Reducing the Risk of Anaphylaxis During Anesthesia: 2011 Updated Guidelines for Clinical Practice

PM Mertes,[1] JM Malinovsky,[2] L Jouffroy,[3] and the Working Group of the SFAR[*] and SFA[*] and W Aberer,[4] I Terreehorst,[5] K Brockow,[6] P Demoly,[7] for ENDA[**] and the EAACI Interest Group on Drug Allergy

[1]Service d'Anesthésie-Réanimation Chirurgicale - Inserm U911, CHU de Nancy, Hôpital Central, Nancy, France
[2]Département d'Anesthésie-Réanimation, Hôpital Maison Blanche, Reims, France
[3]Société Française d'Anesthésie et de Réanimation, Paris, France
[4]Department of Environmental Dermatology and Allergy, University of Graz, Graz, Austria
[5]Department of ENT and Department of Pediatrics, AMC Hospital, Amsterdam, The Netherlands
[6]Department of Dermatology and Allergology Biederstein, Technische Universität München, Munich, Germany
[7]Allergy Department - Inserm U657, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, France

[*]SFAR (Société Française d'Anesthésie et de Réanimation) and SFA (Société Française d'Allergologie) with the following additional members in the working group: F Bérard, M Bruyere, I Constant, B Debaene, M Drouet, C Karila, F Lavaud, C Lejus, D Longrois, MM Lucas, A Magnan, DA Moneret-Vautrin, C Mouton, B Plaud, and C Ponvert.
[**]ENDA (European Network for Drug Allergy) and the EAACI interest group on drug hypersensitivity with the following additional members: S Bavbek (Turkey), B Bilo (Italy), PJ Bousquet (France), J Cernadas (Portugal), LH Garvey (Denmark), H Gooi (UK), E Gomes (Portugal), ML Kowalski (Poland), V Kvedariene (Lithuania), H Mosbech, WJ Pichler (Switzerland), A Romano (Italy), R Sargur (UK), M Sanz (Spain), F Saretta (Italy), and A Trautmann (Germany).

■ Abstract

These guidelines represent the updated consensus of experts in the field of immediate hypersensitivity reactions occurring during anesthesia. They provide a series of valid, widely accepted, effective, and easily teachable guidelines that are the fruit of current knowledge, research, and experience. The guidelines are based on the findings of international scientific research and have been implemented in France under the auspices of the French Society for Anaesthesia and Intensive Care (Société Française d'Anesthésie et de Réanimation [SFAR]) and the French Society of Allergology (Société Française d'Allergologie [SFA]). The members of the European Network for Drug Allergy approved the guidelines. This paper presents the most relevant clinical implications of the guidelines.

Key words: Anaphylaxis. Anesthesia. Histamine. Hypersensitivity. IgE. Neuromuscular blocking agents. Hypnotics. Latex. Skin tests. Tryptase.

■ Resumen

Esta guía representa el consenso actualizado de expertos en el ámbito de las reacciones de hipersensibilidad inmediata que tienen lugar durante la anestesia. En ella se proporcionan una serie de pautas válidas, ampliamente aceptadas, eficaces y fáciles de enseñar, que son el fruto del conocimiento, la investigación y la experiencia actuales. La guía se basa en los resultados de investigaciones científicas internacionales y se ha aplicado en Francia bajo el auspicio de la Sociedad Francesa de Anestesia y Cuidados Intensivos (Société Française d'Anesthésie et de Réanimation [SFAR]) y la Sociedad Francesa de Alergología (Société Française d'Allergologie [SFA]). La guía ha sido aprobada por los miembros de la Red Europea de Alergia a Medicamentos. En este artículo se presentan las implicaciones clínicas más relevantes de la guía.

Palabras clave: Anafilaxia. Anestesia. Histamina. Hipersensibilidad. IgE. Bloqueantes neuromusculares. Somníferos. Látex. Pruebas cutáneas. Triptasa.

These guidelines are an abridged version of the first revised guidelines for clinical practice for reducing the risk of anaphylaxis during anesthesia recently developed and implemented in France under the auspices of the French Society for Anaesthesia and Intensive Care (SFAR: Société Française d'Anesthésie et de Réanimation) of the French Society of Allergology (SFA: Société Française d'Allergologie) [1-3].

The guidelines represent a consensus of experts from a variety of disciplines, including anesthetists, allergy specialists, biologists, and physiologists, and are based on the findings of international scientific research. They provide a series of valid, widely accepted, effective, and easily teachable recommendations that are the fruit of current knowledge,

research, and experience. To achieve this goal, experts had to answer a list of pre-established questions. Participants used evidence-based criteria to identify, evaluate, and appraise scientific publications indexed in MEDLINE, Pascal, and Excerpta Medica. All the experts applied the tools and principles of evidence-based medicine concerning levels of evidence and classes of recommendations proposed by the GRADE System and approved by the Guidelines and References Committee of the SFAR (Table 1) [4-6]. Experts provided extensive literature analysis supporting the recommendations. The level of certainty in the area of perioperative hypersensitivity reactions is limited, since provocation tests, which are the gold standard in drug allergy diagnosis, are contraindicated with many anesthetics, such as muscle relaxants. Therefore, many unproven statements have to remain; however, these recommendations have been shown to be helpful in daily clinical practice. To increase the validity of the results obtained, this version was reviewed by an extensive panel of 90 lecturers (topic experts, conference leaders, specialists from disciplines associated with allergy [anesthesiology, critical care, surgery]) for scientific accuracy, but also for possible future effects on safety, cost, effectiveness, education, and training. The present version is a summarized version of the full text in French [7]. This paper presents the main extracts of the recommendations with the more relevant clinical implications, after minor adaptations or modifications, as suggested by a panel of experts from the European Network for Drug Allergy (ENDA) and the European Academy of Allergy and Clinical Immunology (EAACI) interest group on drug allergy [8,9].

Table 1. Levels of Evidence of Studies and Classes of Recommendations

LE I	High level of evidence • Randomized controlled trials • Meta-analyses
LE II	Low level of evidence • All or nothing studies • Validation studies of diagnostic testing • Prospective cohort studies, parallel studies (blinded and nonblinded prospective studies), case-control studies
LE III	Very low level of evidence • Other types of studies
CR 1	Strong evidence (future research is unlikely to affect confidence in estimating risk or effect): • Consistency between meta-analyses • At least 1 advanced-level study in which the results do not contradict other advanced or lower-level studies • At least 2 low-level studies in which there is no contradiction and that demonstrate a relative risk >2 or <0.5 in all such studies
CR 2	Moderate evidence (there is a reasonable possibility that future research will modify the expected effects and risks, or affect the confidence with which these are predicted): • Two or more nonconflicting low-level studies with a relative risk >2 or <0.5 in all or all but one study
CR 3	Weak evidence (there is a probability that future research will modify the effect or the estimated risk and the confidence one can have in this estimate): • Several low-level studies, in which there may be a number of contradictions, but in which there is a strong majority either for or against the hypothesis
CR 4	Very weak evidence (estimates of the effects or risks of a therapeutic or preventive intervention are all uncertain) • Advanced-level contradictory studies • Only very-low-level studies, irrespective of the consistency between them

Abbreviations: CR, class of recommendation; LE, level of evidence.

