

Perioperative Anaphylaxis

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The practice of anesthesiology has become increasingly safe throughout the years. Practicing clinicians and researchers have the opportunity to examine more closely those rare and serious adverse events that may threaten patient well-being. Immediate hypersensitivity reactions, the most severe appearing as anaphylaxis, which sometimes occur during anesthesia, are 1 such example. The effective anticipation, prevention, and treatment of these reactions is largely based on the knowledge and vigilance of the attending clinicians. Immediate hypersensitivity reactions occur, however, only once in every 5000 to 10,000 anesthetics. Therefore, individual anesthesiologists are likely to encounter only a few cases in their working lifetimes, hence the rapidity with which the diagnosis is made and appropriate management instituted varies considerably. For this reason, a structured approach to preventing, diagnosing, and managing perioperative anaphylaxis is justified.

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EPIDEMIOLOGY

General anesthesia is a unique situation described as a reversible state of unconsciousness, amnesia, analgesia, and immobility as a result of administering several drugs in a short period.¹ Many of these drugs can elicit adverse reactions either related to their pharmacologic properties and usually dose dependent, or unrelated to the pharmacologic properties and less dose dependent. The latter reactions comprise drug intolerance, idiosyncratic reactions, and anaphylactic reactions, which can be either immune mediated (allergic) or nonimmune mediated (pseudoallergic or anaphylactoid reactions). In an attempt to counteract unclear and heterogeneous use of terms, the nomenclature task force of the European Academy of Allergy and Immunology, and the World Allergy Organization, have proposed that anaphylactic-type reactions should be reclassified into allergic anaphylaxis and nonallergic anaphylaxis.^{2,3} This proposal has not been universally accepted.⁴

The true incidence of anaphylactic reactions with their associated morbidity and mortality remains poorly defined as a result of uncertainties about reporting accuracy and exhaustiveness. Despite reported variations, probably reflecting differences in clinical practice and reporting systems, overall incidences seem to be similar between countries. The estimated incidence of all immune- and nonimmune-mediated immediate hypersensitivity reactions is 1 in 5000 to 1 in 13,000 anesthetics in Australia, 1 in 5000 in Thailand, 1 in 4600 in France, 1 in 1 250 to 1 in 5000 in New Zealand, and 1 in 3500 in England.⁵⁻⁹ The estimated incidence of allergic anaphylaxis is 1 in 10,000 to 1 in 20,000 in Australia,¹⁰ 1 in 13,000 in France,¹¹ 1 in 10,263 in Spain,¹² 1 in 5500 in Thailand,⁹ and 1 in 1700 to 1 in 20,000 in Norway.¹³ In most series, allergic reactions represent at least 60% of all hypersensitivity reactions observed within the perioperative period.^{12,14-17} Reported expected mortality ranges from 3% to 9%.^{18,19} The overall morbidity remains unknown.

MECHANISM

Allergic anaphylaxis is most commonly caused by the interaction of an allergen with specific immunoglobulin E (IgE) antibodies. These antibodies, in sensitized individuals, bind to high-affinity FcεRI receptors located in the plasma membrane of tissue mast cells and blood basophils, and to low-affinity FcεRII receptors on lymphocytes, eosinophils, and platelets. This interaction stimulates the cells to release preformed and newly synthesized inflammatory mediators, such as histamine, tryptase, phospholipid-derived mediators (eg, prostaglandin D₂, leukotrienes, thromboxane A₂, and platelet-activating factor) as well as several chemokines and cytokines, which account for the clinical features. Target organs commonly include the skin, mucous membranes, cardiovascular and respiratory systems, and the gastrointestinal tract. Allergic anaphylaxis for some substances (eg, dextrans) may be caused by IgG antibodies that produce immune complexes with the antigen (dextran macromolecules), and thereby activate the complement system.²⁰

The precise mechanisms of nonimmune-mediated reactions remain difficult to establish. They are usually considered to result from a direct pharmacologic stimulation of mast cells and basophils, causing release of inflammatory mediators.²¹ However, other mechanisms may be involved.^{22,23} Nonallergic anaphylaxis does not entail an immunologic mechanism and, therefore, previous contact with the culprit substance is not necessary. However, in allergic anaphylaxis, involving drug-specific IgE, previous contact is not obligatory, and sensitization may have occurred via cross-reactive substances (see later discussion).

INVESTIGATION OF AN ALLERGIC REACTION

Any suspected hypersensitivity reaction during anesthesia must be extensively investigated using combined peri- and postoperative testing. It is important to confirm the nature of the reaction, to identify the responsible drug, to detect possible cross-reactivity in cases of anaphylaxis to a neuromuscular blocking agent (NMBA), and to provide recommendations for future anesthetic procedures.^{24,25} Serious attempts have been made to standardize and validate in vitro and in vivo techniques for the diagnosis of drug allergy.^{24–28} However, none of the available diagnostic tests is absolutely accurate. False-positive test results may merely cause an inconvenience (unnecessary avoidance of a safe drug), whereas false-negative or equivocal results may be extremely dangerous and severely undermine correct secondary prevention. Whenever possible, confirmation of the incriminated allergen should be based on immunologic assessment using more than 1 test. In the event of discrepancies between different tests, an alternative compound that tested completely negative is advocated.

The diagnostic strategy is based on a detailed history including concurrent morbidity, previous anesthetic history, and any known allergies, and on a series of investigations performed immediately and days to weeks later. Biologic investigations include mediator release assays at the time of the reaction,²⁹ quantification of specific IgE, immediately or best during the first 6 months after the event took place,^{29,30} skin tests,²⁶ and other biologic assays such as histamine release tests or basophil activation assays.^{28,31} Early tests are essentially designed to determine whether or not an immunologic mechanism is involved, or at least whether mast cells were activated (tryptase determinations). Skin tests are performed later, but best in the first year after the event, and attempt to identify the drug responsible.

Clinical Picture of Anesthesia-related Anaphylaxis

Anaphylaxis is generally an unanticipated reaction. The initial diagnosis is presumptive, although essential, because anaphylaxis may progress within minutes to become life threatening. The first line of evidence for the diagnosis of anaphylaxis includes the features and severity of clinical signs and the timing between the introduction of a suspected allergen and the onset of symptoms, whereas the required dosage of resuscitative medications gives insight as to the severity of the reaction.

The signs and symptoms of anaphylaxis occurring during anesthesia differ to some extent from those of anaphylaxis not associated with anesthesia. All early symptoms usually observed in the awake patient such as malaise, pruritus, dizziness, and dyspnea are absent in the anaesthetized patient. The most commonly reported initial features are pulselessness, difficulty to ventilate, and desaturation.¹⁰ In our experience, a decreased end-tidal CO₂ is also of diagnostic value.³² Cutaneous signs may be difficult to notice in a completely draped patient. In addition, many signs such as tachycardia, hypotension, or increased airway resistance may be the result of an interaction between the clinical status of the patient and the drugs administered during the procedure, dose-related side effect of the drugs, or inadequate depth of anesthesia. The differential diagnosis of anesthesia-related anaphylaxis is shown in **Table 1**.

