaxis can often be delayed, leading to serious clinical outcomes [8]. Patients at risk for late anaphylaxis recognition include beta-blocker users, who do not present the same heart rate elevation that is observed in other patients [6].

Although skin manifestations are very frequent both in IgE- and non-IgE-mediated anaphylaxis, their absence does not exclude the diagnosis [15]. It is important to recognize that cutaneous symptoms, bronchospasm, hypotension, cardiovascular collapse, and cardiac arrest can all occur as isolated features [8].

Surgical drapes can hamper the identification of cutaneous signs, delaying anaphylaxis treatment. Some mild reactions restricted to a single system can resolve spontaneously and go by unnoticed. Under this circumstance, the patient is at greater risk of anaphylaxis in future reexposure to the involved agent; therefore, vigilance is of extreme importance.

Tryptase

Although the diagnosis of anaphylaxis is made based on history and clinical features, measurement of serum tryptase, a marker of mast cell degranulation, can provide additional clues and should be performed whenever it is possible. Tryptase is a mast cell protease released in immediate hypersensitivity reactions, and levels of total serum tryptase above 25 μg/L suggest an IgE-related mechanism [2••]. It can also be elevated in nonimmunological mast cell activation, but its rise tends to be less pronounced and less frequent in these reactions [35, 36]. Conversely, immediate immunological reactions may present with normal tryptase levels, which can be attributed to anaphylaxis secondary to the release of basophil mediators [17, 37, 38].

Tryptase has a half-life of approximately 2 h, returning to baseline values within 12–14 h [39]. The best time to obtain a blood sample to test for tryptase is 1 to 2 h after the onset of reaction [37, 39], with some authors extending this time frame to 1 to 6 h [40]. If initial levels are elevated, anaphylaxis diagnosis is likely, but another blood sample should be withdrawn for comparison at least 2 days after the resolution of the

reaction [17]. This is justified because normal basal values have wide ranges, patients may present byphasic anaphylaxis, and other conditions can elevate baseline tryptase levels, such as systemic mastocytosis and mast cell activation syndrome [2••, 17, 29, 40, 41]. An increase of serum tryptase of 2 ng/mL or 135 % above baseline levels is suggestive of anaphylaxis [33].

In order to help the investigation of an anaphylactic reaction in a patient with systemic mastocytosis, discrimination between mature β tryptase, reflecting mast cell activation, and total serum tryptase should be attempted. Patients with mastocytosis tend to have elevated baseline levels of protryptase, increasing the concentration of total serum tryptase [17, 42].

Perioperative Anaphylaxis: Treatment

Management must begin immediately after recognition of the reaction, and one of the first steps involves withdrawing the possibly offending drug. Initial treatment should be tailored according to clinical presentation.

Mild nonanaphylatic reactions, with manifestations limited to the skin, can be managed with H1 antihistamines (diphenhydramine 25–50 mg or 0.5–1 mg/kg IV or dexchlorpheniramine 5 mg IV) together with H2 antihistamines (ranitidine 50 mg IV) [2, 43]. Treatment of anaphylactic reactions (graded II or more) should rely on early epinephrine administration and volume expansion, as well as on securing airway control and providing oxygen supplementation. Epinephrine can be administered at an initial dose of 10–20 μg IV for grade II reactions and 100–200 μg IV for grade III reactions. Additional doses may be required and should not be delayed [2••].

Isotonic crystalloid solutions are the preferred resuscitation fluids in this setting to compensate for peripheral vasodilation and plasma leakage to extravascular space [43, 44]. The total amount of crystalloids can range from 2 L to up to 10 L IV [44]. ß2-adrenergic agonists such as salbutamol or nebulized epinephrine can be used in reactions presenting with bronchospasm. Corticosteroids can be used in the context of bronchospasm, and their administration also helps to prevent the late phase of anaphylactic shock [44]. Usually proposed regimen is hydrocortisone 200 mg IV bolus (or 5 mg/kg) and then 100 mg (2.5 mg/kg) IV every 6 h or methylprednisolone 125 mg IV every 6 h [44]. Finally, in the event of cardiac arrest, advanced cardiac life support (ACLS) measures should be applied [2••].

There have been reports of increased anaphylaxis severity and impaired response to epinephrine among beta-blocker users [45–47]. However, a study evaluating patients presenting peanut allergy and cardiac disease (congestive heart failure or postmyocardial infarction) observed that beta-blocker use should not be discouraged in these patients, since heart disease mortality was markedly reduced and outweighs beta blocker usage risks [48].

It is important to point out that prompt administration of epinephrine is one of the major cornerstones of treatment. The main factor associated with mortality from anaphylaxis in an Australian study was delayed epinephrine administration [28], and a report of a series of fatal anaphylactic reactions showed that epinephrine was used in only 14 % of patients before cardiac arrest [49].

