Practical Guidelines for Perioperative Hypersensitivity Reactions

Brief running title: Perioperative hypersensitivity reactions

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ABSTRACT

Perioperative hypersensitivity reactions constitute a first-line problem for anesthesiologists and allergists, so it is advisable that hospitals have a consensus protocol for the diagnosis and management of these reactions. However, this kind of protocols is not present in many hospitals, leading to problems in treatment, the communication of incidents and subsequent etiological diagnosis. In this document we present a systematic review of the available scientific evidence and provide general guidelines for the management of acute episodes and for referral of patients with perioperative hypersensitivity reactions to Allergy Units. Members of the Drug Allergy Committee of the Spanish Society of Allergy and Clinical Immunology (SEAIC) have created this document in collaboration with members of the Spanish Anaesthesia Society (SEDAR). A practical algorithm is proposed for the etiologic diagnosis and recommendations are provided for the management of hypersensitive patients.

Key words: Anaesthesia, Allergy, Anaphylaxis, Hypersensitivity, Perioperative, Skin tests; Tryptase

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Resumen:

Las reacciones de hipersensibilidad perioperatorias constituyen un problema de primera línea para los anestesiólogos y alergólogos, por lo que es recomendable que los hospitales tengan un protocolo de consenso para el diagnóstico y el tratamiento de estas reacciones. Sin embargo, este tipo de protocolos no está presente en muchos hospitales, lo que conlleva problemas en el tratamiento, la comunicación de incidentes y el posterior diagnóstico etiológico. Este documento ha sido creado por miembros del Comité de Alergia a Medicamentos de la Sociedad Española de Alergia e Inmunología Clínica (SEAIC) en colaboración con miembros de la Sociedad Española de Anestesia (SEDAR). Se ha realizado una revisión sistemática de la evidencia científica disponible y se proporcionan pautas generales para el manejo de episodios agudos y para la derivación de pacientes con reacciones de hipersensibilidad perioperatoria a los Servicios de Alergología. Se propone un algoritmo práctico para el diagnóstico etiológico y se brindan recomendaciones para el manejo de pacientes con reacciones alérgicas perioperatorias.

Palabras clave: Anesteisa, Alergia, Anafilaxia, Hipersensibilidad, Periperatorias, Tests cutaneous, triptasa.

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INTRODUCTION

During the perioperative period, patients are exposed to multiple agents that can induce hypersensitivity reactions, with an estimated incidence of 1:10000 anaesthesia procedures [1, 2, 3]. However, prospective studies suggest that this is an underestimate and quote incidences of 1:3180 [4] and 1:1480 [5], respectively. In a recent prospective Spanish study the incidence of perioperative reactions was 1:381, being 48% mild, involving only the skin, and 52% anaphylaxis [6].

Perioperative anaphylaxis, due to its low incidence, is an unexpected and severe event, which makes its identification and early treatment difficult, and partially explains its high mortality (3-10% of cases) [1, 7]. These reactions constitute a first-line problem for anaesthesiologists and allergists, and although it is advisable that hospitals have a consensus protocol of action for diagnosis and treatment of these reactions [8], there are few [9-12, 13] and none of them specifically applicable to the Spanish population. Furthermore, there are no protocols of action for patients with a prior history of perioperative hypersensitivity reactions; these patients must be identified in pre-anaesthesia consultations and referred to an allergy specialist for evaluation. All this lack of specific protocols can lead to a greater potential risk of re-exposure for the patient.

The management of perioperative hypersensitivity reactions is extremely complex, and should be a combined effort between allergists and anaesthesiologists [14, 15]. This comprises two well-differentiated parts [16, 17]: i) the acute phase of the reaction, which is anaesthesiologists' responsibility [14]; ii) later diagnosis in which the causal agent should be confirmed if possible, which is allergist's responsibility. The aim of the present study is to develop clinical guidelines for the management of patients with a hypersensitivity reaction during the perioperative period and the later allergological diagnosis.

METHODOLOGY

A bibliographic search was performed using key words agreed on by the authors. This search was performed using electronic databases (MEDLINE and PubMed), electronic libraries (Science Direct, OVID), and a systematic review database (Cochrane Library). Publications were selected from between January 1985 and March 2016. The selection took into account the prevalence, pathogenesis, clinical manifestations, diagnosis, and treatment of perioperative hypersensitivity. The key terms used were: perioperative anaphylaxis, perianaesthetic anaphylaxis, and perioperative hypersensitivity reactions. In addition, the names of drugs commonly involved in perioperative reactions were searched for in combination with the

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terms skin tests, prick test, intradermal test, in vitro tests, and drug provocation tests. This search found 323 publications. Original research articles and systematic reviews were included; non-systematic reviews, comments, and other types of article were excluded. We also included studies examining incidence, prevalence, natural history, clinical manifestations, pathogenesis, diagnosis and treatment. Studies not addressing perianaesthetic/perioperative hypersensitivity were excluded. Following this review process by the expert panel, 195 publications were finally selected. Moreover, the expert panel evaluated the quality of the evidence and provided grades of recommendation according to the Scottish Intercollegiate Guidelines Network [18]. Wherever evidence was lacking, a consensus was reached among the experts.

MECHANISMS OF PERIOPERATIVE HYPERSENSITIVITY

Although the clinical presentation and the early management are similar, two mechanisms can be involved: immunological (allergic reactions) or non-immunological [19]. IgE-mediated immunological reactions represent 60% of all reactions and their severity can increase in a subsequent surgery [20-23]. These reactions need a sensitization phase, with activation of Th2 and B lymphocytes, with production of specific IgE antibodies that bind to high affinity receptors of mast cells and basophils. In a second contact with the sensitizing agent and its binding to specific IgE, release of mediators such as histamine, tryptase, PG2, leukotrienes, thromboxane A2, platelet activating factor, chemokines and cytokines such as tumor necrosis factor occur leading to the development of the reaction [24]. It should be noted that in some cases a reaction could occur upon first contact, which could be due to cross-reactivity with other substances to which the patient is sensitized. On rare occasions, immunological reactions may not be IgE mediated, as have been described for dextrans, which create immunocomplexes with IgG and activate the complement system, being these reactions less severe [25].

Though the mechanisms are not well established, it is accepted that non-immunological reactions are caused by the direct stimulation (pharmacological or toxic) of mast cells and basophils, which induces their degranulation [26] and therefore previous contact with the causative agent is not required [20]. These reactions are generally milder than immunologically mediated ones [7], except for subgroup of patients who are over-responders to the histamine released by neuromuscular blocking agents (NMBAs) [3, 27, 28].