1. How real is the risk of an allergic hypersensitivity reaction in anesthesia? Classification, incidence, clinical aspects (immediate and delayed), morbidity, mortality, and substances responsible

1.1. About 60%-70% of the immediate hypersensitivity reactions that occur during anesthesia are mediated by immunoglobulin (Ig) E (immediate hypersensitivity allergic reactions) (class of recommendation [CR] 2).

1.2. More than 7000 cases of immediate IgE-dependent hypersensitivity reactions to the drugs used in anesthesia have been published in the last 25 years (CR 2).

1.3. Most cases from France, Australia, New Zealand, and, more recently, Scandinavia feature in the world medical literature thanks to a diagnosis reporting system established by these countries and communication within the international medical community.

1.4. There should be a systematic approach to investigations and reports by those monitoring hypersensitivity reactions to pharmaceutical drugs and materials. Registration facilities and specialized consultation networks should be established.

1.5. The mortality associated with immediate hypersensitivity reactions during anesthesia varies from 3% to 9%, depending on the country. The most severe morbidity occurs in patients who experience an anoxic cerebral injury.

1.6. The incidence of an immediate allergic hypersensitivity reaction during anesthesia varies between different countries from 1/10 000 to 1/20 000 (CR 2). In 1996, the incidence in

France was 1/13 000 when both general and local anesthesia (and the drugs used) were considered together. The incidence of anaphylaxis associated with the use of a muscle relaxant also varies from country to country, eg, 1/5500 in France and 1/5200 in Norway (CR 2).

1.7. Substances responsible for immediate allergic reactions during anesthesia have been recognized within the French-language and English-language literature on anaphylaxis since 1980. Neuromuscular blockers account for 63% of reactions, latex 14%, hypnotics 7%, antibiotics 6%, plasma substitutes 3%, and morphine-like substances 2% (CR 2). The incidence of reactions to latex is decreasing, thanks to effective avoidance measures. Allergic reactions to local anesthetics are very rare, especially when one considers how often they are used. No anaphylactic reaction to halogenated anesthetic agents has been published. Other substances that may cause immediate allergies during anesthesia include aprotinin, chlorhexidine, papain, heparin, patent or methylene blue, and nonsteroidal anti-inflammatory drugs (NSAIDs).

1.8. All relaxants may precipitate an immediate hypersensitivity reaction, even on first exposure, and the most frequently implicated is suxamethonium (CR 2). Cross-sensitivity between different relaxants is frequent.

1.9. Four grades of immediate clinical manifestations are described (Table 2), depending on the severity of the reaction.

1.10. Clinical manifestations are frequently of greater severity and duration in the case of an immediate allergic hypersensitivity reaction than in an immediate nonallergic hypersensitivity reaction (CR 2). The absence of cutaneous signs does not exclude the diagnosis of anaphylaxis (CR 2). Symptoms of a reaction to anesthetics occur immediately after the injection to induce anesthesia; however, if they appear later (up to 1 hour or more), they are probably due to latex or dyes.

1.11. The substances responsible for anaphylactic shock in infants are similar to those used in adults, although latex is the most common allergen in infants, particularly those who frequently undergo surgery (eg, patients with spina bifida). A primary prevention strategy of latex sensitization (CR 1) is required in such circumstances.

1.12. Delayed hypersensitivity reactions caused by anesthetic agents are less frequent. They are reported mostly in association with local anesthetics (CR 2), heparin, antibiotics, antiseptics, and substances such as iodine contrast media (CR 2).

2. Mechanisms of sensitivity and hypersensitivity associated with anesthesia

2.1. The immediate hypersensitivity reaction in an allergic patient is a specific immune response to an allergen. This follows recognition of the allergen by the effectors of the patient's immune system.

The antigenic profile will determine the allergic effector response (helper T cell [T_H] type 1 or T_H2 CD4 T cells, CD8 cytotoxic lymphocytes, B cells producing IgE). Tolerance is a consequence of lymphocyte differentiation within the T lymphocyte regulator group (CR 2).

2.2. Immediate allergic hypersensitivity is initiated by activation of T_H2 lymphocytes, leading to sensitization. This reaction is associated with the production of IgE. Few drug antigens have been identified to date.

2.3. Delayed allergic hypersensitivity is associated with activation of lymphocytes, predominantly T_H1 lymphocytes, which produce interferon γ. This activation represents the beginning of the cytotoxic process (CR 2).

2.4. In drugs, the part of the molecule known as the epitope is responsible for the allergic reaction. The native molecule or its metabolites may act as the hapten and bind to a protein. Part of this complex binds to a molecule of the major histocompatibility complex (MHC) during digestion in the antigen-presenting cell. The combination thus formed is specifically recognized and triggers the allergic reaction (CR 2). Another mechanism of sensitization, pharmacological interaction with immune receptors, is unique and specific to drug allergies and involves non-covalent binding of haptens with major histocompatibility complex molecules and with the T-cell receptor without passing through the antigen-presenting cell (CR 3).

2.5. The mechanisms of action lead to clinical manifestations of immediate hypersensitivity.

2.5.1. Immediate allergic hypersensitivity reactions result from activation of mast cells and basophils by the allergen recognized through IgE attached to the surface of these cells (CR 2). The mediators released include histamine, tryptase, and other preformed granule mediators, lipid arachidonic acid metabolites, and cytokines, such as tumor necrosis factor α. These induce an alteration in capillary permeability (urticaria, edema), vasodilatation, bronchoconstriction, hypotension with tachycardia, and the other signs and symptoms observed in anaphylaxis (CR 1).

2.5.2. Immediate nonallergic hypersensitivity (formerly anaphylactoid hypersensitivity) reactions tend to cause manifestations of lesser severity than those associated with the immediate allergic response. They result from activation of basophils and mast cells by a stimulus that is independent of specific IgE.

2.5.3. The first phase of anaphylactic shock corresponds to that of hyperkinetic shock with tachycardia, collapse of systemic vascular resistance, and peripheral arteriolar vasodilatation causing a decrease in venous return and reduced cardiac output. This phase is followed by one of hypotensive,

Table 2. Grade of Severity for Quantification of Immediate Hypersensitivity Reactions

Grade	Symptoms
I	Cutaneous signs: generalized erythema, urticaria, angioedema
II	Measurable but not life-threatening symptoms Cutaneous signs, hypotension, tachycardia Respiratory disturbances: cough, difficulty inflating
III	Life-threatening symptoms: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm
IV	Cardiac and/or respiratory arrest

hypovolemic shock that develops secondary to transcapillary extravasation of plasma. The effects of arachidonic acid metabolites, through their action on smooth vascular muscle and platelets, magnify the circulatory effects (CR 2). Delay in treatment or incorrect management can result in tissue anoxia leading to an organ failure syndrome culminating in irreversible shock.

2.5.4. Prior long-term administration of ß-blockers may reduce treatment effectiveness (CR2).

3. Diagnostic procedures in an immediate hypersensitivity reaction

3.1. Patients presenting an immediate hypersensitivity reaction during anesthesia should be investigated immediately. Follow-up should involve determination of the type of reaction (IgE-dependent or not) and the responsible agent. Cross-sensitivity should be investigated as appropriate.

3.2. The responsibilities of the anesthetist/resuscitator are as follows:

3.2.1. Ensure that a joint investigation is undertaken with experts in the field of anesthesia and allergy.

3.2.2. Inform the patient about the nature of the reaction during anesthesia, and the absolute necessity to undergo monitoring at an allergy center. A copy of the anesthesia report should be provided with the allergy card.