Preventive Measures

Patients who present with perioperative anaphylaxis should be thoroughly investigated by an allergist after the event in order to avoid reexposure to the culprit drug and prevent potentially fatal outcomes. Perioperative anaphylactic reactions should be reported by anesthesiologists, and intraoperative charts with medication names and their time of administration should be carefully filled out, allowing adequate interpretation. As a secondary prevention measure, the assessment of the patient's previous medical records before any surgical procedure is of fundamental importance, since reports of past reactions may be found and are not always known by the patient in detail.

In order to reduce latex sensitization among high-risk individuals, the substitution of latex materials and the implementation of latex-safe environments are effective as primary prevention measures and must be proposed [2••]. When latex allergy is previously known, surgery should take place in a latex-safe operating room and be preferably the room's first procedure of the day. Proper notification of patient's latex allergy should be present, and health staff in all hospital facilities have to be aware.

Causal Agents and Specific Investigation

Investigation of a drug adverse reaction is challenging. In allergic reactions, most of drugs or their metabolites act as haptens, complicating the diagnosis. Specific investigation should ideally be conducted 4 to 6 weeks after the reaction, since there can be a depletion in both mast cell/basophil mediators and in specific IgE antibodies after anaphylaxis [2••, 43, 50, 51].

Investigation relies on skin tests (prick test (SPT) and intradermal test (IDT)), serum-specific IgE, but it is rarely available, and challenge procedures (Fig. 1) [52]. In this section, we will review the main agents and some of their particular features.

NMBAs

Anaphylaxis secondary to exposure to NMBAs can be elicited either by an IgE-dependent mechanism or by direct mast cell activation. In the first scenario, the main antigenic epitopes are

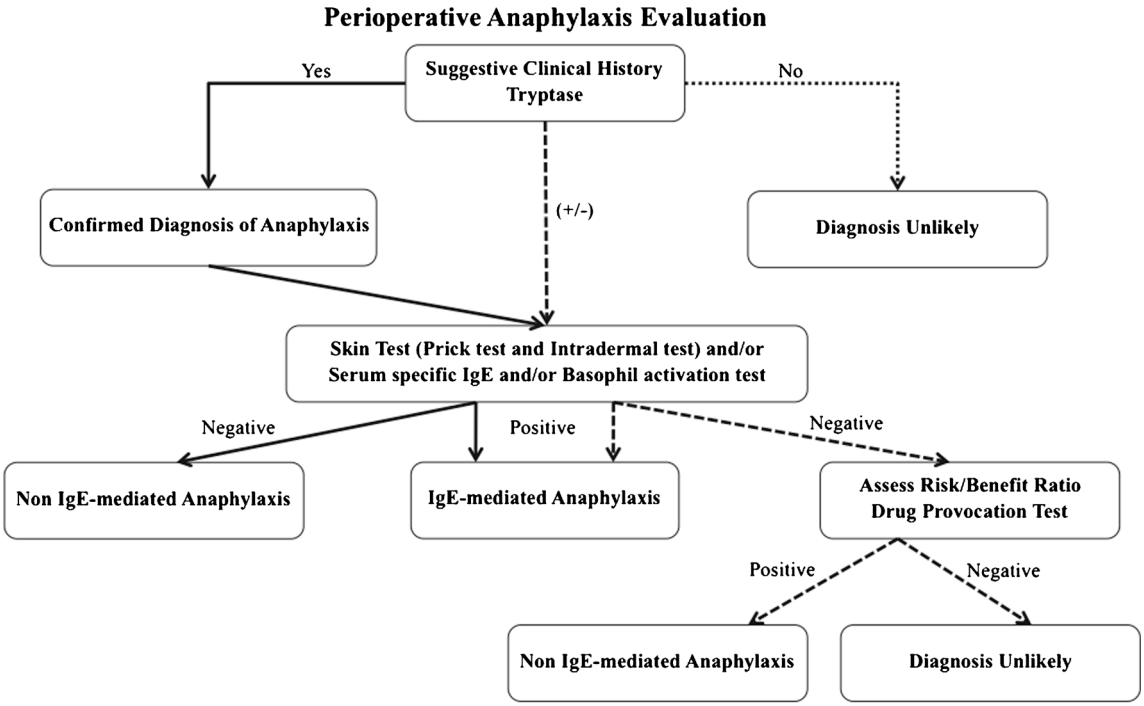

Fig. 1 Perioperative anaphylaxis evaluation

tertiary and quaternary ammonium ions (QAI), and previous contact with NMBAs is not necessary to trigger an immune response, since cross-reactivity with other substances is possible. Regarding nonallergic reactions, benzylisoquinolinium compounds, such as d-tubocurarine, atracurium, and mivacurium, are most likely to cause direct mast cell activation.