CLINICAL SYMPTOMS

The clinical presentation of anaphylaxis due to anaesthesia is similar to other forms of anaphylaxis but presents some particular aspects [16, 29]. The patient is generally unconscious, covered by surgical drapes and cannot express what is happening, so the prodromal symptoms (pruritus, dyspnoea or discomfort) may not be recognized. Instead, the reaction is often first recognized by the anaesthesiologist, who notices some non-specific symptoms such as a drop in blood pressure and arterial saturation, difficulty in the mechanical ventilation, severe arrhythmias and cardiovascular collapse [1, 30, 31]. This implies that some mild cases may recover spontaneously, meaning the reaction passes unnoticed. Subsequently, re-exposure can lead to a more severe, potentially life threatening reaction [4].

Reactions may occur at any moment during anaesthesia [32], however around 90% have been shown to occur suddenly during the induction phase after intravenous administration of the culprit agent (especially antibiotics, NMBAs and hypnotic drugs) [32]. Sometimes reactions may occur with a more delayed latency period, depending on several factors: i) agents, such as dyes [33] and colloids; ii) routes of administration (cutaneous, mucosal, intraperitoneal or subcutaneous) that delay the absorption [34, 35] of agents such as latex [9], chlorhexidine or surgical glues [9, 10, 36]; iii) some surgical procedures, such as gynaecological, due to the release of latex particles in utero after the injection of oxytocin [31], or some orthopaedic procedures, after the release of the tourniquet used in surgeries with ischemia [37].

Considering the organs involved, cutaneous symptoms, such as erythema, urticaria and angioedema, are observed in 66%-70% of IgE-mediated reactions and in more than 90% of non-IgE mediated reactions [38], with up to 10-20% of cases do not having any cutaneous symptoms [39, 40]. Cardiovascular symptoms often include hypotension and tachycardia, which may rapidly progress to severe arrhythmia and cardiovascular collapse if they are not immediately treated [31, 41-43]. These are the most frequent signs of severe anaphylaxis, and sometimes the cardiovascular collapse or cardio respiratory arrest might be the initial presentation symptoms [40, 44]. In some cases bradycardia might be the first sign of anaphylaxis; this is problematic because the reaction could be confused with other, non-allergic anaesthesia related effects, especially if the patient is being treated with beta-blockers. Other rare symptoms include acute coronary events associated with an immediate hypersensitivity reaction, such as Kounis syndrome, caused by the release of mediators from the cardiac mast cells [45, 46]. Respiratory symptoms such as bronchospasm are less frequent, being present in only around half of all cases [47], particularly for those patients with a prior diagnosis of asthma [47]. The first sign may be an increase in pulmonary resistance or a decrease in oxygen saturation [48]. Other symptoms, such as alteration of coagulation [49], pulmonary oedema and rhabdomyolysis are very rare and are usually related to a severe and

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prolonged anaphylactic shock. These symptoms are usually related to the coexistence of cardiac disease, use of beta-blockers or angiotensin converting enzyme inhibitors (ACE inhibitors). Many clinical symptoms of anaphylaxis reactions can be unspecific, and may resemble the symptoms of other problems that can occur during anaesthesia [9], so it is critical to perform a differential diagnosis (Table 1).

There are several factors that has been identified as main contributors to the clinical severity of anaphylaxis [11, 40]: i) age of patients, related to a lower pulmonary capacity; ii) prior diseases, specially cardiac or respiratory; iii) systemic mastocytosis or elevated baseline tryptase [50]; iv) current treatment of the patient; this may alter their response to catecholamine treatment, thereby potentially increasing mortality for medicines such as beta-blockers, ACE inhibitors, angiotensin receptor antagonists II, monoaminoxidase inhibitors, tricyclic antidepressants, and serotonin uptake inhibitors; v) form of administration, with the reaction occurring more rapidly when the drug is administered intravenously; vi) initial presentation of the reaction, such as vascular collapse or cardiorespiratory arrest; vii) the speed of the clinical evolution: the faster the evolution, the more severe the reaction and the higher the risk of a fatal outcome; viii) the delay in administering epinephrine in the case of severe anaphylaxis [51, 52].

Several classification systems have been proposed to evaluate the severity of reactions occurring during anaesthesia [11].

IMMEDIATE MANAGEMENT OF PERIOPERATIVE REACTIONS

The anaesthesiologist has a major role to play in both the prevention and treatment of hypersensitivity reactions, should they occur.

1. PREVENTIVE MEASURES

Prior to surgery, the anaesthesiologist should evaluate the clinical history of the patient with regards to any previous history of allergy (especially relating to medicines and latex), any previous reactions during surgical procedures, any concomitant diseases and their treatments. Any of these factors may affect the development of an allergic reaction during anaesthesia and will influence the actions of the anaesthesia for the management of the patient.

If there is suspicion of latex allergy, the patient must be referred to an allergist for an allergological study prior to surgery. In the case of emergency surgery for a patient with suspected latex allergy the surgery must be performed in a latex-free environment. Similarly, for emergency patients with a suspected drug allergy the suspected drugs should be avoided. If possible, loco-regional anaesthesia is preferred for such patients. Premedication with

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steroids and antihistamines should be considered, especially if there is a suspicion of a non-immunologically mediated reaction.

2. REACTION MANAGEMENT

In the event a reaction occur a step process must be followed:

2.1. Recognising the allergic reaction

The anaesthesiologist must evaluate the signs the patient is presenting and decide whether they are indicative of anaphylaxis by performing differential diagnosis (Table 1), establishing the severity of the reaction and identifying the possible culprit agents.

2.2. Treatment of the reaction

The reaction must be treated immediately since this will influence the patient's prognosis, especially for severe reactions. This will include a general and specific pharmacological treatment depending on the severity of the reaction (Figure 1). Agents used in the treatment of the reaction can be classified as first and second-line treatments:

a) First line treatment

Epinephrine. Anaphylactic reactions involve alterations of the vascular permeability, which implies that up to 35-50% of the intravascular volume can migrate to the interstitial space in 10 minutes. Epinephrine is the drug of choice for treatment of anaphylaxis and delay in its administration negatively influences the prognosis of severe reactions. There is no contraindication for the use of epinephrine during a reaction, but dosage should be adjusted based on severity, in order to avoid severe side effects, especially in patients with cardiac disease.

Vasoactive drugs. In cases where the patient is taking beta-blockers or suffers from cardiac disease, other vasoactive agents can be given. Norepinephrine, ephedrine, methoxamine, phenylephrine and dopamine can be used in intravenous bolus or continuous infusion [53].

Glucagon. This drug can be also used as a rescue medication in patients that normally receive treatments with beta-blockers, which may not respond to epinephrine. As with non-epinephrine vasoactive drugs use has also been proposed for patients with cardiac diseases to avoid the use of epinephrine [40, 54].