3.2.3. Report the incident to the regional center for pharmacovigilance if a drug is suspected. Where latex is suspected, a report should be made to the relevant material monitoring authority.

3.3. Biological investigations, which aid diagnosis, should be requested immediately after an anesthetic hypersensitivity reaction.

3.3.1. The probability that symptoms are linked to an immediate hypersensitivity reaction is increased in the presence of elevated levels of markers such as serum tryptase and plasma histamine (CR 1). Normal levels do not absolutely exclude the diagnosis (CR 3).

3.3.2. Serum tryptase levels

3.3.2.1. A definite increase in the concentration of serum tryptase (>25 µg/L) suggests an IgE-mediated mechanism (CR 2). In the case of a mucocutaneous reaction (grade 1), the concentrations are often normal and tend to be only slightly elevated if the systemic reaction is moderate (grade 2).

3.3.2.2. The optimal time for sampling is 15-60 minutes for grades 1 and 2, and 30 minutes to 2 hours for grades 3 and 4. The results remain positive for more than 6 hours in severe cases (CR 3).

3.3.2.3. Because of the wide range of normal basal values between one individual and another, a sample drawn after complete resolution of the reaction is necessary to interpret small increases.

3.3.2.4. Increased concentrations in basal tryptase unrelated to the allergic incident may be observed in patients with systemic mastocytosis, mast cell activation syndrome, or hematologic diseases (CR 2).

3.3.3. Plasma histamine levels

3.3.3.1. The available evidence suggests that an increased concentration of histamine without elevation of tryptase in plasma may be due to an immediate allergic or nonallergic hypersensitivity reaction activated exclusively by basophils.

3.3.3.2. The histamine peak is observed in the first minutes following the reaction, the severity of which increases as the histamine peak rises. The elimination half-life is 15-20 minutes.

3.3.3.3. The plasma histamine concentration, when available, should be measured at the earliest opportunity after the start of the reaction, especially when it is mild (although the assay is not available in all countries). For isolated mucocutaneous (grade 1) reactions, the ideal delay should be less than 15 minutes after the reaction, for grade 2 reactions within 30 minutes, and for more severe reactions within 2 hours.

3.3.3.4. Spontaneous lysis, or lysis provoked by basophils within the sampling tube, results in false-positive readings. Increased values have been measured even when whole blood was conserved overnight at 4°C or for 2 hours at ambient temperature. After centrifugation, the plasma should be aspirated carefully to avoid aspirating basophils (CR 2) and then frozen at –20°C.

3.3.3.5. Plasma histamine assays should not be performed in clinical situations associated with false positives, for example, women more than 6 months pregnant (due to placental synthesis of diamine oxidase) and patients on heparin (the increase in diamine oxidase is directly proportional to the dose of heparin administered).

3.3.3.6. The diagnostic accuracy of these assays is increased when histamine and tryptase are combined.

3.3.4. Urinary leukotrienes

Although an assay is available, its usefulness has yet to be determined for reactions during anesthesia.

3.3.5. IgE assay

3.3.5.1. The total IgE assay has no diagnostic value.

3.3.5.2. The search for specific IgE in serum is based mainly on quaternary ammonium ions (reflecting IgE to neuromuscular blocking agents, thiopental, latex, ß-lactams, and chlorhexidine). It is useful to investigate these drug-specific IgEs during investigation of immediate hypersensitivity reactions or when a difficulty arises in the interpretation of a negative skin test with clinical symptoms of an immediate hypersensitivity reaction (CR 2).

3.3.5.3. It is possible to investigate specific IgE to quaternary ammonium ions as the immediate hypersensitivity reaction fades—investigate immediately at the onset of shock or immediately after induction when a neuromuscular blocker is suspected—or during assessment by allergy specialists/anesthetists off site. This assay is not a substitute for skin testing. The presence of specific IgE to quaternary ammonium ions can be detected several years after an immediate hypersensitivity reaction to a neuromuscular blocker (CR 1).

3.3.5.4 The most sensitive techniques must be used; currently these are the specific antiquaternary test (SAQ) or the P-aminophenylphosphoryl-choline radioimmunoassay (PAPPC-RIA) (CR 2). If the result is positive, a specific inhibition test should be performed with the neuromuscular blocker used during anesthesia. The diagnostic results of ImmunoCap C260 (specific antiquaternary ammonium compounds IgE) approximate those of the SAQ, PAPPC-RIA, and RIA.

3.3.5.5. IgE to quaternary ammonium ions has also been detected in 3%-10% of tolerating controls/patients with no previous reactions, thus limiting specificity. On the other hand, 65%-88% of patients with hypersensitivity reactions have been shown to have these antibodies. As provocation with relaxants is not possible, detection of IgE antibodies remains very helpful in diagnosis.

3.3.5.6. The techniques marketed to investigate and measure latex-specific IgE are extremely sensitive (CR 2). False positives may be recorded and require further exploration (ie, recombinant allergen IgE measurements).

3.3.5.7 Currently available antibiotic-specific IgE assays are limited to antibiotics such as penicillin G and V, amoxicillin, ampicillin, and cefaclor. They are not investigated routinely. Given the low sensitivity of these tests, only the allergist responsible for a particular case may request and interpret such assays. These tests may assist in the interpretation of the allergy investigations, especially when skin tests are negative, and clinical symptoms and signs are suggestive of immediate hypersensitivity to these drugs (CR 2).

3.3.6. Sampling procedures

3.3.6.1. In the practice of SFAR-SFA, histamine assays require a 5-mL blood sample in an EDTA tube and tryptase assays require a dry or an EDTA tube. The EDTA tube into which blood has been drawn for the tryptase assay may also be used to assay for histamine. IgE determination requires 7 mL in a dry tube. The tubes should be sent to the local laboratory within 2 hours. When this is not possible, positive values can be measured in samples refrigerated at 4°C for up to 12 hours. After centrifugation, plasma and serum should be frozen at –20°C in several aliquots. Plasma must be collected from above the leukocytes without inclusions from this cell layer (CR 2).

3.3.6.2. If the reaction is severe, blood must be taken for tryptase assay even if outside the optimal time frame (a positive result for tryptase can remain more than 6 hours) (CR 2).

3.3.6.3. In the case of a reaction after injection of neuromuscular blockers, it is still possible to measure IgE to quaternary ammonium ions without waiting for the skin test results; however, sensitivity is lower (CR 2).

3.3.6.4. In the case of an ultimately fatal reaction, blood samples taken for the determination of tryptase and specific IgE associated with the suspected allergen should preferably be taken before abandoning resuscitation rather than after death (CR 4). Sampling should be from the femoral area (CR 3).

3.3.6.5. Because of the risk of an extremely severe situation, and because a number of the mediators have a short plasma half-life, it is advisable to have the following available in the operating room: a container of sampling tubes, the sampling protocol, and a file of relevant clinical data.

3.3.6.6. Samples for determination of histamine, tryptase, and IgE (3 blood samples must be collected within the recommended time frame (Table 3).

3.4. Skin tests

At present, skin testing, including skin prick-tests (SPT) and intradermal tests (IDT), are indirect means for diagnosis of IgE-dependent allergies. The allergist performing the relevant tests must be experienced with the techniques used for drug allergies.

3.4.1. In order to recover allergic mediators from mast cells and basophils, skin tests should be performed 4-6 weeks after the hypersensitivity reaction (immediate type) (CR 3). If necessary, they can be performed earlier. This, however, increases the risk of false negatives, and only positive results are taken into account (CR 4). Early assessment does not replace that performed after a period of 4 to 6 weeks.

