

Diagnostic procedure after an immediate hypersensitivity reaction in the operating room

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■ Key points

The diagnosis of a perioperative allergic reaction is based on clinical features associated with a suggestive timeline, the exclusion of other diagnoses, elevated concentrations of degranulation markers (histamine, tryptase), and positive allergy assessments (skin tests, specific IgE). After initiating appropriate treatment, the anesthesiologist should take blood samples to measure histamine and tryptase concentrations just after the reaction and repeat them 1–2 hours later to validate the diagnosis of immediate hypersensitivity. A delayed measurement of basal tryptase is useful to rule out mastocytosis and to interpret moderate tryptase levels. The anesthesiologist must inform the patient of the reaction to obtain adhesion and consent to subsequent investigations and must record the timing of the reaction and of the blood sampling, the possible causal agents, and the treatment administered. These data must be shared with the laboratory and the allergist. An adverse drug reaction report must be filed. The gold standard for allergy assessment is skin testing. These tests should be done in an appropriate facility, with experienced staff and in compliance with current guidelines. Specific IgE assays and cellular assays can help when clinical features and skin tests are discordant. Provocation tests are sometimes required. After allergy assessment, the safest protocol for subsequent anesthesia is determined in collaboration with the anesthesiologist. The patient must be informed and carry an allergy alert card.

■ Points essentiels

Démarche diagnostique après une réaction d'hypersensibilité immédiate au bloc opératoire

Le diagnostic de réaction d'hypersensibilité immédiate allergique se base sur les signes cliniques associés à une chronologie évocatrice, l'exclusion des diagnostics différentiels, l'augmentation de la concentration des marqueurs de dégranulation (histamine ; tryptase) et le bilan allergologique (tests cutanés ; IgE spécifiques). Après la mise en œuvre des traitements appropriés, l'anesthésiste doit prélever des tubes de sang pour mesurer la concentration d'histamine et de tryptase juste après la réaction et 1 à 2 heures plus tard pour valider le diagnostic de réaction d'hypersensibilité immédiate. Un taux basal de tryptase à distance est utile pour éliminer une mastocytose et interpréter une faible libération de tryptase. L'anesthésiste doit informer le patient de la réaction pour obtenir son adhésion à la prise en charge et son consentement pour les investigations à venir. Il doit également noter la chronologie de la réaction et des prélèvements sanguins, les agents potentiellement responsables et les traitements administrés. Ces informations doivent être partagées avec le biologiste et l'allergologue. Une déclaration à la pharmacovigilance doit être effectuée. Les tests cutanés sont la référence pour le bilan allergologique. Ces tests doivent être effectués dans une structure appropriée avec une équipe expérimentée et dans le respect des recommandations actuelles. Le dosage des IgE spécifiques et les tests cellulaires peuvent aider quand les tests cutanés et la clinique sont discordants. Les tests de provocation sont parfois nécessaires. À la fin de l'évaluation allergologique, l'allergologue détermine, en collaboration avec l'anesthésiste, quel est le protocole anesthésique le plus sûr pour le futur. Le patient doit en être informé et doit être doté d'une carte définitive mentionnant ses allergies.

When an immediate hypersensitivity reaction occurs during surgery, the mechanism of the reaction must be determined to ensure safe subsequent anesthesia. In immunoglobulin E (IgE)-mediated reactions, identification of the causal agent is necessary to exclude this agent from further anesthesia protocols. When neuromuscular blocking agents (NMBAs) or antibiotics are involved, an assessment of cross-sensitivity is mandatory to determine which agents of the same class can be used safely in the future. In non-IgE-mediated reactions, however, several mechanisms may be responsible for signs: non-specific histamine release, activation of the complement system, induction of the bradykinin system, and direct mast cell activation. Identification of the causal agent is rarely possible. In cases of drug-induced histamine release, the use of adequate pretreatment, the choice of low histamine-releasing drugs, and slow drug administration of drugs may prevent subsequent reactions.

Hypersensitivity reactions are assessed in two stages: the first immediately after the reaction, based on laboratory analyses to determine the allergic nature of this reaction, and the second 4–6 weeks afterwards, based on a specialized allergy assessment to identify the causal agent.

Anesthesiologists play an important role in this diagnostic process. They are often the only witness to the reaction. They must therefore record the timing and signs of the reaction, the

possible responsible agents, and the treatments that were administered. They must take blood samples to characterize mediator release just after the reaction. Finally, they must encourage the patient to have the reaction investigated. Patients often do not perceive the severity of the reaction, as they were under general anesthesia. It is essential to provide them with clear and precise information about the reaction and explain the need for perform allergy testing in an allergy center. Patients must leave the post-anesthesia recovery unit with a temporary allergy alert card listing all the substances suspected.