Clinical manifestations show striking variations of intensity in different patients, ranging from mild hypersensitivity reactions to severe anaphylactic shock and death.^{7,14} However, when a classification based on symptom severity is applied, allergic reactions are usually more severe than nonimmune-mediated reactions (**Table 2**).^{16,17} The absence of cutaneous symptoms does not exclude the diagnosis

Table 1
Differential diagnosis of anaphylaxis during anesthesia

Drug overdose and interactions
Cardiac/vascular drug effects
Asthma
Arrhythmia
Myocardial infarction
Pericardial tamponade
Pulmonary edema
Pulmonary embolism
Tension pneumothorax
Hemorrhagic shock
Venous embolism
Sepsis
C1 esterase inhibitor deficiency
Mastocytosis
Malignant hyperthermia (succinylcholine)
Myotonias and masseter spasm (succinylcholine)
Hyperkalemia (succinylcholine)

of anaphylaxis. In addition, clinical features may occur in isolation such as a sudden cardiac arrest without any other clinical signs.¹⁷ As a result, an anaphylactic reaction restricted to a single clinical symptom (eg, bronchospasm, tachycardia with hypotension) can easily be misdiagnosed because many other pathologic conditions may have an identical clinical presentation. In mild cases restricted to a single symptom, spontaneous recovery may be observed even in the absence of any specific treatment. Under such circumstances, the lack of a proper diagnosis and appropriate allergy assessment may lead to fatal reexposure.

Anaphylaxis may occur at any time during anesthesia, and may progress slowly or rapidly. Ninety percent of reactions appear at anesthesia induction, within minutes or seconds after the intravenous injection of the offending agent such as an NMBA or an antibiotic.^{7,33} If the signs appear later, during the maintenance of anesthesia, they suggest an allergy to latex, volume expanders, or dyes. Latex allergy should also be considered when gynecologic procedures are performed. Particles from obstetricians' gloves, which accumulate in the uterus during obstetric maneuvers, could suddenly be released into the systemic blood flow following oxytocin injection.¹¹ Anaphylactic reactions to antibiotics have also been reported following removal of tourniquet during orthopedic surgery.³⁴

Table 2
Grade of severity: classification of immediate hypersensitivity reactions

Grade	Symptoms
I	Generalized cutaneous signs: erythema, urticaria, with or without angioedema
II	Moderate multiorgan involvement with cutaneous signs, hypotension and tachycardia, bronchial hyperreactivity: cough, difficulty to ventilate
III	Severe life-threatening multiorgan involvement: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm. Cutaneous signs may be present or may occur only after arterial blood pressure is restored
IV	Cardiac and/or respiratory arrest

Histamine and Tryptase

During an IgE-mediated reaction, basophils and mast cells are activated, then degranulate and release mediators into the extracellular fluid compartment. These mediators can be measured in the patient's serum and have proved to be useful for the diagnosis of anaphylaxis during anesthesia.^{16,29,35-37} Histamine concentrations are maximal almost immediately and decrease thereafter, with a half-life of about 20 minutes. Therefore, circulating levels should be assayed within the first hour of a reaction. In mild cases, only early serum levels may be increased.³⁵ Histamine assays should be avoided during pregnancy (particularly near term) and in patients receiving high doses of heparin because of a high rate of false negativity caused by accelerated histamine degradation. When increased, circulating histamine levels confirm basophil cell degranulation, which can result from direct or IgE-mediated activation. In our most recent study, the sensitivity of this test for the diagnosis of anaphylaxis was estimated at 75%, its specificity at 51%, the positive predictive value at 75%, and the negative predictive value at 51%. Urinary methylhistamine assays are no longer recommended in view of their low sensitivity compared with tryptase and histamine assays.

Tryptase reaches a peak in the patient's serum 30 minutes after the first clinical manifestations. Its half-life is 90 minutes, and the levels usually decrease with time but in some cases increased levels can still be detected for up to 6 hours or more after the onset of anaphylaxis.²⁹ Basophils and mast cells differ in the amount of tryptase contained in their granules. Mast cells contain high tryptase levels (12-35 pg/cell) and basophils low levels (<0.05 pg/cell). Thus, although increased tryptase levels can be observed in different situations, an increased tryptase concentration of more than 25 µg/L is usually regarded as specific for mast cell activation, independent of its cause.^{29,31} The absence of an increased serum tryptase level, however, does not rule out an allergic reaction.³¹ In our most recent series, the sensitivity of tryptase measurement for the diagnosis of anaphylaxis was estimated at 64%, its specificity at 89.3%, positive predictive value at 92.6%, and negative predictive value at 54.3%.¹⁶ To rule out an underlying mastocytosis with constitutive increased tryptase levels and higher tendency to anaphylaxis, tryptase levels should be determined again after 2 to 3 days.

Specific IgE Assay

In vitro tests are available to detect the presence of serum-specific IgE antibodies. Baldo and Fisher³⁸ were the first to show that drug-reactive IgEs were involved in anaphylactic reactions, using NMBA's coupled to epoxy Sepharose in a radioimmunoassay (RIA). The detection of antidrug-specific IgEs in serum is performed by a sandwich-type immunoassay in which the serum IgE is first adsorbed to a reactive phase and subsequently quantified via the binding of an anti-IgE tracer. The reactive phase is prepared by covalently coupling a drug derivative to a solid-phase such as nitrocellulose membrane or a polymer.

IgE binding on different NMBA solid phases and competitive inhibition assays with several muscle relaxants and other drugs and chemicals including morphine showed a cross-reactivity of specific IgE.³⁸⁻⁴⁰ However, some patients do not react with all NMBA, showing that the substituted ammonium ion is at least not always the only part of the epitope. Gueant and colleagues⁴¹ improved an RIA method for detecting NMBA IgE in serum using a quaternary ammonium compound coupled to Sepharose (QAS-RIA). The sensitivity of this test was estimated at 88%. An inhibition step in the presence of 130 nmol of soluble drug is performed and the highest percentage is observed with the incriminated drug in most cases (83.3%). Guillox and colleagues⁴²

have developed an RIA test by coupling a *p*-aminophenylphosphorylcholine on agarose (PAPPC RIA). PAPPC contains a larger choline derivative (quaternary ammonium ion), including a secondary ammonium group, an aromatic ring, and a phosphate group. Both methods were found to have similar sensitivity and specificity. Recently, Fisher and Baldo⁴⁰ suggested the use of a morphine-based immunoassay for the detection of specific IgE to ammonium ions in the sera of sensitized subjects. More recently, Ebo and colleagues⁴³ investigated the diagnostic value of quantification of IgE by ImmunoCAP (Phadia AB, Uppsala, Sweden) in the diagnosis of rocuronium allergy. They also studied whether IgE inhibition tests can predict clinical cross-reactivity between NMBA. They concluded that the rocuronium ImmunoCAP constitutes a reliable technique to diagnose rocuronium allergy, provided an assay-specific decision threshold is applied, because these assays reach a sensitivity of more than 85% and absolute specificity.