3.4.2. In order to determine the etiology of the reaction, the following conditions need to be met:

3.4.2.1. Training and regular updating of knowledge on anesthesia-related allergies for the allergists and anesthesiologists who investigate and interpret the results are mandatory.

3.4.2.2. A supply of products necessary to perform skin testing and storage facilities in accordance with the highest standards of the pharmaceutical industry (accepting that these are not licensed products), as well as the highest standards of hygiene and asepsis.

3.4.2.3. An environment geared for rapid resuscitation of patients.

3.4.3. The diagnosis of an immediate hypersensitivity reaction is based on a combination of clinical signs, measurement of mediators, and the performance of allergy skin tests, laboratory tests, and, where possible, challenge tests.

3.4.4. When skin tests are carried out, they can be interpreted only when accompanied by detailed clinical information, including the timing of events as provided by the anesthesiologist. Ideally, this information should include a copy of the anesthesia record, the recovery room record, and the results of tryptase and histamine assays from samples taken as the reaction subsided.

3.4.5. Before performing skin tests, the patient's informed consent should be obtained, and drugs known to inhibit skin reactivity (eg, antihistamines and some psychotropics) (CR 2) should be stopped some days before testing.

Table 3. Timing of Sampling for Histamine, Tryptase, and Specific Immunoglobulin E Against Quaternary Ammonium Ions

Parameter	Type of Vial	Sampling <30 min	Sampling 1 to 2 h	Sampling >24 h
Histamine	EDTA	+	(+)	
Tryptase	EDTA/dry	+	+	+
Anti-QA IgE	Dry	+	(+)	(+)

Abbreviation: Ig, immunoglobulin; QA, quaternary ammonium.
+, recommended; (+), if not collected at the time of the reaction

3.4.6. The following conditions are not contraindications to the performance of skin tests for SFAR-SFA: young age, treatment with ß-blockers (except for ß-lactams), medium to high dose maintenance or short-term high-dose oral corticosteroids and angiotensin-converting enzyme inhibitors (CR 3).

3.4.7. It is recommended to perform skin tests for the drugs listed in the anesthetic record, latex, and other medications or products administered during the perianesthetic period. Consultation between the allergy and anesthesia teams will lead to the decision on what should be tested. In some exceptional cases (especially severe cases with a negative workup), we should investigate unrecorded products that may have been used during the procedure and have to be tested.

3.4.8. Skin testing procedures

3.4.8.1. For most drugs, skin tests (SPT and IDT) are the reference tests for the diagnosis of immediate allergic hypersensitivity reactions (Tables 4 and 5) (CR 1). When they are not available, other allergy tests should be conducted (CR 2).

3.4.8.2. It is recommended to use SPT (CR 2) when investigating latex-triggered anaphylaxis.

3.4.8.3. Immediate hypersensitivity reaction to anesthetic drugs is investigated using SPT, IDT, or both, with commercial solutions. These may be pure or diluted in saline or phenol.

3.4.8.4. The sensitivity of SPT is inferior to that of IDT (CR 4).

3.4.8.5. The result of an SPT guides the choice of the first concentration tested with IDT. When the SPT is negative, IDT testing starts at a 1/1000 dilution of the stock solution for neuromuscular blocking agents and a 1/10 000 dilution for morphine. If the IDT is negative, the subsequent concentration

(10 times stronger) is used with a 20-minute interval between each test. The maximum concentrations should not be exceeded in order to avoid the false positives featured in Tables 4 and 5 (CR 2). In the case of a grade IV reaction, the suspect drug is tested, starting with a concentration of 1/100 of the stock solution used for SPT.

3.4.8.6. Interpretation of skin tests requires verification of the normal reactivity of the skin with a positive control (SPT with codeine phosphate 9% or with histamine 10 mg/mL) and a negative control (SPT and IDT with the same volume of solvent) (CR 2).

3.4.8.7. Positive skin test results with relaxants are specific. Positive reactions to skin tests in normal controls at the concentrations listed in Table 4 are below 5% when measured by the SFAR-SFA method.

3.4.8.8. The site for performance of skin tests (back, arm, or forearm) is at the allergist's discretion, providing the interpretation of results takes into account the normal reactivity of skin at the test site and the size of the wheal following the intradermal injection of test material (CR 2).

3.4.8.9. According to SFAR-SFA criteria, a positive SPT result is defined as the appearance, after 20 minutes, of a wheal that has a diameter 3 mm greater than that of the negative control or a diameter of at least half the diameter of the positive control wheal (CR 2).

3.4.8.10. It is necessary to ensure that the IDT extract is injected into the dermis in 0.02 to 0.05 mL of a diluted commercial solution in order to create a postinjection wheal of up to 4 mm in diameter. The SFAR-SFA criterion for a positive IDT result is the appearance after 20 minutes of an erythematous wheal (often pruritic), the diameter of which is at least equal to twice that of the postinjection wheal (CR 2).

Table 4. Concentrations of Anesthetic Agents That Are Normally Nonreactive in Skin Testing

Available Agents	Skin Prick Tests		Intradermal Tests		
	mg/mL	Dilution	mg/mL	Dilution	µg/mL
Atracurium	10	1/10	1	1/1000	10
Cisatracurium	2	Undiluted	2	1/100	20
Mivacurium	2	1/10	0,2	1/1000	2
Pancuronium	2	Undiluted	2	1/10	200
Rocuronium	10	Undiluted	10	1/200	50
Suxamethonium	50	1/5	10	1/500	100
Vecuronium	4	Undiluted	4	1/10	400
Etomidate	2	Undiluted	2	1/10	200
Midazolam	5	Undiluted	5	1/10	500
Propofol	10	Undiluted	10	1/10	1000
Thiopental	25	Undiluted	25	1/10	2500
Ketamine	10	1/10	10	1/10	1000
Alfentanil	0.5	Undiluted	0.5	1/10	50
Fentanyl	0.05	Undiluted	0.05	1/10	5
Morphine	10	1/10	1	1/1000	10
Remifentanil	0.05	Undiluted	0.05	1/10	5
Sufentanil	0.005	Undiluted	0.005	1/10	0.5
Bupivacaine	2.5	Undiluted	2.5	1/10	250
Lidocaine	10	Undiluted	10	1/10	1000
Mepivacaine	10	Undiluted	10	1/10	1000
Ropivacaine	2	Undiluted	2	1/10	200

Table 5. Concentrations of Antiseptic and Dyes That Are Normally Nonreactive in Skin Tests

Available Agents	Skin Prick Tests		Intradermal Tests	
	Dilution	mg/mL	Dilution	µg/mL
Chlorhexidine	Undiluted	0.5	1/100	5
Povidone iodine	Undiluted	100	1/10	10 000
Patent blue	Undiluted	25	1/10	2500
Methylene blue	Undiluted	10	1/100	100

3.4.8.11. It is mandatory to investigate cross-sensitivity with other neuromuscular blocking agents in the case of a positive SPT or IDT result for a particular neuromuscular blocking agent. Potential cross-sensitization should be investigated using all other commercially available neuromuscular blocking agents, taking into account the need to avoid exceeding the maximum recommended concentrations (Table 4) (CR 2).