Vasopressin. Its use in anaphylactic shock is accepted, since it is considered that vasopressin may be consumed during the reaction and therefore there is no response to vasopressor drugs.

Methylene Blue. This drug can be useful due to its capacity to interfere with the action of nitric oxide in the smooth muscle of vascular walls. This drug should be administered in combination with epinephrine [55-57].

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b) Second line of treatment.

Antihistamines and corticosteroids. These drugs should not replace the use of first line drugs such as epinephrine for severe reactions, but can be used in cases of mild reactions (grade I). Corticosteroids are not indicated in the acute phase of the reaction, but may be used to avoid delayed symptoms. Systematic reviews suggest that these drugs are not useful for the treatment of anaphylaxis [57, 58].

Salbutamol. Indicated in patients that present bronchospasm as a main symptom or if this symptom does not respond to epinephrine.

Atropine. Its use is restricted to cases of severe bradycardia refractory to epinephrine and/or fluid therapy, and in those patients treated with beta-blockers, as they can induce cardiac arrest in the early phases of the anaphylaxis.

Other treatments. Sugammadex has been proposed as a useful treatment for anaphylaxis symptoms caused by rocuronium [59, 60]. However, in a recently published series of cases, sugammadex did not modify the course of the reaction [61]. Magnesium sulphate may be useful in cases of bronchospasm that are refractory to other treatments [62].

2.3. Actions after treatment

a) Obtaining biological samples for diagnosis. Blood should be taken during this stage in order to measure serum tryptase, an indicator of mast cell/basophil degranulation [63]. Other markers such as histamine and methyl-histamine in urine have been used, however these are not recommended in routine practice due to difficulties in measurement and low sensitivity [64].

b) Discharge. For mild reactions (Grade I) the patient can be discharged after the resolution of symptoms. For severe reactions the patient should be observed for at least next 24 hours in a post-surgical recovery unit, in intensive care unit or in a regular hospitalization area. Extreme caution must be taken with patients that: present severe symptoms and/or do not respond to treatment and/or have involvement of airways and/or severe comorbidities, or poor access to emergency treatment after discharge.

c) Informing the patient. Before the patient is discharged, the anaesthesiologists should give the patient a clinical report containing all relevant information about the reaction, including its severity, any treatments administered and the possible drugs/causative agents. The patient should be warned that, in case that anaesthesia is needed again prior to the allergological evaluation, it should only be for emergency procedures and the patient must inform the hospital and present their clinical report.

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d) Referral for Allergy evaluation. It is crucial that, in relation to a future diagnosis, the anaesthesiologist contacts the allergist so that all the information about the event can be properly recorded.

In order to standardize the diagnosis and treatment of anaphylactic reactions, it is advisable to have ready-to-use kits in all areas of anaesthesiology departments [8, 15, 41] including: i) simple anaphylaxis treatment algorithms, with the dosage of different drugs, route of administration, especially epinephrine and rescue medication in case of severe/refractory anaphylaxis (Figure 1). ii) Instructions to obtain biological samples from the patient, including laboratory orders, sample tubes and instructions on where the samples must be sent (Figure 2). This will be crucial to help establish a chronological sequence of the events leading to the reaction. iii) Standardized data sheets that should be filled in after the reaction has been treated and sent to the relevant Allergy Department. This sheet should include details of the drugs administered and the temporal sequence of symptom onset. Any treatments administered to resolve the reaction should also be described [15] (Figure 2).

ALLERGY EVALUATION

The diagnosis of perioperative hypersensitivity reactions is based on the combination of clinical history of the patient, *in vitro* determinations performed during the acute phase of the reaction and different tests performed once the reaction has disappeared, such as STs, *in vitro* tests and eventually DPT. The diagnosis algorithm is shown in Figure 3.

1. CLINICAL HISTORY

This is the first step for establishing diagnosis, although all the information comes from the anaesthesiologist report (grade of recommendation, D) [9, 12, 65]. It is important to evaluate different aspects: clinical signs and symptoms of the reaction; grade of severity [11]; drugs administered for treating the reaction and the time needed to solve the reaction; personal history of allergy, including atopy and allergy to other drugs; risk factors, such as age; underlying diseases and treatments, such as beta-blockers and angiotensin-converting-enzyme inhibitors; and all possible drugs and agents used during the perioperative period, alongside details on their temporal sequence of administration. The agents most frequently involved include:

a) Drugs

Antibiotics. They are usually administered prior the induction phase of anaesthesia [12] and constitute the most common cause of perioperative anaphylaxis in Spain [5]. It would be useful to separate the administration of the prophylactic antibiotic therapy and anaesthetic induction in order to identify and treat the reaction as early as possible. Betalactams are

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responsible for 70% of reactions due to antibiotics [20], especially cephalosporins [5], being cefazolin the most frequent causal agent in Spain [66]. Vancomycin is the second most common antibiotic involved, although reactions are almost always due to a non-immunological mechanism [67]. Quinolones are the third most important group with an increase incidence [68]. Finally, other potentially important antibiotics include gentamicin, metronidazole and tobramycin, mainly used in abdominal surgery [69].

NMBAs. In some studies these drugs are the most frequently involved [20, 70, 71]. The diagnosis is complex, as in some cases reactions can appear in patients receiving these drugs for the first time. This could be explained by the existence of cross-reactivity with other substances containing tertiary or quaternary ammonium groups such as cosmetics, foods, industrial material and disinfectants [72]. Although this hypothesis has not been proven, it has been recently shown that contact with quaternary ammonium in hairdressing students is associated with an increase in the incidence of IgE antibodies against NMBAs [22]. It has also been shown that the use of pholcodine, present in some cough medicines, is related to an increase in the incidence of NMBA allergy, and this may explain differences in incidence between countries, as the consumption of such medicines is variable [37]. Finally, diagnosis is complicated by the fact that all NMBAs are by themselves histamine-releasing drugs, especially benzylisoquinoline derivatives (d-tubocurarine, atracurium and mivacurium) [26].

Sugammadex. This is a modified gamma cyclodextrin that acts as a blocking agent of the aminosteroids NMBAs, especially rocuronium, that it can induce IgE mediated reactions [73-76]

***Hypnotics*.** These include two groups of chemically unrelated drugs (barbiturates and non-barbiturates). Drugs from the barbiturate group are used infrequently nowadays. Thiopental is the most highly consumed and although IgE mediated reactions have been reported, the majority of reactions are induced by unspecific histamine release [77].