Pholcodine (PHO) is a morphine analog constituent of antitussive drugs marketed in several countries and also contains the QAI epitope. The association between its primary IgE-sensitizing potential and the risk of NMBAs anaphylaxis remains controversial, since there are no randomized controlled trials assessing. One study reported an increase of 200 to 300 times in the risk of an IgE-mediated anaphylactic reaction during general anesthesia with suxamethonium among individuals who had been previously IgE-sensitized to the QAI epitope through PHO exposure [53]. Additionally, after withdrawal of one PHO-containing drug from the Norwegian market in 2007, the prevalence of IgE antibodies to PHO, morphine, and suxamethonium decreased, alongside NMBA-suspected anaphylaxis [54]. On the other hand, the USA, a country that does not market PHO-containing medicines nor reports PHO consumption, also observes a significant prevalence of IgE sensitization to PHO [55], suggesting that there might be other environmental sensitizing agents [56].

NMBAs commonly implicated in anaphylaxis include suxamethonium, rocuronium, and succinilcoline. Rocuronium was reported as one of the main inducers of IgE-mediated anaphylaxis among NMBAs in Norwegian [23], Spanish [26], and Australian series [57•]. This could be in part explained by its usage increase [58] and by geographic-determined exposure to PHO. American reports have not confirmed the same findings towards rocuronium [25•], and controversy has arisen regarding skin testing to NMBAs and their nonstandardized methods [59].

Skin testing to NMBAs is the preferred method of investigation of suspected NMBA anaphylaxis. In selected cases, when clinical suspicion is high and skin tests are negative, serum-specific IgE to QAI can be performed. Antibodies prevalence among patients that presented with immediate hypersensitivity reaction to NMBAs varies between 65 and 88 % [2••]. Detection of specific IgE to NMBAs is restricted to suxamethonium and has poor sensitivity [17, 23].

Cross-reactivity among NMBAs is approximately 65 % by skin testing and 80 % by radioimmunoassay inhibition tests [17], although in vitro cross-reactivity should be interpreted with caution, since it might not be of clinical relevance. It should be kept in mind that although skin tests to NMBAs are reliable and provide important information in conducting the investigation and in suggesting alternative agents, they also have limitations, mainly due to lack of standardization.

Latex

Natural rubber latex is derived from the *Hevea brasiliensis* tree, and among its allergens of clinical relevance are Hev b 1, 3, 5, 6.02, and 7 [60••]. Latex allergy is still a major cause of perioperative anaphylaxis worldwide, but this entity currently presents a downward trend because of the reduction in the use

of latex gloves and the propagation of latex-safe surgical environments [2••, 24, 25•].

Individuals at risk of developing latex allergy include atopic patients and those who experience high latex exposure, such as health-care workers and patients who have undergone several surgical procedures or medical interventions [2••, 60••]. Symptoms associated with latex allergy in the perioperative context include cardiovascular collapse, skin rash, and bronchospasm [60••], and differently from those originated by NMBAs, they tend to appear in the maintenance phase of anesthesia [2••, 59, 61]. Gynecologic, obstetric, abdominal, and orthopedic surgeries present the greatest association with the occurrence of latex-related symptoms [60••, 62, 63].

Diagnosis can be made by SPT with standardized commercial natural rubber extracts, available in Europe, which carry both high sensitivity and specificity [64]. Prick-to-prick with a latex glove or SPT with latex glove extracts is not reliable a method because the amount of latex proteins in these scenarios presents great variations [29].

In countries where standardized extracts for SPT are not available, investigation relies on the detection of serum-specific IgE to latex and its allergens (rHev b 1, 3, 5, 6.01, 6.02, 8, 9, and 11). A Brazilian prospective cohort of 400 patients with neural tube defects was able to distinguish patients presenting latex allergy from those with asymptomatic sensitization using serum-specific latex IgE (cutoff value of 0.77 kU_A/L). Serum-specific IgE to rHev b 1 also presented great accuracy for the diagnosis of latex allergy in this study (81.6 % sensitivity and 97.3 % specificity) [65]. Challenge tests, such as glove use test, should be applied whenever there is a clinical history highly suggestive of latex allergy but diagnostic tests are negative or inconclusive [60••].

Antibiotics

Penicillins and cephalosporins are responsible for the majority of antibiotic-induced perioperative anaphylaxis reactions in some series [7, 22, 25•, 66]. The incidence of reactions associated with these drugs has been increasing due to a widespread use of perioperative antibiotic prophylaxis [25•], which relies mainly on beta-lactams.

Investigation methods include in vivo tests, such as SPT and IDT, and in vitro assays. SPT can be performed with the suspected agent, and there are also available commercial reagents, such as benzylpenicilloyl poly-L-lysine (PPL) and minor determinants mixture. Investigation should start with SPT and then progress to IDT if the former is negative.

Since antibiotic-specific IgE assays show poor sensitivity, their use should be reserved in cases presenting with negative skin tests and with a clinical presentation highly suggestive of an IgE-mediated mechanism [2••]. Available assays include penicilloyl G, penicilloyl V, amoxycilloyl, ampicilloyl, and cefaclor [17].