3.4.8.12. It is recommended to investigate cross-sensitivity with the newer neuromuscular blockers in the case of a previous anaphylactic reaction to a neuromuscular agent during anesthesia, providing that this has been confirmed by positive skin test results (CR 3). The maximum concentration, which must have been established in healthy controls, should not be exceeded with the new neuromuscular blocking agent (or any new anesthetic drug introduced on the market).

3.4.8.13. In the case of a hypersensitivity reaction occurring more than 24 hours after anesthesia, it is recommended to perform patch tests later, especially if eczema-like skin signs and delayed cutaneous symptoms occur. The likely allergens are antibiotics, iodinated contrast agents, and contact allergens (metals, rubber, dyes, antiseptics) (CR 3). The patch testing procedure and interpretation are as set out in the ENDA/EAACI guidelines.

3.4.8.14. The result of a skin test should be clearly positive or negative (not doubtful). If necessary, repeat the test at a distance from the initially chosen site (CR 4).

3.4.8.15 The sensitivity of skin testing may decrease over time, depending on the drugs tested. It is rather stable with muscle relaxants, but decreased with antibiotics (CR 2).

3.5. Cellular assays

3.5.1. The currently available cellular assays are the histamine release assay, the basophil activation test (by flow cytometry), and the leukotriene release test (cellular antigen stimulation test).

3.5.2. There is no general evidence that any one of these assays is clearly superior to the other two. Initial studies show promising results for the basophil activation test. The level of laboratory expertise available will determine those that should be requested.

3.5.3. These tests may complement skin tests, but they are not a substitute (CR 4). Such tests are unnecessary if the diagnosis is obtained with skin tests or specific IgE assays.

3.5.4. In the case of a grade II or higher reaction with negative skin test results for all suspected substances, a cellular assay may be performed.

3.5.5. Cellular assays are performed when skin test results are difficult to interpret (as in patients with dermographism, very young and elderly patients, patients with extensive atopic skin lesions, or patients on medication with antihistaminergic effects, such as antidepressants and antihistamines which cannot be stopped).

3.5.6. In the case of an immediate hypersensitivity reaction to a neuromuscular blocking agent, cellular assays may confirm the responsibility of the agent, even when the skin tests are negative (CR 3).

3.5.7. Hypersensitivity to NSAIDs can be diagnosed using a flow cytometry test or a leukotriene release test (CR 3).

3.6. Provocation tests

3.6.1. Provocation testing has limited indications in perianesthetic anaphylaxis. When the clinical history is compatible with the report of an immediate hypersensitivity reaction, these tests can be performed with drugs for which skin tests cannot be conducted or when skin tests are negative (local anesthetics, antibiotics, or, exceptionally, latex) or not validated (NSAIDs). For anesthetics, this gold standard allergy test cannot normally be used because of the pharmacological effects of these drugs. Thus, it is only possible to demonstrate sensitization to a drug indirectly, eg, by a positive skin test result or demonstration of specific IgE with no final confirmation.

3.6.2. When the allergen is not present in a suitably reactive form (drug metabolites), only provocation tests can confirm the diagnosis. This is particularly so when skin tests for ß-lactams are negative, as well as for some other non–ß-lactam antibiotics and NSAIDs (CR 2).

3.6.3. Tests are conducted at least 1 month after the hypersensitivity reaction using the same drug and often the same route of administration (if the preferred route of oral provocation is not suitable) as when the reaction occurred. They should be conducted under strict supervision and only in specialized centers with monitoring and resuscitation facilities (CR 1).

3.6.4. Before informed consent is obtained, the patient must be fully informed about the tests and the associated risks and receive a comprehensive information sheet(s).

3.6.5. A favorable risk-benefit ratio is a prerequisite for conducting these tests (CR 3).

3.6.6. In provocation tests using local anesthetics, a dose of 0.5 to 1 mL of undiluted local anesthetic solution (without adrenaline) is injected subcutaneously. The result is considered

negative if no immediate hypersensitivity reaction occurs within 30 minutes of injection. In the parturient, this test should be conducted in the labor ward 30 minutes before epidural anesthesia and after having informed the obstetric team (CR 4). In an emergency, a provocation test may be performed if a negative skin test has not been confirmed and if the clinical history is not suggestive of a severe reaction. However, skin testing by an allergist is a priority.

3.6.7. In provocation tests with latex, a natural latex glove is worn for 15 minutes (check the glove is powder-free and has a latex-rich composition). The test is considered negative if no signs of an immediate hypersensitivity reaction appear, ie, within 30 minutes of wearing the glove. If bronchospasm occurs during the initial reaction, a bronchial provocation test should be considered using glove powder and ensuring that all necessary facilities to treat bronchospasm—which may be severe—are available (CR 3).

3.7. Results of an allergy investigation

3.7.1. A positive diagnosis of an immediate allergic hypersensitivity reaction is based on a positive skin test result, the results of laboratory tests, consistency between the results and the clinical picture, and the anesthesia protocol.

3.7.2. Close collaboration and consultation between the allergist and anesthesiologist is a key goal when investigating allergy.

3.7.3. The allergist's report should be sent to the anesthetist concerned and must be included in the patient's medical record. A duplicate must be forwarded by the allergist to the regional pharmacovigilance center, together with a clinical description of the incident, which should also be sent to the attending physician. Finally a duplicate record and an allergy card (eg, a medical alert bracelet or tags) should be given to the patient.

3.7.4. The patient is informed—by letter and on the allergy card—of the conclusions of the allergist/anesthetist. Advice on matters relating to anesthesia can only originate from anesthetists.

3.7.5. The patient should be encouraged to carry the letter and allergy card at all times, eg, with personal identity papers. The wearing of medical alert bracelets or tags should be encouraged.

3.7.6. When test results are difficult to interpret during investigation of an allergy, and bearing in mind the consequences for a patient who may subsequently have to receive anesthesia, consultation should be possible with a group of trained local (or regional) allergists and anesthetists who are regularly updated on allergy during anesthesia. A list of these key individuals or groups should be readily available to practitioners who require consultation.

3.8. The incidence of hypersensitivity reactions during anesthesia should be regularly monitored.

3.8.1. Monitoring involves collecting data from referral and regional pharmacovigilance centers.

3.8.2. Monitoring can also involve inspecting the results of national surveys, including that of the French network (Groupe d'Etude des Réactions Anaphylactiques Peranesthésiques [Group for the Study of Perianesthetic Anaphylactic Reactions]), for mortality and morbidity data related to anesthesia.

4. Factors favoring a hypersensitivity reaction and the role of the anesthetic allergy workup

4.1. The types of patients at risk of hypersensitivity reactions are as follows:

4.1.1. Patients diagnosed with an allergy to drugs (or products likely to have been used during anesthesia) established by means of a prior workup.

4.1.2. Patients who have demonstrated clinical signs of allergy during previous anesthesia.

4.1.3. Patients exhibiting clinical signs of allergy on exposure to latex (CR 2), irrespective of the exposure circumstances.

4.1.4. Children who have undergone several interventions (notably spina bifida or myelomeningocele) are at risk due to the high frequency of sensitization to latex (CR 1) and the high incidence of immediate hypersensitivity reactions to latex (CR 1).

4.1.5. Patients who exhibit symptoms following ingestion of foods such as avocado, kiwi, banana, chestnut, and buckwheat or during exposure to *Ficus benjamina* (high frequency of cross-sensitization between foods or plants and latex) (CR 2).