The allergist must perform a complete and detailed assessment, including testing for cross-sensitivity. Finally, the allergist and anesthesiologist should jointly determine the safest protocol for each patient's future anesthesia and provide him or her with a definitive allergy alert card.

The diagnosis of a perioperative allergic reaction is based on clinical features, associated with a suggestive timeline, the exclusion of other diagnoses, an increase in degranulation marker concentrations (histamine and tryptase), and positive allergy tests (*figure 1*). Specific IgE or basophil activation testing can help, notably when skin tests cannot be interpreted (i.e., due to dermatographism or use of irritating products). Challenge tests may be helpful for some drugs when findings are negative or discordant.

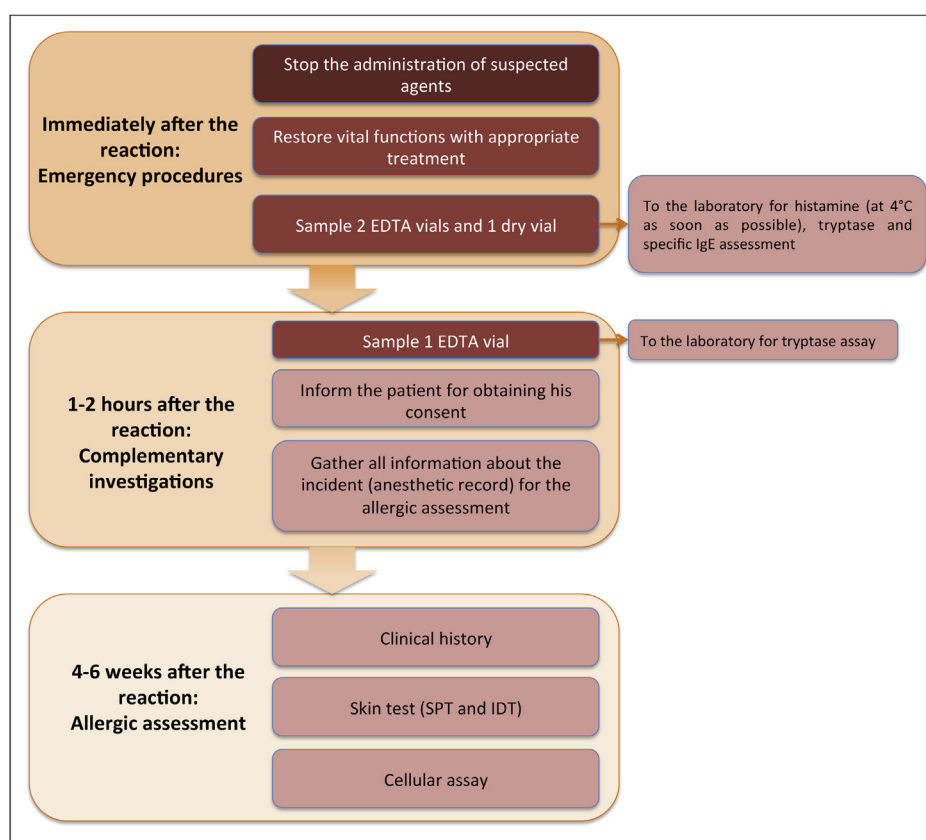


FIGURE 1
The allergy assessment pathway

Immediate assessment after the reaction

Immediate hypersensitivity is defined by specific clinical symptoms (*table 1*). In the operating room, the anesthesiologist must suspect the diagnosis when these symptoms occur shortly after

drug administration and must immediately start adequate treatment without waiting for blood test results. Laboratory results are useful after the reaction to confirm the diagnosis of immediate hypersensitivity.

Tryptase

Tryptase is released by mast cells activated by the IgE pathway, or direct activation (through the MRGPRX2 receptor), or direct leakage in mastocytosis [1,2]. Its plasma half-life is 90–120 minutes. The optimal timing for a blood sample is 15 to 60 minutes after low-grade reactions (I–II) and 30 minutes to 2 hours after severe reactions (grades III–IV). Tryptase concentrations are correlated with the severity of the reaction and often not elevated at all in low-grade reactions. Serum/plasma tryptase concentrations may remain elevated up to 6 hours after the most severe reactions. Kinetic characterization of tryptase is the most useful procedure, but requires that accurate records of the timing of the reaction and the blood sample. Differential diagnoses for high tryptase concentrations are systemic mastocytosis, mast cell activation syndrome, and hematologic diseases. These diagnoses can be ruled out by a measurement of basal tryptase, either before the reaction or after its complete

TABLE 1

Symptoms of immediate hypersensitivity reactions according to their severity grade

Severity grade	Symptoms
I	Cutaneous signs: erythema, urticaria with or without angioedema
II	Presence of measurable but not life-threatening symptoms: cutaneous effects, arterial hypotension, cough or difficulty in mechanical ventilation
III	Presence of life-threatening symptoms: cardiovascular collapse, tachycardia or bradycardia, arrhythmia, severe bronchospasm
IV	Circulatory failure, cardiac and/or respiratory arrest

resolution (at least 24 hours afterwards). The standard tryptase threshold proposed to support the diagnosis of an IgE-mediated reaction is 25 µg/L [3].