The non-barbiturate group includes propofol, ketamine, etomidate, benzodiazepines and inhaled anaesthetics. Propofol is the cause of 2.3-2.6% of perioperative anaphylactic reactions [20, 78], most of which are IgE mediated, being the antigenic determinant the two-isopropyl groups of the molecule (2,3 diisopropylphenol). Soybean oil and egg-derived lecithin are both used during its formulation, and although it has been suggested that in patients with severe anaphylaxis to egg and/or soy should undergo allergological study or use alternative treatment [79], this drug seems to be safe in most patients. One study, including 99 patients with positive specific IgE to egg, soya or peanut (although only 44% had immediate clinical symptoms), found that none had an allergic reaction following exposure to propofol [78]. In a Spanish study, including 52 adult patients with eosinophilic esophagitis sensitized to egg, soy, or

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peanut, also found that no patients who received propofol before an endoscopy procedure reacted to the drug [80]. In fact, according to our literature search, no reactions to propofol have been documented for soy or egg allergic patients. Moreover, prick test with soya oil and propofol have been done, results have been always negative indicating that there are no reasons for contraindicate its use [79, 80].

Hypersensitivity reactions to benzodiazepines are extremely rare, being midazolam the most frequent aetiological agent in the few cases that have been reported [7, 20]. Reactions to etomidate and ketamine are also rare; in fact etomidate is considered one of the safest drugs in anaesthesia concerning allergic reactions [7, 81].

Opioids. Reactions are rare and although there have been some IgE mediated reactions most are due to non-specific histamine release [82-85]. Semisynthetic opioids such as fentanyl, alfentanil, remifentanil and sulfentanil do not by themselves cause histamine release. Morphine derivatives are chemically different from phenylpiperidines and there is no cross-reactivity between them [82-86]. Allergic reactions to opioids represent an important problem because, although rare, these drugs are essential for the anaesthesia and it is difficult to find a safe alternative.

Non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are responsible for an important number of perioperative reactions [5, 20]. In general, non-immunological reactions due to COX-1 inhibition are more common [29]. In some cases the underlying mechanism can be immunological, most often due to pyrazolones, followed by diclofenac, although again specific studies relating to incidence in perioperative reactions are needed [87].

Local anaesthetics. Although well known, they rarely induce adverse effects related to overdose or accidental intravascular administration [88]. In exceptional cases, they induce hypersensitivity reactions; these have been mainly described as relating to the amide group [39, 89].

Other drugs. Anecdotic case reports exist of anaphylaxis induced by heparins [39], tranexamic acid [90], uterotonics [91, 92], atropine [93] and neostigmine [93].

b) High molecular weight agents

Colloids. These can cause up to 4% of perioperative anaphylactic reactions, usually appearing from 20-30 minutes after starting the infusion [1]. Gelatines are responsible for the majority of reactions (95%), followed by dextrans, and although both can induce non-specific histamine release, IgE-mediated reactions due to gelatines and IgG-mediated reactions due to complement activation by dextran have been reported [39, 94]. Gelatines can be a cause of anaphylaxis in patients sensitised to the carbohydrate epitope Alfa-gal [95]. Reaction incidence is much lower for albumin and exceptional for hydroxyethyl starch [96, 97].

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Protamine. Hypersensitivity reactions mediated by IgG, IgE, complement activation, and non-specific histamine release have been reported [17, 98]. Patients who have been previously exposed to this drug are at higher risk of developing a reaction, whether the drug was given for blocking heparin effect or combined with insulin. Protamine is derived from fish sperm; however there is no increased risk for patients undergoing vasectomy or those allergic to fish [58]. It is important to be aware that rapid protamine infusion can induce hypotension.

Aprotinin. This is a bovine-derived protease inhibitor used via the parenteral route as a fibrinolysis inhibitor or topically as a surgical glue [17]. The incidence of reactions in cardiac surgery is 0.5% but it can increase to 2.5-2.8% in patients who have previously undergone multiple surgeries [99, 100], especially in the previous six months [31]. Perioperative anaphylaxis has also occurred upon the first parenteral administration in patients that had previously received topical aprotinin [17].

Hyaluronidase. This is a bovine or ovine-derived enzyme that degrades hyaluronic acid and can be used as a drug or fluid adjuvant. Both immediate [101] and delayed [102] reactions have been reported during ocular surgery and epidural injection.

c) Antiseptics and sterilizers

Antiseptics. Significant geographical differences are reported concerning the incidence of chlorhexidine-perioperative induced anaphylaxis. Reactions are quite frequent in UK and Scandinavian countries [71, 103, 104], representing the 8.7%-9.6% of cause inducing perioperative anaphylaxis but relatively rare in France [22] perhaps because of its limited use in the operating room. The mechanism is IgE mediated and although reactions usually appear 20-30 minutes after its administration, onset and severity depend on the administration route, with cutaneous application rarely causing severe reaction [36]. However, when it is applied to mucous membranes (urinary catheters or oral cavity washes), or by parenteral routes (venous catheters or surgical meshes), the onset of clinical symptoms can be faster and more severe [36, 104, 105]. The appearance of anaphylaxis induced by povidone is unusual, and it is of note that no cross-reactivity with iodinated contrast media exists [12, 70].

Sterilizers. Ethylene oxide is a gas used for sterilizing multiple medical devices. Reactions have mainly been described in dialyzed patients and in those with bifid spine, being extremely rare during perioperative reactions [1].Performing anaesthesia without ethylene oxide is a challenge for the anaesthesiologist because in some cases it cannot be substituted; as is the case for some intra-arterial catheters, pump infusion systems and intratracheal tubes.

d) Dyes

Isosulfan blue, its isomer patent blue V and methylene blue are used for mapping sentinel lymph nodes in patients with breast cancer or melanoma. They are all capable of inducing

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hypersensitivity reactions, and the incidence of such reactions has been on the increase in the last decade due to a rise in their intraoperative use [106]. Isosulfan blue and patent blue V can induce anaphylaxis in up to 1% of individuals who receive it, with reactions usually appearing 10-30 minutes after administration [107]. The typical reaction involves the appearance of blue wheals [108], although in some cases severe reactions with shock can appear. In most cases there has been no previous medical exposure to these dyes, and it is thought that sensitization occurs through exposure to cosmetics or other objects. Anaphylaxis induced by methylene blue is less frequent and this agent can be an alternative in patients sensitized to isosulfan blue [107], although cross-reactivity has been described for a handful of cases [109].

e) Latex

A decrease of the number of reactions to latex has been reported in several countries due to the reduction to both latex exposure and sensitization by decreasing the protein content and stopping the use of powdered gloves [110, 111]. The absorption of latex allergens usually occurs through the skin and mucous membranes, and although reactions can appear at any moment during surgery, symptoms usually appear with some delay. Abdominal, gynaecological and orthopaedic surgery are usually associated with increased risk, and incidence will likely be higher for: atopic patients, health system personnel, workers exposed to latex, patients with multiple surgeries, women undergoing *in vitro* fertilization, children with urogenital malformation or bifid spine and those with a history of perioperative anaphylaxis [112, 113].