4.2. Pre-anesthetic allergy testing

4.2.1. Risk factors for allergy should be investigated systematically before procedures involving anesthesia.

4.2.2. In the general population, it is not necessary to perform routine screening before anesthesia for sensitization to drug(s) and/or product(s) used in anesthesia. The justification is the insufficient knowledge on the predictive values of positive and negative allergy skin tests and laboratory tests in the general population. Indeed, both a false negative and a false positive may have adverse effects on anesthesia by inducing a change of technique, which may not be appropriate. In fact, the risk-benefit ratio of this practice is unknown.

4.2.3. In patients with atopy or patients with an allergy to a drug not used in anesthesia, it is not necessary to test for drugs or other substances used during anesthesia.

4.2.4. For patients previously defined as at risk (4.1), investigations are necessary to detect allergic sensitization before anesthesia is administered. When tests are conducted 6 months or more after the reaction, there is a risk of false-negative results.

4.2.4.1. Investigations for those patients indicated in 4.1.1.
• Retain the results of previous allergy workups
• In the case of a previous allergic response to muscle relaxants, newly available muscle relaxants should be tested.

4.2.4.2. Investigations for those patients indicated in 4.1.2. Depending on the circumstances of the intervention, the procedure is outlined in the Figure.

4.2.4.2.1. In the case of an established reaction, the anesthetist must investigate the anesthetic procedure and forward findings to the allergist who will perform the relevant tests.
• Anesthesia procedure not known: Test all muscle relaxants and latex (skin tests, specific IgE, or both).
• Anesthesia procedure known: Test the drugs in the anesthetic record and latex (skin tests, specific IgE, or
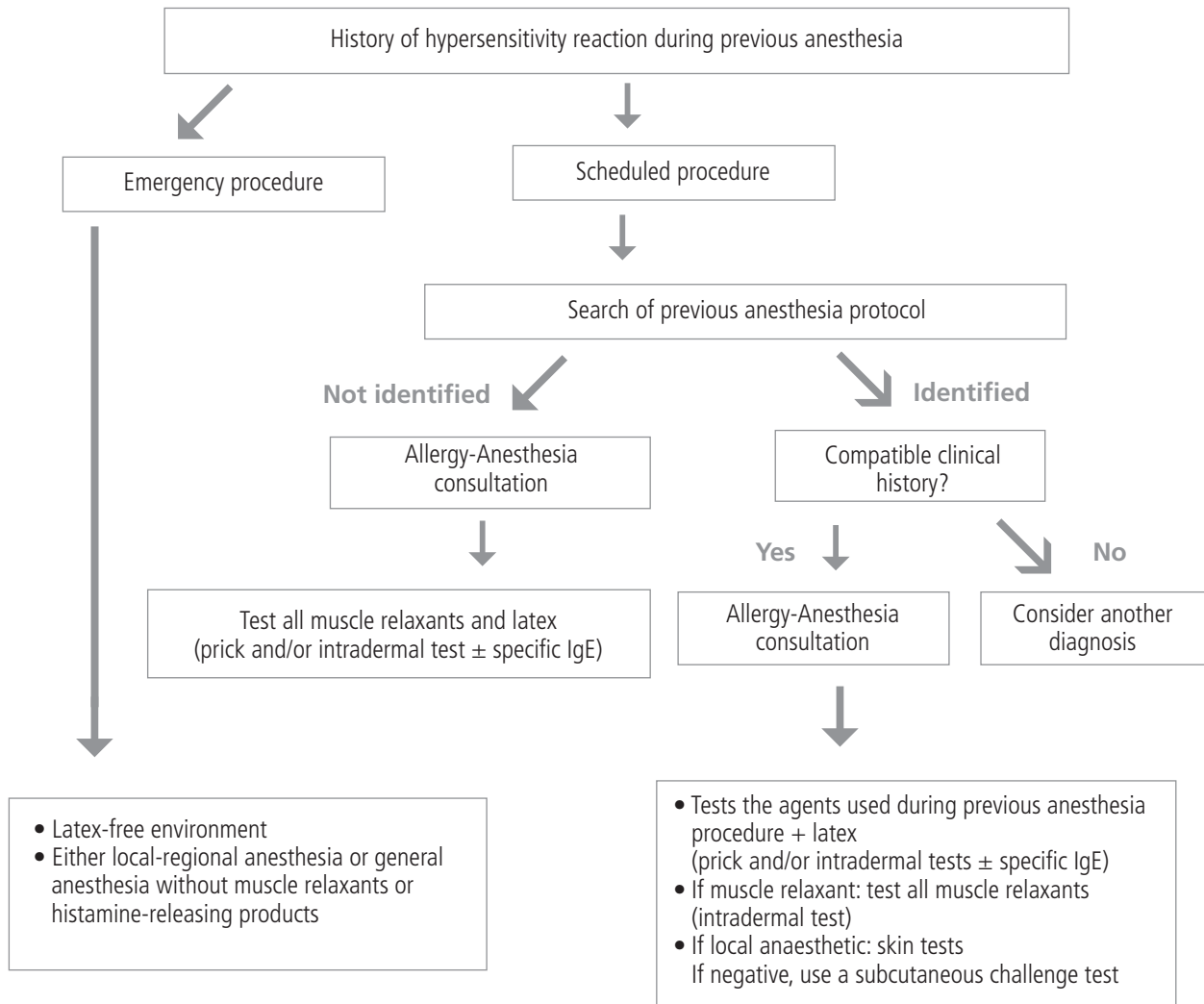
Figure. Decisional algorithm for a patient reporting a hypersensitivity reaction during previous anesthesia and who has not undergone an allergy workup.

both). If a local anesthetic technique was used, conduct a challenge test, but first ensure skin test results are negative.

4.2.4.2.2. In an emergency situation, it would be prudent to exclude latex from the patient's environment and use regional anesthesia. If general anesthesia is chosen, avoid muscle relaxants and histamine-release drugs (CR 4).

4.2.4.3. Investigations in patients defined in 4.1.3 to 4.1.5: SPT to commercial latex extract, serum latex-specific IgE, or both.

4.3. Special situations and requests for allergy testing

4.3.1. Immediate hypersensitivity reaction suggestive of anti-COX-1 nonselective NSAID hypersensitivity.

4.3.1.1. If the intervention is not urgent, an allergy assessment including drug provocation tests must be conducted in a hospital setting.

4.3.1.2. In an emergency, do not administer anti-COX-1 NSAIDs. In contrast, patients usually tolerate COX-2 inhibitors

(celecoxib and parecoxib). It is also generally possible to administer paracetamol at a reduced dosage (an anti–COX-1 effect is possible at high doses) (CR 2).

4.3.2. Where there is suspicion of hypersensitivity to paracetamol and the situation is not an emergency, investigations should be performed at a hospital specialized in drug allergy workups, including provocation tests.

4.3.3. If the case of a reaction to morphine or codeine, neither morphine nor codeine should be injected, although all other opioids are permitted.

4.3.4. In the case of a food allergy to egg or soy, propofol can be administered in patients allergic to eggs. Similarly, the presence of purified soybean oil in the excipient of propofol does not contraindicate its use in patients with a food allergy to soy (CR 4). A single case of hypersensitivity to propofol in a patient allergic to eggs has been reported in the literature [10].

4.3.5. In allergy to seafood or fish, iodine-containing medications are not contraindicated (CR 3).

4.3.6. In the case of a documented protamine allergy, protamine itself is contraindicated. Although an anaphylactic reaction to protamine in a patient allergic to fish has been reported, a recent review of the literature does not justify its prohibition in cases of fish allergy [11] (CR 2).