Vancomycin can elicit reactions through an IgE-mediated mechanism or via mast cell and basophil direct mediator release, a reaction commonly known as the "red man syndrome." The latter is characterized by flushing, pruritus, and an erythematous rash typically spreading over the face, neck, and upper torso, and it is associated with a rapid infusion of the first dose of the drug [43, 67, 68]. In less frequent cases, patients can also present dyspnea, angioedema, and hypotension [17]. Vancomycin IgE-mediated reactions are rare and should be investigated with IDT [17, 43, 69].

Hypnotics

Propofol is a hypnotic agent that has been associated with anaphylactic reactions [70–72]. It contains two isopropyl groups that act as antigenic epitopes, and it is formulated in a lipid solution containing 10 % soybean oil, 2.25 % glycerol, and 1.2 % egg lecithin [43].

Some authors speculate the occurrence of propofol-related anaphylactic reactions is associated with the presence of egg lecithin and soybean oil in its vehicle, leading to the assumption that patients allergic either to egg or soy should avoid propofol [70, 71]. It is important to point out that the lecithin found in propofol is a highly purified egg yolk protein, and egg-allergic patients tend to show sensitization and react to egg white proteins [43]. The major allergen in egg yolk is chicken serum albumin (Gal d 5). Soybean oil used in propofol formulation is refined, leaving allergenic proteins out of the final product and therefore making it difficult to elicit an immediate hypersensitivity reaction.

Currently, there are no consistent reports confirming the relationship between egg or soy allergy and an increased risk of anaphylactic reactions due to propofol [2••, 73]. Immediate reactions involving propofol are most frequently due to isopropyl groups and phenol and should be investigated through skin tests, specific IgE, and histamine-release tests [17].

Benzodiazepines are rarely the cause of immediate hypersensitivity reactions. Among this drug class, midazolam [7, 15, 22, 25•, 30, 74, 75] is the main causative agent in the perioperative setting, and SPT with the undiluted drug and IDT can be performed when investigating the reaction [17].

Opioids

Opioids, like morphine and meperidine, typically trigger non-IgE-mediated reactions caused by nonspecific mast cell activation [43]. A study evaluating the role of SPT in investigating morphine, meperidine, and papaveratum hypersensitivity showed that opiate-sensitive individuals responded similarly as the control study in the SPT, suggesting that this test should not be performed and that placebo-controlled challenge should be considered when possible [76].

Some anaphylactic reports involving opioids have been published, including a recent case of anaphylaxis with codeine, with a positive investigation that included SPT (with negative tests in three healthy controls), histamine-release test, and oral challenge test [77]. However, there is data supporting the safe use of codeine in patients presenting chronic urticaria [78].

Fentanyl is a fast-acting narcotic analgesic and sedative widely used in surgical procedures, which does not tend to cause nonimmunological histamine release [43, 79]. There are few case reports describing fentanyl-related anaphylactic reactions [80–82], and IDT was used to investigate the reported cases.

Colloids

Plasma substitutes account for 1 to 4 % of perioperative anaphylaxis cases [15, 22, 23]. The main substances used in surgical procedures include albumin, hydroxyethyl starch compounds, gelatin, and dextrans. Gelatin and dextran pose the greatest risk of eliciting an anaphylactic reaction among colloids [83].

Previous medical history of gelatin allergy points out the need to avoid gelatin-based colloids, since it is associated with an IgE-mediated mechanism [83, 84]. Suspected cases can be investigated with skin tests (SPT and IDT) and also via specific serum IgE (Phadia c74).

Dextrans can induce the formation of dextran-reactive IgG antibodies, and these are linked to dextran-induced anaphylactic reactions (DIAR) [85, 86]. Dextran-reactive antibodies form immune complexes with dextran, and clinical manifestations of the reaction include bronchospasm, severe hypotension, and cardiorespiratory arrest. Investigation with skin tests is not helpful, since DIAR does not involve an IgE-mediated mechanism. The preinfusion of dextran 1 is an effective preventive measure, since it competitively inhibits dextran from binding to IgG antibodies. Dextran 1 is a small fraction of the entire dextran complex that binds antidextran antibodies, but does not create immune complexes.

Hydroxyethyl starch compounds have been reported as anaphylaxis etiologic agents [87, 88], and investigation should include skin tests. The role of IgM and IgG in reactions mediated by these compounds remains uncertain [89]. Regarding albumin, egg allergy does not preclude the use of albumin-based colloids, since the allergenic proteins are different [90].

Chlorhexidine

Chlorhexidine is widely used as an antiseptic agent with potentially allergenic properties that may cause severe hypersensitivity reactions. Studies showed that immediate hypersensitivity reactions to chlorhexidine appear to be more common than previously thought and they are underreported [91, 92]. Centers investigating patients with reactions during anesthesia and surgery should maintain high index of suspicion and routinely include testing for chlorhexidine allergy.