Specific IgE against thiopental, morphine, phenoperidine, and propofol have also been detected in serum of sensitized patients, using IgE-RIA.^{44,45} The presence of hydrophobic IgE reacting nonspecifically with propofol has been reported.⁴⁶ With respect to latex, a radioallergosorbent test is available. Although considered less sensitive than the skin-prick test (SPT), 92.8% sensitivity has been reported.⁴⁷ In vitro assays to quantify specific IgEs for several penicillin determinants (Phadia penicilloyl G [c1], penicilloyl V [c2], amoxycilloyl [c6], ampicilloyl [c5], and cefaclor [c7]) are available but are generally considered less sensitive than skin tests.⁴⁸

These factors have recently led to limiting the recommended indications for specific IgE assays to the diagnosis of anaphylaxis to NMBA, thiopental, and latex.²⁴ These tests are usually performed several weeks after the reaction but can already be performed at the time of the reaction.^{24,29,30}

Skin Testing

Skin tests coupled with history remain the mainstay of the diagnosis of an IgE-mediated reaction. Intradermal or SPTs are usually performed 4 to 6 weeks after a reaction. Up to 4 weeks following an allergic reaction, the intracellular stocks of histamine and other mediators are still lower than normal.⁴⁹ Skin tests to NMBA may remain positive for years, whereas positivity to β -lactams declines with time. Ideally, testing should be performed by a professional experienced in performing and interpreting tests with anesthetic agents.²⁴

SPTs and intradermal tests (IDTs) with dilutions of commercially available drug preparations are advised. Although highly reliable, skin tests are not infallible.⁵⁰ Standardized procedures and dilutions must be precisely defined for each agent tested to avoid false-positive results. Control tests using saline (negative control) and codeine (positive control) must accompany skin tests, to determine whether or not the skin is apt to release histamine and react to it. Skin tests are interpreted after 15 to 20 minutes. An SPT is considered positive when the diameter of the wheal is at least equal to half of that produced by the positive control test and at least 3 mm greater than the negative control. IDTs are considered positive when the diameter of the wheal is twice or more the diameter of the injection wheal.

A certain degree of controversy remains as to the maximal concentrations to be used when sensitization to NMBA is investigated.^{51,52} Detailed recommendations for skin and intradermal test dilutions of anesthetic drugs including NMBA have been proposed by the Société Française d'Anesthésie et de Réanimation (SFAR; French Society of Anesthesia and Intensive Care Medicine) and the Société Française d'Allergologie (SFA; French Society of Allergology) (**Table 3**).²⁴ The accuracy of these recommended maximal concentrations has been further confirmed in a prospective

Table 3
Maximal concentrations normally nonreactive for SPT and IDT

Available Agents	Concentration (mg/mL)	SPT		IDT	
		Dilution	C _{max} (mg/mL)	Dilution	C _{max} (mg/mL)
NMBAs					
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
Hypnotics					
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	100	1/10	10	1/100	1000
Opioids					
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
Local anesthetics					
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
Antibiotics					
PPL		Undiluted	0.035	Undiluted	35
MDM (penicillin)		Undiluted	1	Undiluted	1000
Penicillin G		Undiluted	20–25 × 10 ^{3,a}	Undiluted	20–25 × 10 ^{3,a}
AX, AMP		Undiluted	20–25	Undiluted	20–25 × 10 ³
Other penicillins					
Cephalosporins		Undiluted	1–2	Undiluted	1–2 × 10 ³
Vancomycin	500			1/5 × 10 ⁶	0.1
Gentamycin	40	Undiluted		1/10 ²	400
Miscellaneous					
Chlorhexidine	0.5	Undiluted	0.5	1/10	50
Patent blue	25	Undiluted	25	1/10	2500
Methylene blue	10	Undiluted	10	1/100	100

Abbreviation: C_{max}, maximal concentration.

^a For penicillin G, concentrations are expressed in IU/ml (not mg/ml).

study conducted in 120 healthy volunteers tested with all available NMBA's at increasing concentrations on the anterior part of the forearm and on the back. Results were similar at both injection sites.²⁶ Because of the frequent but not systematic cross-reactivity observed with muscle relaxants, all available NMBA's should be tested.^{14,24,31,53} This practice may help avoid future adverse reactions and provide documented advice for the future administration of anesthesia.^{14,24} However, no diagnostic procedure is devoid of false-positive or -negative results. Although rare, some cases of renewed allergic reactions following exposure to an NMBA considered to be safe have been reported in the literature.^{50,54} Therefore when administering an NMBA to a sensitized patient with a negative skin test, one should bear in mind the risk/benefit ratio. In addition, any new muscle relaxant should be routinely tested in patients known to be allergic to NMBA's to detect possible cross-reactivity.²⁴

The estimated sensitivity of skin tests for muscle relaxants is approximately 94% to 97%.⁵⁵ There has been some controversy concerning the advantages of prick versus intradermal testing. Studies comparing both techniques show little difference between them.^{56,57} However, reliability of prick testing over time has not been assessed, and the reliability of prick tests alone in the individual patient has been questioned by some investigators.⁵⁸ Consequently, prick testing is advised for the diagnosis of the muscle relaxant responsible for an anaphylactic reaction, but intradermal testing should be preferred when investigating cross-reaction.

The diagnostic approach to β -lactam antibiotic-related allergic reactions has recently been standardized under the aegis of the European Network for Drug Allergy, the European Academy of Allergy and Clinical Immunology (EAACI) interest group on drug hypersensitivity.^{59,60} Skin tests start with SPT, which are, if negative, followed by IDT. Skin testing should not be limited to the classic and commercial reagents benzylpenicilloyl poly-L-lysine (PPL) and so-called minor determinants mixture (MDM), but should include amoxicillin (AX) and ampicillin (AMP), as well as the culprit compound(s). Maximum concentrations for SPT and IDT for PPL, MDM, AX, AMP and other penicillins, and for most cephalosporins are summarized in **Table 3**. The specificity of skin testing with β -lactams is between 97% and 99%, whereas the sensitivity is only around 50% to 70%. Therefore, oral provocation tests in patients with suggestive clinical history and negative skin test is recommended.

Skin test sensitivity for other substances varies. It is optimal for synthetic gelatins, but poor for barbiturates, opioids, and benzodiazepines.¹⁴ Latex sensitization must be investigated by SPTs.⁶¹ SPTs and IDTs have been proposed in the literature for the diagnosis of sensitization to blue dyes. However, false-negative SPTs have been occasionally reported. These reports strongly suggest favoring IDTs using up to a 1:100 dilution for the diagnosis of sensitization to blue dyes in patients with a history of a possible immediate hypersensitivity reaction to dyes.⁶²

Mediator Release Tests

Basophil activation assays

Allergen-induced mediator release tests quantify mediators released during effector cell degranulation, mainly peripheral blood basophils, following stimulation with specific antigen. There are 2 categories of mediator release tests: histamine release tests and sulphidoleukotriene release tests (cellular allergen stimulation test [CAST]). Mata and colleagues⁶³ have evaluated the in vitro leukocyte histamine release (LHR) tests for the diagnosis of allergy to muscle relaxant drugs in 40 patients and a control group of 44 subjects with negative LHR. LHR tests were positive in 65% of the allergic patients, for a threshold corresponding to specificity at 100%. The concordance between LHR test and QAS-RIA was 64%.^{63,64} Despite a good specificity, their

diagnostic application remains limited because of the labor-intensive experimental conditions and insufficient sensitivity. Therefore they are not used as routine diagnostic tests.²⁴ They could be useful when cross-reactivity among muscle relaxants is investigated with a view to future anesthesia in sensitized patients. Similarly, monitoring of serotonin,⁶⁵ eosinophil cationic protein,⁶⁶ or leukotriene C4 (LTC4)⁶⁷ release have also been published; however, these assays cannot be recommended for routine clinical use at the present time.