5. Primary and secondary prevention. Premedication and anesthetic technique: patient preparation

5.1. Primary prevention

5.1.1. Primary prevention of sensitization is achieved by ensuring there is no exposure to the drug or material.

5.1.2. Primary prevention is not possible for anesthetic agents, but can be proposed for materials such as latex. The choice of drugs for anesthesia should be determined rationally. In particular, administration of neuromuscular blocking agents must be in accordance with the indications for neuromuscular blockade in anesthesia (CR 4).

5.1.3. In order to reduce the risk of sensitizing patients to latex, prevent contact or exposure to it. The decision of the institution to create a latex-free environment constitutes effective primary prevention (CR 1).

5.2. Secondary prevention

5.2.1. The optimum mode of secondary prevention is to withhold the medication to which a patient is sensitized. The allergen responsible for an immediate hypersensitivity reaction must be identified to avoid a similar reaction during subsequent use of the drug (CR 2).

5.2.2. The risk factors for latex sensitization are as follows: atopic conditions, occupational or repeated contact with latex, urinary abnormalities (eg, spina bifida and neurogenic bladder), and need for multiple surgical interventions. Such patients are at an increased risk of allergic hypersensitivity reaction to latex.

5.2.3. Patients sensitized to latex must be scheduled at the beginning of the operating list and in a latex-free environment. Sufficient warning of the patient's latex sensitivity should be given to all relevant parties during the hospital stay (in-patient unit, operating room, recovery room) (CR 3).

5.2.4. A pre-operative questionnaire may be used to screen for latex allergy during the pre-anesthetic consultation. This could reduce the incidence of reactions to latex (CR 4).

5.2.5. When latex sensitization is suspected, the patient must be referred for consultation to the allergy department before surgery (CR 3).

5.2.6. In collaboration with the pharmacy, regularly updated lists of latex-containing materials must be available in anesthesiology departments (CR 3).

5.2.7. It is not necessary to systematically investigate sensitization before anesthesia, except for patients in recognized risk groups (CR 2).

5.2.8. Prior to anesthesia, a consultation at the allergy department must be undertaken in those patients at risk of an allergic reaction to drugs and materials used during the perioperative period, as follows:

• Patients who have had an unexplained reaction to an unidentified allergen during previous anesthesia.

• Individuals known to be allergic to drug classes that will be used during the anesthetic period and patients at a risk of latex allergy.

5.2.9. The intravenous route should not be used to perform a test dose for sensitivity to anesthetic agents (CR 4).

5.3. Premedication

5.3.1. Premedication is not effective in preventing an immediate allergic hypersensitivity reaction.

5.3.2. It is possible that the effects of histamine binding to its H_1 receptors will be reduced by prior administration of an H_1 antihistamine. The use of H_1 antihistamines has reduced the incidence and intensity of nonallergic immediate hypersensitivity reactions (CR 2).

5.3.3. The combination of an H_1 and H_2 antihistamine is not superior to an H_1 antihistamine alone in preventing the peripheral effects of histamine (CR 3).

5.3.4. There is no evidence that premedication with a single dose of a corticosteroid is effective in preventing an immediate hypersensitivity reaction (CR 4). Asthmatic patients on long-term corticosteroid therapy exhibit decreased incidence of bronchial hyperreactivity during anesthesia (CR 3).

5.4. Anesthesia for patients with allergy or those at risk of developing one

5.4.1. Antibiotic prophylaxis should be administered preoperatively to a monitored awake patient in the operating room before induction of anesthesia. In this case, the role of the antibiotic in symptoms is easier to determine. Resuscitation of the cardiovascular system is easier in patients who have not been on anesthetic drugs that can alter cardiovascular function (CR 4).

5.4.2. The choice of anesthetic technique will depend on the patient and the surgical procedure. In an emergency, and in the absence of an allergy workup, local and regional anesthesia techniques are preferred. Neuromuscular blocking agents and histamine-releasing drugs are to be avoided, and surgery must be conducted in a latex-free environment (CR 3).

5.4.3. The choice of anesthetic agents will be based on the patient's clinical history and the results of any allergy assessment (CR 2).

5.4.3.1. In the hypnotics group, halogenated drugs have never been implicated in immediate hypersensitivity reactions. Exceptionally, there may be an allergy to propofol and benzodiazepines.

5.4.3.2. Hypersensitivity reactions to opiates are mainly described in association with morphine and codeine. These are most frequently nonallergic immediate hypersensitivity reactions.

5.4.3.3. All neuromuscular blocking agents can induce immediate, allergic, hypersensitivity reactions. The choice of neuromuscular agent will be based on the indications for neuromuscular blockade and skin tests (CR 3).

5.4.3.4. A patient who presents with an immediate hypersensitivity reaction to a neuromuscular blocking agent should be investigated systematically for cross-sensitivity to other neuromuscular blocking agents with skin tests. These enable an appropriate neuromuscular blocker to be chosen for a later surgical intervention (CR 3).

6. Treatment of immediate hypersensitivity reactions with emphasis on anaphylactic shock occurring during anesthesia

6.1. Recommendations for the treatment of immediate hypersensitivity reactions during anesthesia should not be

regarded as rigid. Treatment must be tailored according to clinical severity, the patient's history, availability, and response to emergency treatment. Monitoring, as with any anesthetic agent, is obligatory (CR 4).

6.2. General resuscitative measures are applied in all cases (CR 4).

6.2.1. The suspect drug should be withdrawn.

6.2.2. Inform the surgical team and propose an appropriate course of action. This will depend on whether surgery is not performed or whether it is simplified, accelerated, or terminated.

6.2.3. Administer 100% oxygen (CR 4).

6.3. In grade I reactions, the measures described in paragraph 6.2 are generally sufficient. Some international guidelines recommend the administration of H_1 antihistamines (diphenhydramine at doses of 25-50 mg or 0.5 to 1 mg/kg IV) together with H_2 antihistamines (ranitidine 50 mg diluted and injected over 5 minutes). This medicine is not marketed in all countries, including France. As a substitute, dexchlorpheniramine 5 mg IV can be administered and repeated once.

6.4. More severe cases (grade II or III) (CR 3)

6.4.1. Oxygenation and rapid airway control.

6.4.2. Inject adrenaline in intravenous boluses. The initial dose depends on the severity of hypotension (10-20 μg for grade II, 100-200 μg for grade III). This must be repeated every 1-2 minutes in order to establish adequate blood pressure. If the response is insufficient, doses should be increased incrementally without delay. An intravenous infusion at a dose of 0.05 to 0.1 μg/kg/min removes the need for repetitive boluses of adrenaline. In the absence of effective intravenous access, the intramuscular route may be used (0.3 to 0.5 mg) and repeated after 5-10 minutes, depending on the hemodynamic effects. Similarly, the intratracheal route may be used in the intubated patient (it should be understood that only one-third of the dose administered by this route reaches the bloodstream). Monitoring of heart rate and blood pressure is obligatory after injection of adrenaline.

6.4.3. Request the assistance of qualified personnel.

6.4.4. Elevate the lower limbs.

6.4.5. Replenish the vascular space by rapid infusion of isotonic crystalloid solutions. Colloids are substituted when the volume of crystalloids administered exceeds 30 mL/kg; however, products suspected of causing the allergic reaction must be avoided.