Conclusions

Perioperative anaphylaxis is a potentially life-threatening syndrome that requires prompt recognition and intervention. Initial clinical signs can be subtle and not infrequently affect only one system. Fast progression resulting in more serious systemic manifestations can occur, so management has to be aggressive and epinephrine administration must not be postponed. Increased levels of tryptase are often present in immediate hypersensitivity reactions, so a blood sample should be withdrawn during the event to help further investigation. Levels of tryptase obtained during the reaction must be compared to the patient's baseline levels to exclude associated diseases. Subsequent referral to an allergist is central, since each potential culprit agent presents particularities and requires specific testing strategies. Reporting of suspected perioperative anaphylaxis cases should be encouraged since the identification of patients at risk and their correct management could result in the prevention of fatal outcomes.

Compliance with Ethics Guidelines

Conflict of Interest Violeta Régnier Galvão and Pedro Giavina-Bianchi declare that they have no conflict of interest.

Mariana Castells has served as a consultant for Merck & Co. and Sanofi Aventis, has an NIH grant pending, has received royalties from UpToDate, and has had travel/accommodation expenses covered by the AAAAI.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Sampson HA, Muñoz-Furlong A, Bock SA, et al. Symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol. 2005;115:584–91.
2.•• Mertes PM, Malinovsky JM, Jouffroy L, Working Group of the SFAR and SFA, Aberer W, Terreehorst I, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. J Investig Allergol Clin Immunol. 2011;21:442–53.

Important 2011 guidelines on perioperative anaphylaxis elaborated by experts in the field.