Flow cytometry

Flow-assisted allergy diagnosis relies on quantification of shifts in expression of basophilic activation markers after challenge with a specific allergen using specific antibodies conjugated with a fluorochrome or a dye. Activated basophils not only secrete quantifiable bioactive mediators but also upregulate the expression of different markers, which can be detected efficiently by flow cytometry using specific monoclonal antibodies.^{28,68–71} Currently, the most commonly used antibody in allergy diagnosis is anti-CD63 and, to a lesser extent anti-CD203c. This technique has been clinically validated for several classic IgE-mediated allergies including indoor and outdoor inhalational allergies, primary and secondary food allergies, natural rubber latex allergy, hymenoptera venom allergy, and some drug allergies.²⁸ Although it does not allow differentiating between IgE-dependent and IgE-independent basophil activation, it is anticipated that it might constitute a unique tool in the diagnosis of IgE-independent hypersensitivity reactions as well as for the diagnosis of IgE-mediated anaphylaxis when a specific IgE assay is unavailable.^{28,72} However, several methodological issues remain to be addressed. These issues include applying the test to whole blood or isolated basophils, the need for preactivation with interleukin 3 (IL-3), the choice of appropriate dose for different allergens, positive and negative controls, characterization and activation markers, and the appropriate diagnostic threshold for different allergens.²⁸ Nevertheless, once fully validated, the basophil activation test using flow cytometry will probably represent an interesting diagnostic tool for NMBA anaphylaxis and for cross-sensitization studies.

Challenge Tests

Indications for these tests are limited. They are restricted to local anesthetics, β -lactams, and latex.^{73–75} They should be performed only if there is a negative skin test. Local anesthetics can be tested by subcutaneously injecting 0.5 to 2 mL of undiluted anesthetic solution (without epinephrine). The test is considered negative if no adverse reaction occurs within 30 minutes after injection.⁷⁶ Oral provocation tests are useful for the diagnosis of β -lactam hypersensitivity.^{74,75}

Advice to Patients

Because the purpose of investigations is to identify the drug or substance responsible and the mechanism behind the reaction, to make subsequent anesthesia as safe as possible, a close collaboration between allergologist and anesthesiologist is highly desirable. In view of the constantly evolving anesthesiology practices, and of the complexity of allergy investigation, establishing specialized allergeoanesthesia centers should be promoted. At the end of the allergic work-up, the patient should be warned against any substance that has tested positive, and a warning card or bracelet should be issued. A detailed letter containing information on the reaction, on the drugs given, on the results of follow-up investigations, and advice for future anesthetics should be issued to the patient, the referring anesthesiologist, and the patient's general practitioner.

CAUSAL AGENTS

The overall distribution of the various causal agents incriminated in allergic anaphylaxis during anesthesia is similar in most reported series. Every agent used during the perioperative period may be involved. NMBAs represent the most frequently incriminated substances ranging from 50% to 70%, followed by latex (12%–16.7%) and antibiotics (15%) (Table 4). Dyes, hypnotic agents, local anesthetics, opioids, colloids, aprotinin, protamine, chlorhexidine, or nonsteroidal antiinflammatory drugs (NSAIDs) are less frequently involved. Mechanisms and available diagnostic tools are summarized in Table 5.

NMBAs

Hypersensitivity reactions to NMBAs are mainly acute IgE-dependent allergic reactions. However, striking differences can be observed between countries. In France, the incidence of IgE-mediated hypersensitivity reactions to NMBAs in 1996 was estimated at 1 in 6500 anesthetics involving a muscle relaxant,¹¹ representing around 60% of all IgE-mediated reactions. It was estimated at 1 per 3000 to 1 per 110,000 exposures in Norway, representing 93.2% of IgE-mediated reactions.¹³ However, IgE-mediated reactions involving NMBAs seem to be less frequent in Denmark and Sweden.^{33,77,78} Allergic reactions to NMBAs have also been reported for smaller series in the United States.⁷⁹

Differences regarding the relative risk of allergic reactions between NMBAs have been recognized in large epidemiologic surveys.^{11,13–16,80} In most reports, suxamethonium seems to be more frequently involved.^{13–16,19} In contrast, pancuronium and cisatracurium are the NMBAs associated with the lowest incidence of anaphylaxis during anesthesia.^{14–17} Some controversy has arisen concerning a potential increased prevalence of allergic reactions to rocuronium. A trend toward increased frequency of allergic anaphylaxis to rocuronium was initially reported in Norway and France,^{81,82} but not in Australia,⁸³ the United Kingdom,⁸⁴ and the United States.⁷⁹ Because of statistical limitations, analysis of epidemiologic data from Norway was unable to confirm whether or not rocuronium represented an increased risk.¹³ At the same time, surveys conducted in France by the GERAP (Groupe d'Etudes des Réactions

Table 4
Substances responsible for IgE-mediated perioperative hypersensitivity reactions in France (results in percent from 7 consecutive surveys)

	1984–1989	1990–1991	1992–1994	1994–1996	1997–1998	1999–2000	2001–2002
	n = 821	n = 813	n = 1030	n = 734	n = 486	n = 518	n = 502
NMBAs	81	70.2	59.2	61.6	69.2	58.2	54
Latex	0.5	12.5	19	16.6	12.1	16.7	22.3
Hypnotics	11	5.6	8	5.1	3.7	3.4	0.8
Opioids	3	1.7	3.5	2.7	1.4	1.3	2.4
Colloids	0.5	4.6	5	3.1	2.7	4	2.8
Antibiotics	2	2.6	3.1	8.3	8	15.1	14.7
Other	2	2.8	2.2	2.6	2.9	1.3	3
Total	100%	100%	100%	100%	100%	100%	100%

Abbreviation: n = number of cases.

Data from Mertes PM, Laxenaire MC. [Anaphylactic and anaphylactoid reactions occurring during anesthesia in France. Seventh epidemiologic survey (January 2001–December 2002)]. Ann Fr Anesth Reanim 2004;23(12):1133–43.

Table 5
Usual mechanisms and diagnostic procedures for the most frequently involved substances in immediate hypersensitivity reactions during the perioperative period

		NMBAs	Latex	β -Lactam Antibiotics	Hypnotics	Opioids	Gelatines	LA	NSAIDs	Dyes
Mechanism		IgE	IgE	IgE	IgE	NSHR	IgE	Non-IgE	COX-1	IgE ?
History		S	S	S	S	S	S	S	S	S
In vitro tests ^a	Tryptase (and histamine)	S	S	S	S	S	S	S	S	S
	Specific IgE	Succinylcholine Rocuronium Morphine-based QAS PAPPC	S	S	NA	NR	S	NA	NR	NA
	BAT	S	S	S	NR	NR	S	NR	S	S
In vivo tests ^b	SPT	S	S	S	S	S	S	S	NR	S
	IDT	S	NR	S	S	S	S	S	NR	S
	Challenge test	NR	S	S	NR	NR	NR	S	S	NR

Abbreviations: LA, local anesthetic; NA, not available; NR, not relevant; NSHR, nonspecific histamine release; S, standard.

^a Tryptase (and histamine) measurement during the acute event can be helpful in discriminating anaphylaxis from other types of reaction; tryptase determination should be repeated 2–4 days or later after the incidence to rule out a mastocytosis. In vitro tests have rarely been validated. Prudence is called on their interpretation. BAT is not considered a standard technique yet by all laboratories in all situations.

^b Skin and challenge tests have to be performed according to existing guidelines.