In cases of death from cardiac arrest, a delayed allergy workup is evidently impossible, but tryptase measurements remain important in this situation. A recent study showed that resuscitation maneuvers have no effect on tryptase concentrations. Accordingly, when clinical symptoms are highly suggestive and other causes have been ruled out, an elevated tryptase concentration has an obvious forensic interest. The optimal threshold of tryptase for the diagnosis of an allergic reaction has been established at 7.35 µg/L with a sensitivity of 92% and a specificity of 92% if the blood is sampled during resuscitation maneuvers [4].

Histamine

Histamine is synthesized by basophil and mast cells and released when they are activated. It has a short plasma half-life (15–20 minutes), and its concentration peaks in the first minutes after allergen exposure, before clinical symptoms appear. Not all guidelines recommend histamine measurement. A high histamine concentration confirms the activation of effector cells. It is the only routine method currently available to investigate non-IgE-mediated reactions, which account for about 40% of immediate hypersensitivity reactions during anesthesia. In these cases, elevated histamine levels are an indication to avoid all histamine-releasing drugs in the future.

During IgE-mediated reactions, histamine concentrations can rise without concomitant increases in tryptase levels, especially during mild reactions. In these reactions (grades I or II), histamine is often the only available mediator that is positive [5]. Isolated elevation of histamine is thus not sufficient to rule out an IgE-mediated hypersensitivity reaction [6]. The plasma histamine level is correlated to the severity of the reaction [7,8]. False negatives are seen in case of delayed sampling, especially for low-grade reactions (I–II). Blood should be sampled at the earliest opportunity after the initiation of treatment. False positives due to spontaneous activation or lysis of basophils can be prevented by cooling the sample at 4 °C immediately after taking it, early centrifugation, and careful aspiration of the plasma before freezing at –20 °C. Clinical situations associated with false negatives involve women more than 3 months pregnant and patients on high doses of heparin. Accelerated degradation makes histamine measurement useless for them.

Delayed investigations

Skin tests

Skin tests include prick tests (SPT) and intradermal tests (IDT), currently the gold standard to investigate immediate hypersensitivity reactions. Their reliability depends on the class of drug tested. The tests are interpreted in light of detailed clinical data, including the exact timing of the drug administration and

reaction, provided by the anesthesiologists. Testing without clear knowledge of the complete anesthetic procedure is a source of error. A copy of the anesthesia record and all blood sample results must be sent to the allergic outpatient clinic. Tests should be performed at least 4 to 6 weeks after the reaction [9]. Although they can be performed earlier in emergencies, the risk of false negative tests is high before 4 weeks because of the post-reaction refractory period. Accordingly, in early testing, only positive tests can be taken into account. A second delayed assessment is then recommended [10].

Skin tests must be performed by trained physicians whose knowledge of anesthesia-related allergies is up-to-date. A validated protocol should be used with standardized concentrations of drugs in accordance with the most recent recommendations (table II) [3,11]. Although severe reactions to skin tests are rare, resuscitation equipment must be available at all times and the staff must be trained to use it. The patient's informed consent is mandatory before the test. To determine the ability of the patient's skin to release and react to histamine, control tests using codeine or histamine (positive control) and saline (negative control) must accompany the skin tests.

The sensitivity of IDT is higher than that of SPT. The severity of the reaction and the results of the SPT guide the choice of the lowest drug concentration used for the first IDT. The SPT test is positive when after 20 minutes the diameter of the wheal is at least 3 mm greater than that of the negative control or at least half that of the positive control. For IDT, 0.02 to 0.03 mL of the diluted drug is injected into the dermis to obtain a wheal of up to 4 mm in diameter. IDT is positive when a wheal-and-flare response is obtained at 20 minutes, with a wheal diameter at least twice that of the injection wheal. Because guidelines for this protocol differ between countries, it is difficult to compare results between studies.

In case of positive SPT or IDT to a neuromuscular blocking agent (NMBA), it is mandatory to investigate cross-sensitivity to other NMBAs [3]. After reactions to penicillin, investigation of cross-sensitivity between beta-lactams should be considered, particularly for surgery associated with a high risk of infectious complications (e.g., cardiovascular surgery or transplantation), where the possibility of penicillin use is relatively high. Sensitization patterns have changed in Europe: because of the high proportion of patients sensitized to beta-lactam side chains, the substitution of penicillin by cephalosporin can be dangerous if their side chains are similar.