3. Mitsuhata H, Matsumoto S, Hasegawa J. The epidemiology and clinical features of anaphylactic and anaphylactoid reactions in the perioperative period in Japan. Masui. 1992;41:1664–9.
4. Light KP, Lovell AT, Butt H, Fauvel NJ, Holdcroft A. Adverse effects of neuromuscular blocking agents based on yellow card reporting in the U.K.: are there differences between males and females? Pharmacoepidemiol Drug Saf. 2006;15:151–60.
5. Mertes PM, Laxenaire MC, Lienhart A, Aberer W, Ring J, Pichler WJ, et al. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. J Investig Allergol Clin Immunol. 2005;15:91–101.
6. Mertes PM, Lambert M, Guéant-Rodriguez RM, Aimone-Gastin I, Mouton-Faivre C, Moneret-Vautrin DA, et al. Perioperative anaphylaxis. Immunol Allergy Clin North Am. 2009;29:429–51.
7. Mertes PM, Alla F, Tréchot P, Auroy Y, Jougla E, Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. Anaphylaxis during anesthesia in France: an 8-year national survey. J Allergy Clin Immunol. 2011;128:366–73.
8. Harper NJN, Dixon T, Dugué P, et al. Suspected anaphylactic reactions associated with anaesthesia. Anaesthesia. 2009;64:199–211.
9. Johansson SGO, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113:832–6.
10. Simons FER, Ardusso LRF, Bilò MB, et al. World Allergy Organization anaphylaxis guidelines: summary. J Allergy Clin Immunol. 2011;127:587–593.e1–22.
11. Lieberman P, Camargo Jr CA, Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. Ann Allergy Asthma Immunol. 2006;97:596–602.
12. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391–7.
13. Campbell RL, Hagan JB, Manivannan V, Decker WW, Kanthala AR, Bellolio MF, et al. Evaluation of national institute of allergy and infectious diseases/food allergy and anaphylaxis network criteria for the diagnosis of anaphylaxis in emergency department patients. J Allergy Clin Immunol. 2012;129:748–52.
14. Farnam K, Chang C, Teuber S, Gershwin ME. Nonallergic drug hypersensitivity reactions. Int Arch Allergy Immunol. 2012;159:327–45.
15. Mertes PM, Laxenaire M-C, Alla F, Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. Anesthesiology. 2003;99:536–45.
16. Dewachter P, Mouton-Faivre C. What investigation after an anaphylactic reaction during anaesthesia? Curr Opin Anaesthesiol. 2008;21:363–8.
17. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. Allergy. 2007;62:471–87.
18. Woessner KM, Castells M. NSAID single-drug-induced reactions. Immunol Allergy Clin North Am. 2013;33:237–49.
19. Trcka J, Schmidt C, Seitz CS, Bröcker E-B, Gross GE, Trautmann A. Anaphylaxis to iodinated contrast material: nonallergic hypersensitivity or IgE-mediated allergy? AJR Am J Roentgenol. 2008;190:666–70.
20. Kowalski ML, Makowska JS, Blanca M, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs)—classification, diagnosis and management: review of the EAACI/ENDA(#) and GA2LEN/HANNA*. Allergy. 2011;66:818–29.
21. Prieto-García A, Tomás M, Pineda R, Tornero P, Herrero T, Fuentes V, et al. Skin test-positive immediate hypersensitivity reaction to iodinated contrast media: the role of controlled challenge testing. J Investig Allergol Clin Immunol. 2013;23:183–9.
22. Laxenaire MC. Epidemiology of anesthetic anaphylactoid reactions. Fourth multicenter survey (July 1994-December 1996). Ann Françaises Anesthèsie Rèanimation. 1999;18:796–809.
23. Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during anesthesia in Norway: a 6-year single-center follow-up study. Anesthesiology. 2005;102:897–903.
24. Levy JH, Castells MC. Perioperative anaphylaxis and the United States perspective. Anesth Analg. 2011;113:979–81.
25.• Gurrieri C, Weingarten TN, Martin DP, Babovic N, Narr BJ, Sprung J, et al. Allergic reactions during anesthesia at a large United States referral center. Anesth Analg. 2011;113:1202–12. *American retrospective study evaluating 38 cases of perioperative anaphylaxis from 1992 to 2010. An IgE-mediated mechanism was identified in 47.3% of cases, and among those reactions, antibiotics were the most prevalent likely causative agent (50%). Neuromuscular blocking drugs were implicated in 11% of the reactions*.
26. Lobera T, Audicana MT, Pozo MD, Blasco A, Fernández E, Cañada P, et al. Study of hypersensitivity reactions and anaphylaxis during anesthesia in Spain. J Investig Allergol Clin Immunol. 2008;18:350–6.
27. Garro LS, Rodrigues AT, Ribeiro MR, Aun MV, Kalil J, Motta AA, et al. Perioperative anaphylaxis: clinical features of 51 patients. J Allergy Clin Immunol. 2012;129:AB180.
28. Liew WK, Williamson E, Tang MLK. Anaphylaxis fatalities and admissions in Australia. J Allergy Clin Immunol. 2009;123:434–42.
29. Dewachter P, Mouton-Faivre C, Emala CW. Anaphylaxis and anesthesia: controversies and new insights. Anesthesiology. 2009;111:1141–50.
30. Karila C, Brunet-Langot D, Labbez F, Jacqmarcq O, Ponvert C, Paupe J, et al. Anaphylaxis during anesthesia: results of a 12-year survey at a French pediatric center. Allergy. 2005;60:828–34.
31. Bridgman DE, Clarke R, Sadleir PHM, Stedmon JJ, Platt P. Systemic mastocytosis presenting as intraoperative anaphylaxis with atypical features: a report of two cases. Anaesth Intensive Care. 2013;41:116–21.
32. Aygören-Pürsün E, Martinez Saguer I, Kreuz W, Klingebiel T, Schwabe D. Risk of angioedema following invasive or surgical procedures in HAE type I and II—the natural history. Allergy. 2013;68:1034–9.
33. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004;114:371–6.
34. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol. 2010;125:569–74. *574.e1–574.e7*.
35. Mertes P-M, Laxenaire M-C, GERAP. Anaphylactic and anaphylactoid reactions occurring during anaesthesia in France. Seventh epidemiologic survey (January 2001-December 2002). Ann Françaises Anesthèsie Rèanimation. 2004;23:1133–43.
36. Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. Br J Anaesth. 1998;80:26–9.
37. Laroche D, Vergnaud MC, Sillard B, Soufarapis H, Bricard H. Biochemical markers of anaphylactoid reactions to drugs. Comparison of plasma histamine and tryptase. Anesthesiology. 1991;75:945–9.
38. Sala-Cunill A, Cardona V, Labrador-Horrillo M, Luengo O, Esteso O, Garriga T, et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. Int Arch Allergy Immunol. 2013;160:192–9.