Anaphylactoïdes Peranesthésiques), a network of 40 French allergeoanesthesia outpatient clinics whose aim is to promote the survey of allergic and nonimmune-mediated reactions occurring during anesthesia, still seem to indicate a trend toward an increased risk when the respective market shares of the different NMBA are taken into account.^{15–17} This apparent increased incidence of anaphylaxis to rocuronium might be a result of biased reporting of adverse effects of new drugs,⁸⁵ statistical issues,⁸⁶ differences in the influence of environmental factors⁸⁷ or genotypic differences.⁸⁸ Further large epidemiologic studies are necessary to elucidate this problem.

Structure-activity studies designed to explore the molecular basis of specific IgE binding have established that quaternary and tertiary ammonium ions were the main component of the allergenic sites on the reactive drugs.³⁹ To explain the possible differences observed regarding the risk of allergic reactions with the different NMBA, it has been suggested that the flexibility of the chain between the ammonium ions as well as the distance between the substituted ammonium ions might be of importance during the elicitation phase of IgE-mediated reactions.⁸⁹ Flexible molecules, such as succinylcholine, were considered more potent in stimulating sensitized cells than rigid molecules, such as pancuronium. This hypothesis would be contradicted if a higher risk of sensitization associated with rocuronium were to be confirmed. Similarly, in the past, alcuronium has been claimed to be a high risk for anaphylaxis. If an increased risk with rocuronium is further confirmed by epidemiologic surveys, propenyl ammonium groups present in rocuronium and alcuronium might be involved in this apparent increased allergenicity. These considerations represent an important issue in the design of an ideal NMBA with a reduced risk of allergic reactions.

Cross-sensitization among the different agents has been reported to be frequent, varying between 60% and 70% of patients allergic to NMBA, but it is not constant.^{11,16,17} The patterns of cross-reactivity vary considerably between patients. Cross-reactivity to all NMBA is unusual, but seems to be more frequent with aminosteroid NMBA than with benzylisoquinoline-derived NMBA.²³

Quaternary and tertiary ammonium ions are the main component of the allergenic sites on the reactive drugs.³⁹ However, the IgE recognition site of the molecule depends also on the molecular environment of the ammonium ion, a function of the hydrophobicity and distance with polar groups such as hydroxyls. This finding may explain the heterogeneity of the cross-reactivity among patients. Another possible hypothesis is that the antigenic determinant may extend to the adjacent part of the molecule. IgE antibodies could also be complementary to structures other than the ammonium group.⁸²

Another intriguing aspect of allergic reactions to NMBA concerns the dogma of previous exposure. In 15% to 50% of cases, these reactions are reported at the first known contact with an NMBA.^{7,14,16,80} This finding suggests a possible cross-reaction with IgE antibodies generated by previous contact with apparently unrelated chemicals. This is a particularly attractive hypothesis in patients who react to small and ubiquitous epitopes such as a substituted ammonium group. These structures occur widely in many drugs but also in foods, cosmetics, disinfectants, and industrial materials. Hence, there seems to be ample opportunity for sensitive individuals to come into contact with and synthesize IgE antibodies to these unusual, and previously unsuspected, antigenic determinants. Recently, Florvaag and colleagues⁷⁷ hypothesized that the striking difference in the rate of allergic reactions to NMBA, which is more than 6 times as common in Norway as in Sweden, could be caused by differences in preoperative sensitization. They reported a higher prevalence of IgE antibodies to quaternary and/or tertiary ammonium ion among blood donors and atopic patients from Norway when compared with Sweden. This study also pointed out

that amongst the common quaternary ammonium ion-containing household chemicals and drugs present in the environment of both populations, the only difference was cough mixtures containing pholcodine, which were present in Norway but not in Sweden. The later report that pholcodine exposure in patients having experienced an allergic reaction to an NMBA⁹⁰ was responsible for a significant increase in specific IgEs to NMBAs led to the hypothesis that pholcodine exposure could lead to IgE-sensitization to pholcodine and other quaternary ammonium ions and thereby increase the risk of allergic reaction to NMBAs. This hypothesis is further supported by the results of an international prevalence study involving several countries across Europe and the United States, showing a statistically significant association between pholcodine consumption and prevalence of IgE-sensitization to pholcodine and succinylcholine in several countries.⁹¹ However, the results also indicate that other, yet unknown, substances may be involved in IgE-sensitization toward NMBAs.

Nonallergic anaphylaxis may represent 20% to 50% of adverse reactions to NMBAs.^{13,15–17,19} Although the precise mechanisms of these reactions remain difficult to establish, they usually result from direct nonspecific mast cell and basophil activation.²¹ Reactions resulting from direct histamine release are usually less severe than IgE-mediated reactions,^{16,17} with the exception of a subset of patients who have been considered as superresponders to the histamine-releasing effect of NMBAs. Histamine release is predominantly found with the use of the benzylisoquinolines d-tubocurarine, atracurium, and mivacurium, and the aminosteroid rapacuronium.⁹² Recently, severe bronchospasm following administration of rapacuronium was reported in children. Increased airway resistance related to rapacuronium administration has been reported in children and adults. It has been suggested that the higher affinity of rapacuronium for M₂ versus M₃ muscarinic receptors could account for the high incidence of bronchospasm observed in clinical practice.⁹³ As a result of these adverse reactions, rapacuronium has been withdrawn from the market in the United States.

Latex

IgE-mediated latex allergy is a well-defined condition with recognized risk groups, established diagnostic tools, and adequate prevention strategies. It is the second most common cause of anaphylaxis during anesthesia in the general population.¹⁷ The prevalence of latex sensitization varies depending on the population studied. As with all allergy-causing substances, it increases with increased exposure. Genetic factors may also be involved.⁹⁴ In children subjected to numerous operations, particularly those suffering from spina bifida, it is the primary cause of anaphylaxis.^{95–97} Adults requiring multiple surgical procedures or health care workers are also at increased risk,⁷ as well as patients allergic to several plant allergens (especially avocado, banana, kiwi, chestnut, *Ficus benjamina*) because of cross-allergy with latex (latex fruit syndrome).⁹⁸

Primary prevention by providing a latex-free environment during surgery and anesthesia and on pediatric wards has been shown to significantly reduce the prevalence of latex sensitization.^{99,100} In addition, a low incidence of allergic reactions caused by latex has been reported in countries where a strategy aimed to reduce latex exposure has been implemented.¹³ Therefore, attempts to ban latex from use in clinical products should be encouraged.

In Europe, investigation of sensitization to latex is performed by SPTs using commercial extracts with an excellent sensitivity (75%–90%). If commercial latex extracts are not available, latex gloves extracts can be used, although their amount of latex proteins is not standardized. Sensitization can also be confirmed by quantification of specific IgEs. The use of latex recombinant proteins seems promising and

may help to discriminate between sensitizations to anaphylaxis-related latex proteins (eg, Hev b1, 2, 5, 6, 13) or sensitization to less relevant proteins (eg, the profilin Hev b8).^{101–103} Although these tests are reliable, in case of equivocal results some patients might need additional tests such as basophil activation or challenge tests (wearing latex gloves for 15 minutes) to establish diagnosis.