6.4.6. In the case of bronchospasm without arterial hypotension, one should administer an inhaled ß$_2$-adrenergic receptor agonist such as salbutamol (using a metered dose inhaler) or nebulized adrenaline. With refractory cases or in patients with severe symptoms, an intravenous bolus of ß-agonist (100-200 μg) followed by a continuous infusion (5-25 μg/min) can be administered. Symptoms of even greater severity may be relieved by a continuous infusion of adrenaline.

6.4.7. For patients on ß-blockers, the dose of adrenaline must be increased without delay. If not effective, the first dose of 100 μg should be followed by 1 mg at 1-2 minute intervals. In the case of a persistent refractory response, glucagon should be administered at 1-2 mg intravenously and repeated

every 5 minutes. A continuous perfusion of glucagon can be administered at 5-15 μg/min or 0.3-1 mg/h.

6.4.8. In cases of extreme refractoriness to high-dose adrenaline, various other drugs, vasoconstrictors, or agonists have been suggested, in particular noradrenaline at a starting dose of 0.1 μg/kg/min or others such as terlipressin (a synthetic analog of vasopressin, which is not marketed in all countries) in a 2-mg bolus.

6.5. Cardiac arrest (grade IV) (CR 4)

6.5.1. Initiate cardiac massage.

6.5.2. Administer a 1-mg bolus of adrenaline every 1-2 minutes.

6.5.3. Institute the usual resuscitation measures for failing circulation.

6.6. Second-line treatment in severe reactions (CR 4).

6.6.1. Corticosteroids may attenuate late manifestations of shock: inject 200 mg of hydrocortisone hemisuccinate IV every 6 hours.

6.6.2. Because there is a risk of labile blood pressures, intensive monitoring should be maintained for at least 24 hours.

6.7. Characteristics of cardiac arrest in the pregnant woman

6.7.1. Fetal resuscitation is achieved by stabilizing the hemodynamic situation of the mother. The management algorithm for cardiac arrest in terms of drug therapy, intubation, and defibrillation is unchanged.

6.7.2. There are no distinctive features in the treatment of grade I reactions. In some cases, ß$_2$-adrenergic agonists, H_1 and H_2 antihistamines, and corticosteroids have been be used.

6.7.3. The specifics of managing anaphylactic shock are applicable to the pregnant woman (CR 3), as follows:

6.7.3.1. Control the mother's airway, oxygenate without delay, and bear in mind the anatomical and physiological changes affecting the respiratory system in pregnancy.

6.7.3.2. Position the patient in the left lateral decubitus position (15°), or manually displace the uterus to the left to reduce aortocaval compression.

6.7.3.3. If circulatory failure persists for more than 5 minutes in spite of a well-conducted maternal resuscitation effort (aortocaval compression and other less exacting resuscitation procedures), consider cesarean section at 25 weeks.

6.7.4. Adrenaline is used in the same way to treat anaphylactic shock in the pregnant patient as it is in the nonpregnant patient (sequence, route of administration, dosage) (CR 3).

6.7.5. One may use solutions such as hydroxyethyl starch to replenish vascular volume (CR 3).

6.8. Characteristic features of anaphylaxis in the child

6.8.1. The principles of treating anaphylactic reactions in children are identical to those described in adults. The one singular feature is the emphasis on dosage.

6.8.2. In the case of circulatory arrest (grade IV), a bolus of adrenaline (10 μg/kg) is usually recommended (CR 1). Repeated boluses may be replaced by a continuous infusion, as with adults. The initial dosage is 0.1 μg/kg/min.

6.8.3. For grade II and III anaphylactic reactions, it is advisable to titrate the doses of adrenaline against the hemodynamic response, as data on what dose should be administered are lacking. Titrating adrenaline to restore age-

appropriate blood pressure should be effective (CR 4). While a dose of 1 µg/kg may be sufficient, higher doses may be necessary (5-10 µg/kg).

6.8.4. Hypotension can be regarded as a systolic blood pressure with the following values: <70 mmHg in children aged up to 12 months; 70 mmHg + 2 times the age (in years) in children aged between 1 and 10 years; and <90 mmHg in children aged over 10 years.

6.8.5. Vascular volume is replenished with crystalloids (20 mL/kg) and colloids (10 mL/kg). A cumulative dose of 60 mL/kg may be necessary.

6.8.6. Corticosteroids can be used as a second-line approach, as in adults. For asthmatic children with anaphylactic shock, early administration of corticosteroids is beneficial, as for adults. No evidence exists in the literature on the optimal dose in anaphylactic shock. The recommended doses are similar to those administered in cases of severe asthma exacerbation, ie, 1 to 2 mg/kg of methylprednisolone or hydrocortisone, 200 mg in children aged >12 years, 100 mg in children aged between 6 and 12 years, 50 mg in children aged between 6 months and 6 years, and 25 mg in children aged <6 months (CR 4).

6.8.7. In cases of anaphylaxis with a predominance of respiratory symptoms, the recommended dose of salbutamol is 50 µg/kg to a maximum of 1000-1500 µg, which is roughly equivalent to 4-15 puffs of salbutamol. This should be repeated every 10-15 minutes (CR 4). Intravenous administration is an effective alternative in severe acute asthma (CR 4). The recommended dosage is 5 µg/kg (over 5 minutes), followed by a continuous infusion of 0.1 to 0.3 µg/kg/min. However, in practice, these rates seem to be inadequate, and doses of 0.5 to 2 µg/kg/min can be administered according to patient response. There is no apparent advantage in increasing the dose beyond 5 µg/kg/min (CR 4).

6.8.8 For children on ß-blockers, and those in epinephrine-refractory shock, glucagon can be used at 20-30 µg/kg. This can be delivered by an infusion at a rate of 5-15 µg/min according to the arterial pressure response; however, rates should not exceed a total of 1 mg delivered intravenously within 5 minutes.

6.8.9. There are no data in the literature suggesting the use of vasopressin in children.

References

1. Reducing the risk of anaphylaxis during anaesthesia. Abbreviated text. Ann Fr Anesth Reanim. 2002;21 Suppl 1:7s-23s.
2. Prévention du risque allergique peranesthésique. recommandations pour la pratique clinique. Ann Fr Anesth Reanim. 2002;21 Suppl 1:1s-180s.
3. Mertes PM, Laxenaire MC, Lienhart A, SFAR, Aberer W, Ring J, Pichler WJ, Demoly P for ENDA/EAACI. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. J Invest Allergol Clin Immunol. 2005;15:91-101.
4. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer TT, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490.
5. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, Phillips B, Lelgemann M, Lethaby A, Bousquet J, Guyatt GH, Schünemann HJ; GRADE Working Group. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009;64:669-77.
6. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, Raskob G, Lewis SZ, Schünemann H. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American college of chest physicians task force. Chest. 2006;129:174-81.
7. Prévention du risque allergique peranesthésique. Texte court. Ann Fr Anesth Reanim. 2011;3 (in press).
8. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, Brockow K, Pichler WJ, Demoly P; European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy. 2003;58:854-63.
9. 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.
10. Tashkandi J. My patient is allergic to eggs, can I use propofol ? A case report and review. Saudi J Anaesth. 2010;4:207-8.
11. Levy JH, Adkinson NF Jr. Anaphylaxis during cardiac surgery: implications for clinicians. Anesth Analg. 2008;106:392-403.

❚ **PM Mertes**

Service d'Anesthésie-Réanimation
CHU de Nancy
Hôpital Central
Nancy, France