Specific IgE assay

Serum can be sampled either just after the reaction or during the allergy assessment [3,12,13]. A specific IgE assay is particularly relevant when skin tests are uninterpretable, that is, in patients with dermographism, extensive atopic skin lesions, nonreactive skin, or taking medications with antihistaminic effect that cannot be stopped. They are available for NMBAs, latex,

TABLE II

Maximal concentrations normally nonreactive for SPT and IDT. Adapted from Mertes et al. [3]

Available agents	Conc (mg/mL)	SPT		IDR	
		Dilution	Cmax (mg/mL)	Dilution	Cmax (µg/L)
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	10	Undiluted	10	1/10	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
Skin disinfectant					
Chlorhexidine		Undiluted	0,5	1/100	5
Povidone iodine		Undiluted	100	1/10	10 000

beta-lactams, gelatins, and chlorhexidine. The quaternary ammonium-specific IgE assay is the most useful for suspected NMBA allergy when the timing fits (reaction just after anesthesia induction). Different techniques are available. The QAS (quaternary ammonium-specific) and the PAPPC-RIA (P-aminophenylphosphoryl-choline radioimmunoassay) tests are very sensitive (sensitivity 80.7%) techniques although

their "homemade" nature makes comparison between results from different laboratories difficult. Immunocap C260 is commercially available around the world (ThermoFisher Scientific Diagnostics, Phadia, Sweden) and approximates the results of the QAS and PAPPC-RIA tests [12].

These tests cannot be used to predict anaphylaxis, as specific IgE can be detected in 3 to 10% of the general population with no

previous history of anesthesia. The positive predictive value and the negative predictive value of a test depend on the prevalence of the pathology. The very low prevalence of anaphylaxis in the general population precludes the use of these tests; the false positive rate would be too high. In contrast, the prevalence of anaphylaxis in patients with a perioperative immediate hypersensitivity reaction is high enough to use them.

Latex-specific and chlorhexidine-specific IgE assays have good sensitivity and may be useful when these agents are suspected. On the contrary, specific IgE assays directed against penicillin G or V, ampicillin, amoxicillin, and cefaclor have poor sensitivity and are thus reliable only when positive. The alpha-gal-specific IgE assay can be useful if gelatins are suspected [14].

The total IgE assay has no diagnostic value and should be abandoned.

Cellular assays

Cellular assays cannot replace clinical history and skin tests but can be helpful when the clinical history is significant, but the skin tests are negative or uninterpretable [15]. They can also be helpful for cross-sensitivity assessment [16]. The basophil activation test (BAT) is currently replacing the histamine release assay and the leukotriene release test [17,18] because of its better diagnostic performance (through its avoidance of non-specific release of histamine or leukotriene during the manipulation). During the BAT, basophil cells are challenged with the suspected allergen at different dilutions. The shift in expression of basophilic activation markers (CD63 and/or CD203c) is then quantified by flow cytometry [19].

The BAT is used to diagnose allergies to NMBAs, antibiotics, nonsteroidal anti-inflammatory drugs, and latex. Sensitivity varies between 50 and 60%, depending on the drug tested, and specificity approximates 100% with no false-positive results for latex, atracurium, or pristinamycin [15,20–22]. Nonetheless, larger-scale collaborative studies are necessary to optimize test protocols to validate BAT as a diagnostic instrument in drug allergies. This test can also be helpful for cross-sensitivity assessment of NMBAs. Skin tests and BATs have an excellent negative predictive value for NMBAs [16] and quinolones [23].

Provocation tests

Provocation testing is the gold standard to confirm the responsibility of a drug in immediate hypersensitivity reactions, but its indications in perioperative anaphylaxis are limited. In patients with typical clinical histories, 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). This strategy is not possible with NMBAs and not really feasible with hypnotics and opioids because of the risk of cardiovascular and respiratory depression. It has been proposed for propofol but at subtherapeutic doses. Provocation tests should be conducted under strict supervision and only in specialized centers with monitoring and resuscitation facilities. A favorable risk-benefit ratio is a prerequisite for conducting these tests, and informed consent must be obtained.

Conclusion

In 2016, compliance with current guidelines requires that allergists and anesthesiologists obtain a well-documented diagnosis for perioperative immediate hypersensitivity reactions. This diagnosis mandates that blood samples be taken at the appropriate time in relation to the reaction and that skin tests be performed in accordance with guidelines. Cooperation between the two specialists is mandatory to ensure the quality of the diagnosis but also the safety of further anesthesia. Physicians must keep in mind that these situations may have medicolegal ramifications.

The aim of this article is to help every interested physician understand the appropriate approach.

Acknowledgements: none.

Funding: none.

Disclosure of interest: the authors declare that they have no competing interest.

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