Antibiotics

Penicillins and cephalosporins elicit approximately 70% of perioperative anaphylactic reactions to antibiotics. They represent 12% to 15% of the perioperative reactions observed in France.^{16,17} Cross-reactivity between penicillins and cephalosporins is attributed to the common β -lactam ring or the side chains attached to it. A recent meta-analysis suggested that patients allergic to penicillin or AX have a higher incidence of allergic reactions to first-generation cephalosporins and cefamandole but not to later-generation cephalosporins.^{104,105} In Europe, the diagnostic approach for allergic reactions to β -lactam antibiotics has been standardized using algorithms combining skin tests, quantification of specific IgEs, and in selected cases drug provocation tests.⁶⁰

Vancomycin, which is increasingly used for prophylaxis, has also been incriminated in some cases. However, in most cases, the adverse reactions observed are related to the chemically mediated basophil degranulation causing the red-man syndrome, which is associated with rapid vancomycin administration.¹⁰⁶ Allergic reactions with vancomycin remain rare. Sensitization can be confirmed using skin tests at a concentration less than 10 μ g/mL.

Quinolones constitute the third most important group of antibiotics involved in perioperative anaphylaxis. The positive diagnosis of sensitization is hampered by the lack of validated skin test and specific IgE assays. Antibiotics such as bacitracin and rifamycin, applied locally to irrigate wounds, can also elicit potentially life-threatening anaphylaxis.

Hypnotics

Hypnotics commonly used in anesthesia are thiopental, propofol, midazolam, etomidate, ketamine, and inhaled anesthetics. Allergic reactions incriminating these drugs seem to be rare. The incidence of hypersensitivity reactions with thiopental was estimated to be 1:30,000.¹⁰⁷ It has been suggested that most of the generalized reactions were related to its ability to elicit direct LHR. However, there is evidence for IgE-mediated anaphylactic reactions based on skin tests and specific IgE assay.^{108,109} Recently, thiopental was involved in less than 1% of allergic reactions in France,¹⁷ probably as a result of its decreased use. Since Cremophor EL, used as a solvent for some nonbarbiturate hypnotics, has been avoided, many previously reported hypersensitivity reactions have disappeared. In the last French surveys, reactions to propofol accounted for less than 2.5% of allergic reactions. It has been suggested that propofol should be omitted in patients with allergy to eggs or soy, because of the presence of lecithins in the propofol vehicle,¹¹⁰ but this has not been confirmed in daily practice.^{24,48} Allergic reactions to midazolam, etomidate, or ketamine seem to be rare.^{16,17} No immune-mediated immediate hypersensitivity reaction involving isoflurane, desflurane, or sevoflurane has been reported despite their wide use. Allergic reactions to hypnotics can be investigated using the concentration limits provided in **Table 3**.

Opioids

Life-threatening reactions to opioids are uncommon. Because of the capacity of morphine, codeine phosphate, or pethidine to induce direct nonspecific skin mast

cell activation, but not heart or lung mast cell and basophil activation, these reactions are usually limited to pruritus, urticaria, and mild hypotension. They are frequently misinterpreted as drug allergy. Fentanyl and its derivatives do not induce nonspecific mediator release from mast cells. Only 12 cases were recorded in the last 2 years' epidemiologic survey in France, 9 of them being related to morphine administration.¹⁷

There is no evidence of cross-reactivity between the different opioid subclasses phenanthrenes (eg, morphine, codeine), phenylpiperidines (alfentanil, fentanyl, remifentanyl, sufentanyl, and meperidine) and diphenylheptanes (methadone and propoxyphene) in the literature.⁴⁸ Cross-reactivity between morphine and codeine is frequent, whereas cross-reactivity between phenylpiperidines is uncommon. Morphine cross-reacts strongly with IgE antibodies from patients allergic to NMBAs via the tertiary methylamino group they both contain.¹¹¹ However, as narcotics are only monovalent compounds, they are not able to cross-link 2 IgE molecules on the surface of mastocytes and therefore are not able to elicit a clinical reaction. Recently, it has been suggested that exposure to pholcodine may have a role in events leading to allergic sensitization to NMBAs.⁸⁷

The diagnosis of opiate allergy remains a clinical challenge. Skin tests may be helpful; however, because histamine may induce direct histamine release, the maximal concentration recommended for skin testing should not be exceeded (see [Table 3](#)). As discussed earlier, the clinical relevance of specific IgEs to morphine is questionable.

Local Anesthetics

Local anesthetics include amine (lidocaine, mepivacaine, prilocaine, bupivacaine, levobupivacaine, ropivacaine), and ester derivatives of benzoic acid (chloroprocaine, procaine, tetracaine). Allergic reactions to local anesthetics are rare despite their frequent use. It is estimated that less than 1% of all reactions to local anesthetics have an allergic mechanism.^{15,76} Inadvertent intravascular injection leading to excessive blood concentrations of local anesthetics, systemic absorption of epinephrine added to the local anesthetic, or vasovagal near-syncope are by far the most common causes of adverse reactions associated with these drugs. Although severe anaphylactic reactions have been reported with both types of local anesthetics, ester local anesthetics, having the capability of producing metabolites related to para-aminobenzoic acid, are more likely to provoke an allergic reaction. Amide local anesthetics have been involved in less than 0.6% of the perioperative reactions.¹⁷ Allergy to local anesthetics may also be caused by methylparaben, paraben, or metabisulfite used as a preservative in commercial preparations. Challenge tests following negative skin tests remain the gold standard to diagnose anaphylaxis from local anesthetics.²⁴ These tests should be applied liberally, not only to confirm the lack of sensitization following negative skin tests but also to reassure patients of the safe future administration of local anesthetics.

Colloids

All synthetic colloids used to restore intravascular volume have been shown to produce clinical anaphylaxis. The overall incidence of reactions has been estimated to range between 0.033%¹¹² and 0.22%.¹¹³ Gelatins and dextrans are more frequently incriminated than albumin or hetastarch. Direct release of histamine has been reported with urea-linked gelatin, antihistamines being efficient for the prevention of these reactions.¹¹⁴ Evidence for IgE-mediated adverse reactions to gelatin has also been reported.¹¹³ In addition, adverse reactions to urea-linked gelatin (0.852%) seem to be more frequent than with modified fluid gelatin (0.338%),¹¹³ whereas IgG-mediated

adverse reactions to hydroxyethyl starch are less frequent. Adverse reactions to dextrans were estimated at 0.275%, to albumine 0.099%, and to hydroxyethyl starch solutions 0.058%.¹¹³ Allergic reactions to dextrans are related to the presence of dextran-reactive antibodies of the IgG class. They can be prevented by hapten dextran (1 kDa) administration before starting the first administration of dextran. Although rare, several allergic reactions have been reported following application of this prevention protocol.^{115–117}

Diagnosis of IgE-mediated gelatin allergy is generally established using skin tests. Specific IgE assays or basophil activation tests may also be used. Anaphylaxis to hydroxyethyl starch can be confirmed by skin tests. The clinical relevance of IgG, IgM, and IgA antibodies against hydroxyethyl starch remains unknown (159).¹¹⁸ The diagnostic value of skin tests with dextrans is not established.