2. SKIN TESTS

STs are the initial diagnostic approach and its interpretation depends on patient clinical symptoms (grade of recommendation, B). In most cases, the skin prick test will be followed by intradermal test. A skin prick test is considered positive when the mean wheal diameter is larger than 3 mm and surrounded by erythema, and when the saline control is negative [87]. An intradermal test is considered positive when there is an increase greater than 3 mm of the initial wheal made by the intradermal injection of the drug [87] (grade of recommendation, C). ST should be done within 4-6 weeks after the reaction and their sensitivity decreases over time; this decrease is faster for betalactams than for NMBAs (grade of recommendation, D) [114, 115].

The optimal concentration for STs is not clearly defined in all cases for drugs that can induce non-specific histamine release [116, 117]. Therefore, false positive results can occur with drugs such as NMBAs (mivacurium, atracurium, cisatracurium and succinilcoline), thiopental, opioids and some antibiotics such as vancomycin and quinolones. A detailed investigation to

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determine the maximal nonreactive concentration for NMBAs within healthy subjects has been carried out [118]. The concentrations recommended as non-irritant are shown in Table 2 [31, 119].

STs with NMBAs have been considered to have a high sensitivity (>95%) and specificity (96-98%) and therefore mandatory for diagnosis and evaluating cross-reactivity, although this needs to be confirmed in other populations (grade of recommendation, C) [120]. Cross-reactivity among NMBAs can occur, making it necessary to test other NMBAs when looking for a safe alternative (grade of recommendation, C) [9, 12, 121]. Skin prick tests with latex also show a high sensitivity and specificity (grade of recommendation, B) (93% and 100%, respectively) [122]. Clorhexidine also has a high sensitivity and specificity: 95% and 97% respectively for skin prick tests and 68% to 100% for intradermal tests (grade of recommendation, B) [103].

STs can also be useful for diagnosing allergic reactions to antibiotics. However, except for betalactams in which sensitivity have been estimated in 70% [123], sensitivity and specificity is not well established (grade of recommendation, B) [119]. For NSAIDs, STs are only recommended for reactions pyrazolones reactions (grade of recommendation, C) [87, 124]. STs can be used to diagnose hypersensitivity reactions to hypnotic drugs [125], sugammadex [126], local anaesthetics [89], and dyes [127] (grade of recommendation, C). The value of STs with opioids such as morphine to detect perioperative reactions is unclear, due to their capacity to induce non-specific histamine release (grade of recommendation, C) [116]. Given the mechanisms of reactions to dextrans (immune complex mediated or complement activation), the value of skin tests is not established (grade of recommendation, D) [12].

Controversy exists regarding when to perform STs and which agents to use. The allergist has a key role here. Various scenarios can occur in clinical practice: i) patients have no previous clinical history of perioperative allergic reaction. In these cases there is no indication of performing STs (grade of recommendation, B) [12, 118, 128] ii) patients with a previous history of reactions, with detailed information available regarding the reaction kinetics and drugs and agents administered. In these cases, STs are mandatory for all the agents administered plus latex [129] and clorhexidine [71, 103, 104, 130] (grade of recommendation, C), however ST results may not be reliable until 4-6 weeks after the initial reaction [131]; iii) Patients with reactions but without clear information about the episode, which is the most complex scenario, especially when there is a long interval between the reaction and the study. In this case the type of surgery and anaesthesia and severity of the reaction can help to decide the agents to test, nevertheless it is recommended to perform ST with all the essential agents

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needed for anaesthesia, including a muscle relaxant derivative and an opioid (grade of recommendation, D) (Table 3).

3. IN VITRO TESTS

These tests can be performed during the acute phase of the reaction or once it has subsided. The former help to understand the mechanisms involved in and the latter to identify the culprit agent (grade of recommendation, C)

a) Acute phase of the reaction.

These are mainly based on the determination of histamine and tryptase

***Determination of plasmatic histamine*.** Levels of histamine usually increase in the first 5-10 minutes after symptoms onset; their half-life is 15-20 minutes, which is why blood samples need to be taken during the first 15-30 minutes of the reaction [11, 132]. It is important to maintain the tube at 4º C until processing to avoid an unspecific increase due to cellular lysis. This determination is not sufficiently standardized for diagnostic use (grade of recommendation, C).

Determination of serum tryptase. Tryptase is maintained in the blood for hours, with maximum levels appearing after 1-2 hours and remaining high for a further 4-6 hours. This means that blood samples can be obtained between 30 minutes and 6 hours after the reaction. Moreover, the samples are less sensitive to environmental conditions, as determination is performed in serum. Different cut-offs have been considered, ranging from 8.23 µg/L to 11.4 µg/L [94-96], although the best criteria is a 2-fold or 2+1.2x increase above baseline levels (grade of recommendation, B) [63, 133]. Tryptase levels are especially high in more severe reactions [134, 135]. However, the measurement of tryptase also accounts for a high frequency of false negatives and a low predictive value (54%), so a normal tryptase does not rule out real anaphylaxis [93]. Although tryptase is more often increased than histamine, the former suggests an IgE mediated reaction [30, 134]. Moreover, tryptase determination can be performed in deceased patients [11, 30, 136].

b) Resolution phase.

These *in vitro* methods available are further described in Table 4.

Specific IgE determination. This method is useful when combined with ST results, but not in isolation (grade of recommendation, B). The method available is the ImmunoCAP (Thermofisher, Uppsala, Sweden) and can be done with different agents: latex, suxametonium, morphine, pholcodine, bovine gelatine, protamine, clorhexidine, thiopental, ethylene oxide and some antibiotics. It is also possible to determine specific IgE to quaternary ammonium using the same method and this can be used as a marker of sensitization to NMBAs and

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opioids. It must be taken into account that this determination can be positive in 3-10% of non-allergic patients, so interpretation of results should proceed with caution [137].

Basophil activation test (BAT). This test can be useful to confirm ST results for diagnosing or assessing cross-reactivity [138] (grade of recommendation, B). Some authors have obtained promising results in reactions induced by muscle relaxants and they have been recommended for routine analysis [139]. Moreover, some authors consider that BAT to muscle relaxants are useful for diagnosis, even in patients with negative ST results, and can be used for the identification of safe alternatives [137, 139, 140]. However the identification of safe alternatives based on BAT only should be regarded with caution, taking into account that only small series with BAT have been reported.

Other determinations. Histamine and sulphidoleukotriene release assays have a limited utility (grade of recommendation, C) [141, 142].