39. Schwartz LB, Yunginger JW, Miller J, Bokhari R, Dull D. Time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. J Clin Invest. 1989;83:1551–5.
40. Michalska-Krzanowska G. Tryptase in diagnosing adverse suspected anaphylactic reaction. Adv Clin Exp Med Off Organ Wroclaw Med Univ. 2012;21:403–8.
41. Schwartz LB, Sakai K, Bradford TR, Ren S, Zweiman B, Worobec AS, et al. The alpha form of human tryptase is the predominant type present in blood at baseline in normal subjects and is elevated in those with systemic mastocytosis. J Clin Invest. 1995;96:2702–10.
42. Caughey GH. Tryptase genetics and anaphylaxis. J Allergy Clin Immunol. 2006;117:1411–4.
43. Hepner DL, Castells MC. Anaphylaxis during the perioperative period. Anesth Analg. 2003;97:1381–95.
44. Longrois D, Lejus C, Constant I, Bruyère M, Mertes P-M. Treatment of hypersensitivity reactions and anaphylactic shock occurring during anaesthesia. Ann Françaises Anesthèsie Rèanimation. 2011;30:312–22.
45. Jacobs RL, Rake Jr GW, Fournier DC, Chilton RJ, Culver WG, Beckmann CH. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. J Allergy Clin Immunol. 1981;68:125–7.
46. Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. J Allergy Clin Immunol. 1988;81:1–5.
47. Mueller UR. Cardiovascular disease and anaphylaxis. Curr Opin Allergy Clin Immunol. 2007;7:337–41.
48. TenBrook Jr JA, Wolf MP, Hoffman SN, Rosenwasser LJ, Konstam MA, Salem DN, et al. Should β-blockers be given to patients with heart disease and peanut-induced anaphylaxis? A decision analysis. J Allergy Clin Immunol. 2004;113:977–82.
49. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy J Br Soc Allergy Clin Immunol. 2000;30:1144–50.
50. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy. 2002;57:45–51.
51. Soetens F, Rose M, Fisher M. Timing of skin testing after a suspected anaphylactic reaction during anaesthesia. Acta Anaesthesiol Scand. 2012;56:1042–6.
52. Aun MV, Bisaccioni C, Garro LS, Rodrigues AT, Tanno LK, Ensina LF, et al. Outcomes and safety of drug provocation tests. Allergy Asthma Proc. 2011;32:301–6.
53. Florvaag E, Johansson SGO. The pholcodine case. Cough medicines, IgE-sensitization, and anaphylaxis: a devious connection. World Allergy Organ J. 2012;5:73–8.
54. Florvaag E, Johansson SGO, Irgens Å, de Pater GH. IgE-sensitization to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market. Allergy. 2011;66:955–60.
55. Johansson SGO, Florvaag E, Oman H, et al. National pholcodine consumption and prevalence of IgE-sensitization: a multicentre study. Allergy. 2010;65:498–502.
56. Dong S, Acouetey DS, Guéant-Rodriguez RM, Zmirou-Navier D, Rémen T, Blanca M, et al. Prevalence of IgE against neuromuscular blocking agents in hair dressers and bakers. Clin Exp Allergy. 2013;43:1256–62.
57.• Sadleir PHM, Clarke RC, Bunning DL, Platt PR. Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011. Br J Anaesth. 2013;110:981–7. *Australian study evaluating cases of perioperative anaphylaxis caused by NMBAs over a 10 year period. In this report, rocuronium presented a higher rate of IgE-mediated anaphylaxis compared to vecuronium*.
58. Rose M, Fisher M. Rocuronium: high risk for anaphylaxis? Br J Anaesth. 2001;86:678–82.
59. Dhonneur G, Combes X, Chassard D, Merle JC. Skin sensitivity to rocuronium and vecuronium: a randomized controlled prick-testing study in healthy volunteers. Anesth Analg. 2004;98:986–9. *table of contents*.
60.•• Cabañes N, Igea JM, de la Hoz B, et al. Latex allergy: position paper. J Investig Allergol Clin Immunol. 2012;22:313–30. *2012 position paper on latex allergy by the Latex Committee of the Spanish Society of Allergology and Clinical Immunology. Provides essential information on latex allergens, diagnosis and management of latex allergy and also on preventive measures*.
61. Mertes PM, Laxenaire MC. Allergy and anaphylaxis in anaesthesia. Minerva Anestesiol. 2004;70:285–91.
62. Draisci G, Nucera E, Pollastrini E, Forte E, Zanfini B, Pinto R, et al. Anaphylactic reactions during cesarean section. Int J Obstet Anesth. 2007;16:63–7.
63. Lieberman P. Anaphylactic reactions during surgical and medical procedures. J Allergy Clin Immunol. 2002;110:S64–9.
64. Turjanmaa K, Palosuo T, Alenius H, Leynadier F, Autegarden JE, André C, et al. Latex allergy diagnosis: in vivo and in vitro standardization of a natural rubber latex extract. Allergy. 1997;52:41–50.
65. Garro LS, Pelluzzo F, Kalil J, Motta AA, Giavina-Bianchi P. Identification of factors associated with latex sensitization and allergy in patients with spina bifida. J Allergy Clin Immunol. 2011;127:AB250.
66. Mertes PM, Demoly P, Malinovsky JM. Hypersensitivity reactions in the anesthesia setting/allergic reactions to anesthetics. Curr Opin Allergy Clin Immunol. 2012;12:361–8.
67. Polk RE. Anaphylactoid reactions to glycopeptide antibiotics. J Antimicrob Chemother. 1991;27:17–29. *Suppl B*.
68. Sivagnanam S, Deleu D. Red man syndrome. Crit Care Lond Engl. 2003;7:119–20.
69. Anne' S, Middleton Jr E, Reisman RE. Vancomycin anaphylaxis and successful desensitization. Ann Allergy. 1994;73:402–4.
70. Tashkandi J. My patient is allergic to eggs, can i use propofol? A case report and review. Saudi J Anaesth. 2010;4:207–8.
71. Hofer KN, McCarthy MW, Buck ML, Hendrick AE. Possible anaphylaxis after propofol in a child with food allergy. Ann Pharmacother. 2003;37:398–401.
72. You B-C, Jang A-S, Han J-S, Cheon H-W, Park J-S, Lee J-H, et al. A case of propofol-induced oropharyngeal angioedema and bronchospasm. Allergy Asthma Immunol Res. 2012;4:46–8.
73. Dewachter P, Mouton-Faivre C, Castells MC, Hepner DL. Anesthesia in the patient with multiple drug allergies: are all allergies the same? [Miscellaneous article]. Curr Opin Anaesthesiol. 2011;24:320–5.
74. Laxenaire MC, Mertes PM, Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. Anaphylaxis during anaesthesia. Results of a two-year survey in France. Br J Anaesth. 2001;87:549–58.
75. Hwang J-Y, Jeon Y-T, Na H-S, Lee J-H, Choi S-J, Jung SH. Midazolam hypersensitivity during the transportation to theater—a case report. Korean J Anesth. 2010;59:S1–2.
76. Nasser SM, Ewan PW. Opiate-sensitivity: clinical characteristics and the role of skin prick testing. Clin Exp Allergy J Br Soc Allergy Clin Immunol. 2001;31:1014–20.
77. Yoo H-S, Yang E-M, Kim M-A, Hwang S-H, Shin Y-S, Ye Y-M, et al. A case of codeine induced anaphylaxis via oral route. Allergy Asthma Immunol Res. 2014;6:95–7.
78. Giavina-Bianchi P, Dente M, Giavina-Bianchi M, Mota AA, Kalil J. Codeine challenge in chronic urticaria patients. Allergol Immunopathol (Madr). 2007;35:280.
79. Marone G, Stellato C, Mastronardi P, Mazzarella B. Mechanisms of activation of human mast cells and basophils by general anesthetic drugs. Ann Françaises Anesthèsie Rèanimation. 1993;12:116–25.