Dyes

Vital dyes have been used for many years in a variety of clinical situations and have long been considered a rare cause of anaphylaxis. This situation may in part be a result of misleading nomenclature.¹¹⁹ Patent blue V (also called E131, acid blue 3, disulfine blue) and isosulfan blue (also called patent blue violet or lymphazurine), which belong to the group of triarylmethan dyes and share the same formula, are the most commonly used. A recent literature review that includes various names of these dyes reveals an impressive number of case reports of hypersensitivity reactions,¹²⁰ and it has been suggested that sensitization occurs using everyday products containing blue dyes. In view of the increasing use of blue dyes for lymphatic mapping for sentinel lymph node biopsy, the incidence of anaphylaxis to these drugs can be expected to increase. The mechanism underlying the allergic reaction to patent blue remains unclear. Direct mast cell and/or basophil activation and cross-linking of specific IgE antibodies are possible causative factors. Evidence supporting an IgE-mediated mechanism at least in some patients comes from 2 clinical reports: 1 showing an immune-mediated mechanism by a passive transfer test,¹²¹ the second showing the presence of specific IgE detected by an enzyme-linked immunosorbent assay test.¹²²

Methylene blue has also been shown to be an effective dye for sentinel lymph node localization, with only a limited number of complications reported. Anaphylactic reactions involving methylene blue seem to be rare, perhaps because this small molecule does not bind to plasma proteins, thus reducing the risk of sensitization to a hapten-protein complex. This dye differs structurally from isosulfan blue and patent blue V. Therefore, cross-reactivity was not expected. However, several reports of sensitization to patent blue and methylene blue have previously been reported.^{62,123} These reports support the systematic investigation of a possible cross-reactivity before the use of an alternate dye.

The clinical diagnosis of reactions elicited by dyes is difficult. Reactions are usually delayed (ie, 30 minutes following injection), long lasting, and justify prolonged monitoring in intensive care if prolonged epinephrine administration is necessary.⁶² Anaphylaxis can be confirmed by skin and basophil activation tests. Because several false-negative prick tests have been reported in the literature, the use of IDT in case of negative prick test is recommended.⁶² Intradermal and basophil activation tests can also contribute to the identification of potential cross-reactive and safe alternative dyes.

ASPIRIN AND OTHER NSAIDS

With the increase in consumption of NSAIDs used in multimodal postoperative analgesia,¹²⁴ these are likely to be among the most common drugs inducing

hypersensitivity reactions. Bronchospasms, urticaria, angioedema, and anaphylaxis from these drugs are most often of a nonimmunologic nature, and result from inhibition of the cyclooxygenase 1 (COX-1) isoenzyme with subsequent depletion of prostaglandin E₂ and unrestrained synthesis of cysteinyl leukotrienes, and release of mediators from mast cells and eosinophils (see the article by Mario Sánchez-Borges elsewhere in this issue for further exploration of this topic). Several potential genetic polymorphisms have been suggested to play a causative role in aspirin-induced asthma or urticaria.^{125–127} Weak COX-1 inhibitors, such as paracetamol (acetaminophen), and partial inhibitors of COX-1 and COX-2, such as nimesulide and meloxicam, elicit symptoms more rarely and only at high drug doses. Selective COX-2 inhibitors rarely precipitate immediate hypersensitivity reactions and are generally (but not always) well tolerated.^{128,129} Nevertheless, NSAIDs, in particular diclofenac and pyrazolone derivatives, can induce an IgE-mediated hypersensitivity reaction as well. Thus, a history of cross-reactivities between multiple NSAIDs implies a non-IgE-mediated process, whereas a history of monosensitivity to 1 NSAID implies an IgE-mediated process, although specific antibodies are often elusive.¹³⁰

There are no reliable cutaneous tests allowing identification of NSAID hypersensitivity in patients with multiple NSAID intolerance. It has been assumed that there were no reliable in vitro tests for this condition and diagnostic confirmation can be ascertained only by provocation challenge. Several recent studies using a leukotriene release test (CAST) or a basophil activation test (BAT) on blood basophils, or a combination of both tests, yields some positive results (70%–75%) in a sizeable number of clinically validated cases, with high specificity (more than 85%).^{131,132} These studies need to be confirmed. A challenge test is still considered by many investigators the gold standard for establishing or excluding a diagnosis of NSAID hypersensitivity and identifying safe alternatives.^{48,133} In specific cases, drug desensitization can also be performed.¹³⁴

Aprotinin

Aprotinin, a naturally occurring serine protease inhibitor, may be administered either by the intravenous route or as a component of biologic sealants. Its widespread clinical use is based on its ability to decrease blood loss, and, as a consequence, transfusion requirements. Anaphylactic reactions are mediated by IgG and IgE antibodies. The risk of anaphylactic reactions has been estimated between 0.5% and 5.8% when used intravenously during cardiac surgery, and at 5 in 100,000 applications when used as a biologic sealant.^{135,136} Patients previously treated with this drug present an increased risk and any new administration should be avoided for at least 6 months following an initial exposure.¹³⁷ Aprotinin used to reduce blood loss has recently been withdrawn from the market. The diagnosis is confirmed by prick tests (pure solution) followed by IDTs (up to 1:10 dilution) in case of negativity.

Other Agents

Several cases of allergic reactions to antiseptics have been reported in the literature. They mainly entail allergic reactions to chlorhexidine following insertion of central catheters impregnated with this antiseptic, after intraurethral use or topical application.¹³⁸ Only rare cases of anaphylaxis following topical use of povidone-iodine have been reported.¹⁷

Protamine has also been incriminated. Its use to reverse heparin anticoagulation has increased over the last 2 decades. Reactions may involve several mechanisms, including IgE, IgG, and complement activation. In a recent systematic literature review analyzing 9 retrospective studies and 16 prospective studies, the incidence of

anaphylactic reactions was estimated at 0.19% (retrospective studies) and 0.69% (prospective studies), respectively.¹³⁹

Many clinical cases involving many other substances have been published in the literature. This situation underlines the importance of a careful and systematic investigation of all substances used during the procedure in case of perioperative anaphylaxis.

RISK FACTORS FOR PERIOPERATIVE ANAPHYLAXIS

Allergy to anesthetic agents is the first factor to consider. Any unexplained life-threatening reaction during a previous anesthesia might be an allergic reaction and is a major risk factor for a renewed reaction if the responsible drug is readministered.¹⁶ Ideally, all patients having experienced an episode of perioperative anaphylaxis would have undergone complete allergeoanesthetic follow-up before further anesthetics. The practical reality is different. In addition, in many countries, the allergologic assessment is not routinely performed.

Sometimes patients require anesthesia for emergency surgery, at times when little or no information about a previous reaction is available. In this case, regional anesthesia is preferred whenever possible, and a latex-free environment should be provided.^{24,25} If general anesthesia is necessary, volatile anesthetics should be used if possible, as allergy to these has never been described. If a reaction to an NMBA is suspected, it is important to try to avoid other NMBAs, because cross-reactions are not uncommon within this group.^{24,25} If the anesthetic chart from the reaction is available, all drugs and substances administered to the patient before the reaction should be avoided if possible.

A latex-free environment should be made available to patients having experienced clinical manifestations of allergy when exposed to latex, to patients subjected to many surgical or urologic cannulation procedures (because of the high incidence of sensitization to latex), to children who have undergone repeated operations (particularly those with spina bifida), and to patients with clinical manifestations of allergy to tropical fruits (eg, avocado, kiwi, banana, fig, chestnut, sweet pepper, melon, pineapple, papaya) because of a high rate of cross-reactivity with latex.