4. DRUG PROVOCATION TESTS

This is considered the *gold standard* for diagnosing drug hypersensitivity (grade of recommendation, C) and consists of the administration of increasing doses of the drug at 30 minute intervals, in a single blinded and placebo controlled manner, until reaching the therapeutic dose or appearance of the reaction [143, 144]. Many of the drugs administered during the perioperative period such as antibiotics or NSAIDs will be studied following regular procedures and are not going to be described in this review. However, DPT with perioperative drugs has added several limitations and there is not a consensus procedure for its performance (grade of recommendation, C) [10, 145, 146]. The final goal is to reach a total dose of the drug needed for anaesthetic induction (propofol, etomidate, ketamine), or during the anaesthetic procedure (opioids, midazolam...). This dose is not standard for all patients, potentially depending on their weight and underlying diseases (Table 5) [147, 148].

Although some of these agents can be administered in the Allergology Units, many of them will require coordination with the Anaesthesiology Unit. Cardiovascular and respiratory monitoring is mandatory.

a) Drugs administered in the Allergy Unit. In general it is preferable to use the oral and subcutaneous routes (grade of recommendation, D) with close monitoring of the patient, avoiding high risk patients if possible such as older patients or with co-morbidities as drug-exposure might provoke reactions that are hard to control [143]. Among the opioids morphine, pethidine and fentanyl can generally be administered without important adverse effects, and if they do appear can be reversed with naloxone at an initial dose of 0.4 mg, and repeated every 2-3 minutes, until a response is obtained or a maximum dose of 10 mg is achieved [149].

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Benzodiazepine administration is quite safe and their sedative effects can be reversed with flumazenil starting with a dose of 0.2 mg, and if necessary repeating a dose of 0.2 mg every minute until reaching a maximum dose of 1 mg [149].

b) Drugs administered in the Surgery Area. This procedure is only indicated when there are no alternatives to performing the anaesthesia. Risk-benefit analysis should be performed, and administration should be by the intravenous route (grade of recommendation, D) [3, 10]. It should be performed in a setting with adequate cardiovascular and respiratory monitoring, and in the presence of well-trained personnel to manage cardiovascular (hypotension, bradycardia) and respiratory (depression) effects and hypersensitivity reactions (grade of recommendation, C). The most adequate setting is the operating room or the post-anaesthetic units (PU). The following material and personnel are needed: i) one anaesthetist and one allergist during the whole DPT procedure and recovery; ii) nurses trained in the management of airway and cardiovascular events; iii) individualized monitoring of electrocardiography, non-invasive blood pressure, pulse-oximetry and respiratory rate; iv) trolley stop and airway handling material; v) a ventilator or anaesthesia machine especially if the DPT is performed with muscle relaxants or in high risk patients (Physical Status Classification System of the American Society of Anaesthesiology (ASA) 3 and 4 [150].

Extra considerations may include: i) patients need to sign two informed consents, one for the allergological study and the second for the anaesthetic procedure, specifying the risks of each procedure and with a previous study in the Allergology and Anaesthesiology Unit; ii) many of these drugs (succinilcoline, rocuronium, atracurium, mivacurium, morphine and meperidine) can induce non-specific histamine release and hypotension and this can difficult the diagnosis [143, 145, 151]; iii) the procedure is complex so it makes sense to perform the DPT with different drugs consecutively on the same day with 1 hour intervals between each drug. This is possible as drugs are administered intravenously and most reactions appear in less than 30 minutes; iv) after finishing the DPT the patient must be monitored throughout recovery from the anaesthesia.

The drugs that usually need to be tested are opioids, because there is no alternative and hypnotics that are essential for anaesthetic induction, particularly propofol, the most widely used agent for anaesthesia and sedation [78, 80, 152]. It is not recommended for muscle relaxants due to potential effects on breathing, with the exception of those cases where they are suspected to cause a reaction, and where they are absolutely necessary to perform the surgery and no alternatives exist [144]. It is indicated in specific situations where anaesthetist requires to know tolerance to NMBAs such as transplantations, in high-risk patients or when STs are not valuable. As they cannot be used alone it is recommended to test them after other

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drugs, such as propofol, to control the airway by endotracheal intubation that will allow better control in case of a reaction. It is recommended to test a muscle relaxant different to those inducing the reaction, that gives negative ST and BAT and if possible from a different chemical group, in the case of benzylisoquinolines cisatracurium and in the ester group rocuronium [9, 146, 151].

RECOMENDATIONS AFTER THE ALLERGOLOGICAL STUDY

Once the allergological study is finished a medical report must be produced, describing in detail the drugs involved, type of reaction, allergological work-up results, diagnosis and recommendations (grade of recommendation, D). This will be essential for deciding the best anaesthetics procedures for the patient going forward. There are different possibilities:

1.- Patient with a clinical history not suggestive and negative allergological study. If the patient has not presented any hypersensitivity drug reaction the recommendation is to use any anaesthetic procedure with the same risk as the general population (grade of recommendation, D).

2.- Patient with a suggestive clinical history and negative allergological study. In this scenario different possibilities exists:

a) If the allergological study has only been based on the performance of ST accompanied or not by *in vitro* tests and a DPT cannot be done, then it is not possible to rule out an allergic reaction [109]. If the drugs involved in the reaction are known the best approach is to avoid them as well as any that may cause cross-reactivity (grade of recommendation, D). If the drugs involved are not known, the best approach is to use a loco-regional anaesthesia (if possible) or general anaesthesia but without using NMBAs or drugs with a high capacity to induce nonspecific histamine release (grade of recommendation, D) [6]. Moreover, it is important to re-evaluate the patient testing emerging agents such as chlorhexidine, methylcellulose, PEGs/macrogols mannitol and dyes, any other drugs not initially considered due to improbability, and to assess any methodological problems in the testing procedures (failure in concentration or ST reading) (grade of recommendation, D).

b) If the allergological studied was based on DPT the drugs with confirmed tolerance will be recommended (grade of recommendation, D).

c) In cases where non-specific histamine release is suspected the recommendation is to avoid drugs with potent histamine release capacity in next anaesthesia. Pre-treatment with antihistamines is also recommended [11, 153] and all drugs should be administered slowly and one by one [10, 145] (grade of recommendation, D).

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3. Patient with a suggestive clinical history and positive allergological study. The recommendation will be to avoid the agent identified as allergic and those with cross-reactivity. In these cases pre-treatment is not useful to prevent a new reaction [154]. The recommendations will depend on the culprit drug:

NMBAs. The recommendation is to use a muscle relaxant that gives negative intradermal STs and BAT [12, 140]. Although a great cross-reactivity exists between muscle relaxants (65% if the reaction was induced by rocuronium and 29% for succinilcoline) [155] the sensitization to all of them is low [146] (grade of recommendation, C). If this is the case and all NMBAs give positive STs and/or BAT one might consider a loco regional anaesthesia or a tracheal intubation after anaesthetic induction using inhalant agents or combinations of opioids and hypnotics (midazolam, propofol, fentanyl) plus local anaesthetics such as lidocaine [154-156] (grade of recommendation, D).