80. Bennett MJ, Anderson LK, McMillan JC, Ebertz JM, Hanifin JM, Hirshman CA. Anaphylactic reaction during anaesthesia associated with positive intradermal skin test to fentanyl. Can Anaesth Soc J. 1986;33:75–8.
81. Fukuda T, Dohi S. Anaphylactic reaction to fentanyl or preservative. Can Anaesth Soc J. 1986;33:826–7.
82. Tomar GS, Tiwari AK, Chawla S, Mukherjee A, Ganguly S. Anaphylaxis related to fentanyl citrate. J Emerg Trauma Shock. 2012;5:257–61.
83. Laxenaire MC, Charpentier C, Feldman L. Anaphylactoid reactions to colloid plasma substitutes: incidence, risk factors, mechanisms. A French multicenter prospective study. Ann Françaises Anesthèsie Rèanimation. 1994;13:301–10.
84. Wahl R, Kleinhans D. IgE-mediated allergic reactions to fruit gums and investigation of cross-reactivity between gelatine and modified gelatine-containing products. Clin Exp Allergy J Br Soc Allergy Clin Immunol. 1989;19:77–80.
85. Hernández D, de Rojas F, Martínez Escribano C, Arriaga F, Cuellar J, Molins J, et al. Fatal dextran-induced allergic anaphylaxis. Allergy. 2002;57:862.
86. Zinderman CE, Landow L, Wise RP. Anaphylactoid reactions to Dextran 40 and 70: reports to the United States Food and Drug Administration, 1969 to 2004. J Vasc Surg. 2006;43:1004–9.
87. Kim HJ, Kim SY, Oh MJ, Kim JM. Anaphylaxis induced by hydroxyethyl starch during general anesthesia—a case report. Korean J Anesth. 2012;63:260–2.
88. Ebo DG, Schuerwegh A, Stevens WJ. Anaphylaxis to starch. Allergy. 2000;55:1098–9.
89. Dieterich HJ, Kraft D, Sirtl C, Laubenthal H, Schimetta W, Pölz W, et al. Hydroxyethyl starch antibodies in humans: incidence and clinical relevance. Anesth Analg. 1998;86:1123–6.
90. Smith SJ, Geha D, Alston TA. Egg allergy and blood products: you say albumen, I say albumin. Anesthesiology. 2003;98:1304–5.
91. Nakonechna A, Dore P, Dixon T, Khan S, Deacock S, Holding S, et al. Immediate hypersensitivity to chlorhexidine is increasingly recognized in the United Kingdom. Allergol Immunopathol (Madr). 2014;42:44–9.
92. Jee R, Nel L, Gnanakumaran G, Williams A, Eren E. Four cases of anaphylaxis to chlorhexidine impregnated central venous catheters: a case cluster or the tip of the iceberg? Br J Anaesth. 2009;103:614–5.