In contrast, patients who are atopic (except for latex) or those who are allergic to a drug (except for antibiotics that may be injected as perioperative antibiotic prophylaxis because of the risk of cross-reactivity between β -lactams) unlikely to be used during the perioperative period are not considered to be at risk for perioperative anaphylaxis.²⁴

TREATMENT

There is a wide array of reaction severity and responsiveness to treatment. In addition, no controlled trials of treatment in human beings are available. As a result, the ultimate judgment with regards to a particular clinical procedure or treatment scheme must be made by the clinician in light of the clinical presentation and available diagnostic and treatment options.¹⁴⁰ During anesthesia, the patient is usually monitored and has intravenous access, which gives the optimum conditions for prompt and successful treatment, provided that the diagnosis is made early by the attending anesthetist. Treatment is aimed at interrupting contact with the responsible antigen, modulating the effects of the released mediators and inhibiting mediator production and release. Because the identification of the exact offending agent at the time of reaction is virtually impossible, all drugs as well as surgery should be interrupted unless otherwise impossible. Maintenance of airway patency is imperative and oxygen 100% should

be administered. The cornerstones of treatment are epinephrine and fluid therapy (Table 6).^{4,24,25,141–143}

Epinephrine is a highly potent and efficient treatment agent in most cases of anaphylaxis. It opposes the deleterious systemic adverse effects of the released mediators, through its vasoconstricting (α -mediated), positive inotropic (β_1 -mediated), bronchodilating (β_2 -mediated) properties, and by reducing mast-cell and basophil mediator release.¹⁴⁴ There is no absolute contraindication during anaphylaxis for the use of epinephrine. It should be administered as early as possible and titrated carefully to clinical response. Poor outcomes during anaphylaxis, including deaths, are associated with either late or no administration of epinephrine, as well as with inadequate or excessive dosing.^{24,145}

Epinephrine administration should be tailored to the severity of symptoms (see Table 5). It should not be injected during grade I reactions. Administration should be rapid and goal-oriented, using titrated boluses starting at an initial dose of 10 to 20 μg in grade II reactions, and 100 to 200 μg in case of grade III reactions, repeated every 1 to 2 minutes as necessary. Prolonged inotropic support may also be required in some patients (starting dose: 0.05 to 0.1 $\mu\text{g}/\text{kg}/\text{min}$, titrated to effect). Grade IV reactions (cardiac arrest) require cardiopulmonary resuscitation and high doses of epinephrine (1 mg every 2 minutes, repeated and/or increased as needed). Epinephrine doses should be goal oriented and adapted to body weight and age in children (see Table 6).

In some cases, epinephrine may fail to restore cardiovascular homeostasis. In cases resistant to epinephrine, the use of vasoactive drugs such as noradrenaline, metaraminol, glucagon, vasopressin, vasopressin analogs, or even methylene blue has been advocated. Previous treatment with β -blockers is a potential risk factor explaining an absence of tachycardia, as well as resistance of arterial hypotension to epinephrine.⁵³ Glucagon (initial dose 1–5 mg, followed by 1–2.5 mg/h infusion) is recommended in this clinical setting. Several case reports suggest that arginine vasopressin (AVP) might be considered as a potential rescue therapy during anaphylaxis.^{146–152} Experimental work provides support for the possible use of AVP during anaphylaxis.^{153,154} However, AVP was detrimental when injected alone in the early course of anaphylaxis or when higher doses were used. Methylene blue, which interferes with nitric oxide-mediated vascular smooth muscle relaxation, was also recently successfully used in catecholamine- and vasopressin-resistant anaphylaxis.¹⁵⁵ More clinical information is needed to better evaluate the value of these rescue therapies.

Fluid therapy is important to counteract the large fluid shifts associated with vasodilatation and capillary leakage. Similar to epinephrine administration, fluid therapy should be goal oriented. A commonly used sequence is to rapidly restore the vascular volume either with isotonic saline (10–25 mL/kg for 20 minutes repeated if necessary), or with colloid (10 mL/kg). Colloids should replace saline when the volume of this exceeds 30 mL/kg, avoiding the administration of the substance or substances that are suspected to be the cause of the reaction.

Bronchospasm is usually reversible with epinephrine. However, in case of persistent bronchospasm, inhaled β_2 -agonists (salbutamol or albuterol) are indicated. Intravenous administration (5–25 $\mu\text{g}/\text{min}$) should be considered if necessary.

Corticosteroids and antihistamines are often recommended as secondary treatment of anaphylaxis. They could be useful for angioedema, and cutaneous symptoms. Relapse of the anaphylactic reaction can occur up to 24 hours after the initial reaction, therefore careful consideration must be given to the level of monitoring/observation of the patient following successful treatment of an anaphylactic reaction.

Table 6 Emergency management of anaphylactic reactions during anesthesia	
Primary treatment	
General measures	
Inform the surgeon	
Request immediate assistance	
Cease all drugs, colloids, blood products (and latex if suspected)	
Maintain airway with 100% oxygen	
Elevate the legs, if practical	
Epinephrine	Adults
Titrate dose according to symptoms severity and clinical response	Grade 2: 10–20 µg Grade 3: 100–200 µg Grade 4: 1 mg IV infusion starting dose: 0.05–0.1 µg/kg/min
Repeat dose every 1 to 2 min as necessary	
If large doses are needed, use IV infusion	Children
	Grade 2 to 3: 1–5 µg/kg Grade 4: 10 µg/kg
Fluid therapy	
NaCl 9 mg/L or colloids according to clinical response	Crystalloid : 10–25 mL/kg for 20 min, more may be needed Colloid : 10 mL/kg for 20 min, more may be needed
Anaphylaxis resistant to epinephrine	
Glucagon (failure of large doses of epinephrine in patients on β-blockers)	Initial dose 1–5 mg, followed by 1–2.5 mg/h infusion
Norepinephrine	Initial dose 0.05–0.1 mg/kg/min
Vasopressin	Increments of 2–10 IU IV until response
Secondary treatment	
Bronchospasm	
β ₂ -agonist may be used for symptomatic treatment of bronchospasm, but is not first-line treatment. IV administration may be considered if necessary, following hemodynamic recovery	Inhaled β ₂ -agonists (salbutamol or albuterol) IV: 5–25 µg/min
Antihistamines	H ₁ antagonist: diphenhydramine 0.5–1 mg/kg IV H ₂ antagonist: ranitidine 50 mg IV
Corticosteroids	Adults : Hydrocortisone 250 mg IV or methylprednisolone 80 mg IV Children : Hydrocortisone 50–100 mg IV or methylprednisolone 2 mg/kg IV
Further care	
Patient may relapse, admit to intensive care unit in grade 3 or 4 reactions	
Take bloods for testing as soon as possible	
Arrange for allergy testing at 1 month	

Abbreviation: IV, intravenous.

SUMMARY

Perioperative anaphylaxis is a significant adverse event during anesthesia. It remains underestimated because it is underreported. NMBAs, latex, and antibiotics are the most frequently incriminated drugs, although other drugs used during the perioperative period might be involved. Because no premedication can effectively prevent an allergic reaction, any suspected hypersensitivity reaction must be extensively investigated using combined peri- and postoperative testing. Patients must be fully informed of the results of investigations, and advised to provide a detailed report before future anesthesia. Wearing a warning bracelet or possession of a warning card is strongly indicated.

With the exception of high-risk patients, systematic preoperative screening for sensitization against anesthetic drugs is not justified at this time. Particular attention must be paid to patients who have already experienced an anaphylactic reaction during anesthesia, those alleging an allergy to muscle relaxants, or those at risk of latex sensitization. In these cases, the choice of the safest possible anesthetic agents should be based on the result of a rigorously performed allergologic assessment.

In view of the relative complexity of allergy investigation, allgogoanesthesia centers should be promoted to provide all necessary expert support coupled with an active policy to identify patients at risk.

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