Hypnotics. These do not present cross-reactivity, meaning it should be possible to replace a hypnotic with another one. Currently, most reactions are due to propofol. Ketamine and etomidate provide effective sedation with limited effects on hemodynamic function. The better alternative in patients with cardiovascular disease is etomidate. Ketamine induces a dissociative anaesthesia with minimum respiratory depression and without cardio-depressor effects, being especially useful in hemodynamically unstable patients or critically ill patients. Thiopental is rarely used nowadays. In cases of endoscopy a combination of midazolam and fentanyl has been recommended [157].

Opioids. The incidence of anaphylaxis is quite low and most cases are due to non-specific histamine release. In these cases it is important to avoid morphine, meperidine and codeine, drugs with high capacity of stimulating skin mast cells. As alternative drugs it is recommended to use phenylpiperidines (fentanyl, alfentanil, remifentanil, sulfentanil) with a low histamine release capacity. In IgE mediated reactions induced by morphine it seems useful to use remifentanil or fentanyl as well as the use of morphine in fentanyl reactions [83-86].

Colloids/crystalloids. Gelatines followed by dextrans are the substances most frequently involved [158]. There is no reported cross-reactivity between them.

Latex. Every hospital should have protocols for operations involving patients with latex allergy. If there is no specific operating room then the surgery should be performed as the first time of the day also without any material including surgical gloves or other material containing latex to avoid having latex particles in the environment [113]. Similarly, precautions should be taken when the patient is moved to the postsurgery room or any other part of the hospital [113].

Local anaesthetic. Reactions are quite infrequent and generally not due to hypersensitivity. If confirmed, an alternative with confirmed tolerance can be used.

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Dyes. Reactions have been mainly reported for patent blue V and isosulfan blue with cross-reactivity existing between them. As an alternative and if the allergological study is negative, methylene blue can be used [159].

Antiseptics and sterilizers. In cases for which hypersensitivity to clorhexidine or povidone-iodine is confirmed they should be avoided, and other drugs without cross-reactivity should be used. When this is not possible, as with ethylene oxide it is recommended to wash the area several times in physiological saline before use. The same should be done with Cidex-Opa, although this has generally been replaced by peracetic acid due to its higher sensitizer capacity.

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Table 1. Differential diagnosis of perioperative anaphylaxis.

Pharmacological effect of anaesthetic agents	Hypotension, bradycardia
Effect of local anaesthetics or nerve block	Sympathetic blockade, overdosage, accidental intravascular administration
Effect of the surgical technique	Laparoscopy, eye surgery
Effect of airway manipulation	Laryngospasm, bronchospasm
Surgery complications	Pulmonary: Pulmonary oedema, pulmonary embolism, amniotic fluid, fat or air embolism, pneumothorax Cardiovascular: acute coronary syndrome, tachyarrhythmia, cardiac tamponade Shock: haemorrhagic, septic, Bone cement syndrome
Underlying disease	Systemic mastocytosis, hereditary angioedema, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, carcinoid or pheochromocytoma

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Table 2. Recommended concentrations for skin tests: skin prick tests (SPT) and intradermal test (IDT).

	SPT Concentration	IDT Concentration
NMBAs		
Atracurium	1 mg/ml	0,01 mg/ml
Cisatracurium	2 mg/ml	0,02 mg/ml
Mivacurium	0,2 mg/ml	0,002 mg/ml
Pancuronium	2 mg/ml	0,2 mg/ml
Rocuronium	10 mg/ml	0,05 mg/ml
Vecuronium	4 mg/ml	0,4 mg/ml
Suxamethonium	10 mg/ml	0,1 mg/ml
Hypnotics		
Etomidate	2 mg/ml	0.2 mg/ml
Ketamina	10 mg/ml	1 mg/ml
Propofol	10 mg/ml	1 mg/ml
Thyopental	25 mg/ml	2.5 mg/ml
Midazolam	5 mg/ml	0.5 mg/ml
Opioids		
Alfentanil	0.5 mg/ml	0.05 mg/ml
Fentanyl	0.05 mg/ml	0.005 mg/ml
Remifentanil	0.05 mg/ml	0.005 mg/ml
Sufentanil	0.05 mg/ml	0.0005 mg/ml
Morphine	1 mg/ml	0.01 mg/ml
Sugammadex	Undiluted	1/100
Betalactams		
BPO-OL	0,04	0,04
MD	0,5	0,5
Amoxicillin	20 mg/ml	20 mg/ml
Cephalosporins	20 mg/ml	2 mg/ml
Local anaesthetics	Undiluted	1/10
Heparins	Undiluted	1/10
Tranexamic acid	Undiluted	1/10
Protamine	Undiluted	1/1.000-1/10.000
Aprotinin	1/5	1/500
Hyaluronidase	Undiluted	1/10
Antiseptics		
Clorhexidine	5 mg/ml	0.002 mg/ml
Dyes		
Patent blue	Undiluted	1/10
Methylene blue	Undiluted	1/10

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Table 3. Agents and drugs panel to use in skin testing in those patients where the possible culprits are not identified by the clinical history.

Muscle relaxants	Hypnotics	Opioids
Atracurium	Propofol	Alfentanil
Cisatracurium	Etomidate	Fentanyl
Mivacurium	Ketamine	Remifentanil
Pancuronium	Thyopental	Sufentanil
Rocuronium	Midazolam	Morphine
Vecuronium		
Suxamethonium		
Clorhexidine		
Latex		

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Table 4. Available *in vitro* methods for identifying the culprit agent involved in perioperative reactions

DRUGS	ImmunoCAP	BAT
Barbiturates	X*	X
Propofol	X*	X
Local Anaesthetics	X*	X
NMBAs	X**	X
Latex	X	X
Opioids	X***	X
Atropine		X
Protamine		X
Gelatines	X	X
Clorhexidine	X	
Ethylene Oxide		X

* Research: thiopental, mepivacaine, propofol, rocuronium, paracetamol, diclofenac

** Available: suxamethonium

*** Available: pholcodine and morphine

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Table 5. Doses administered in the drug provocation test.

DRUG	SETTING	VIA	MAXIMUM DOSE
Opioids			
Morphine	AU	oral	5 mg; 10 mg in <65 years
Petidine		s.c.	25 mg
Fentanyl		s.c.	50 mcg
Benzodiazepines			
Midazolam	AU	oral	3,5-5 mg
Diazepam		oral	5-10 mg
Opioids			
Morphic Chloride	PU	i.v.	0,1 mg/kg (10 mg)
Meperidine		i.v.	0,5 mg/kg (50 mg)
Fentanyl		i.v.	1-2 mcg/kg
Alfentanil		i.v.	10-20 mcg/kg
Remifentanil		i.v.	Continuous infusion (0,05-0,1 mcg/kg/min)
Sulfentanil		i.v.	0,1 mcg/kg
Hypnotics			
Propofol	PU	i.v.	1-2 mg/kg
Etomidate		i.v.	0,2-0,3 mg/kg
Ketamine		i.v.	0,5-2 mg/kg
NMBAs			
Cisatracurium	PU	i.v.	0,5 mg/kg
Atracurium		i.v.	0,1-0,15 mg/Kg
Rocuronium		i.v.	0,6 mg/Kg
Vecuronium		i.v.	0,1 mg/kg

AU: Allergology Units; PU: Post-anaesthetic Units; s.c.: subcutaneous; i.v.: intravenous

LEGENDS TO FIGURES

Figure 1. Perioperative anaphylaxis treatment

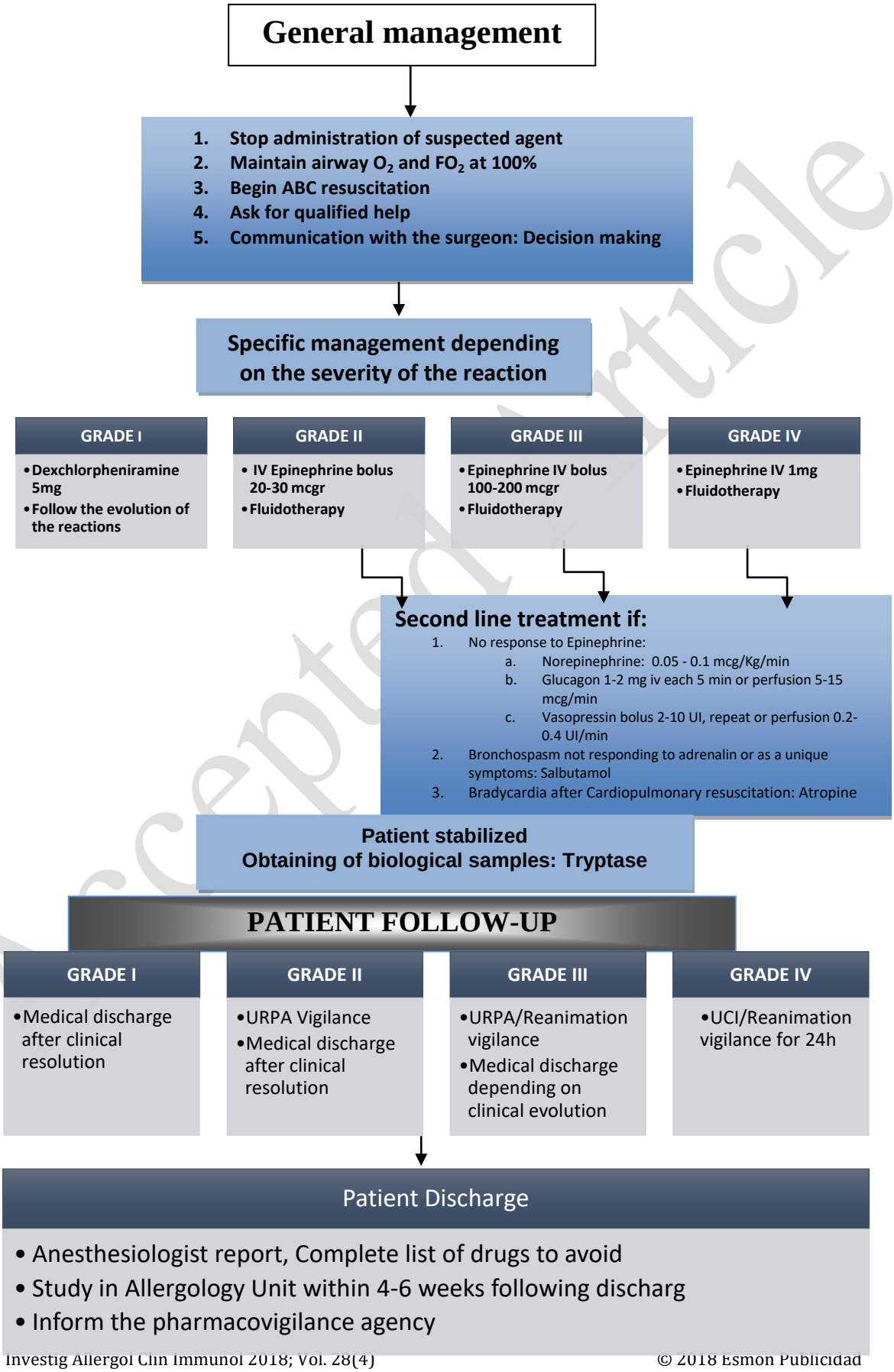

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Figure 2. Data collection document and instructions

Perioperative anaphylaxis.

Indentification: ……

Identification label

First name:……..

Surname:……..

Address: ……..

……..

Phone: ……..

Date of Surgery: ……

Type of surgery:……

Type of Anaesthesia:……

Time surgery started:……Time reaction started:……Time reaction disappeared: ……

Antiseptic used:……..

Drug (pre-anaesthesia and anaesthesia)	Dosage	Time

Symptoms/signs		**Time**
Hypotension	Diastolic pressure (mm Hg):	
Tachycardia	☐	
Bradycardia	☐	
Bronchospasm	☐	
Cyanosis/Desaturation	Saturation (%):	
Angioedema	☐	
Urticaria	☐	
Arrhythmia	☐	
Erythema	☐	
Pruritus	☐	
Other (Specify)	☐	
Treatment		**Time**
Epinephrine	☐	
Corticoids	☐	
Antihistamines	☐	
AntiH2	☐	
Other vasoactive drugs	☐	
Other(specify)	☐	

TRYPTASE

	Tryptase	Sample**		Time	Ref. Nº Serum
1	**Initial***	YES	NO		
2	**After 2 hours**	YES	NO		
3	**After 24 hours**	YES	NO		

***Blood sampling (serum or plasma) for mast cell tryptase immediately after initial treatment**

****Mark with a cross as appropriate**

Send this document to the Allergy Service with:

- **Copy of the anaesthesia chart**
- **Copy of the anaesthesia notes**
- **Treatment sheet in the Reanimation area**

Figure 3.- Algorithm for diagnosing perioperative hypersensitivity reactions