

ALLERGIC REACTIONS AND ANESTHESIA

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SUMMARY

The diagnosis of allergic reactions during anesthesia is difficult. For example, cardio-respiratory symptoms may be due to the accompanying pharmacological effects of anesthetics and poor interpretation of the reaction during anesthesia. It is important to distinguish whether a real allergic reaction has occurred. Accidents with anesthetics and muscle relaxants are observed more often than we expect. Proper anaphylaxis rarely occurs during anesthesia (1: 20000). Muscle relaxants are the most common causes, followed by latex, chlorhexidine, antibiotics and opioids. To confirm the diagnosis it is necessary to perform a larger number of blood and skin tests. Targeted diagnostic approach and therapy allow avoiding more difficult events. Anesthesia should be selected for those medications that have been tested. Additionally, patients should be premedicated with antihistaminics and systemic steroids, as the emergence of intolerance is not completely excluded by negative testing. There is no gold standard for testing, even if every method is precisely performed; there are always false positive and false negative results. When anaphylaxis appears, urgent approach is needed to provide the patient with appropriate treatment. It is necessary to act according to the established algorithms and treatment protocols. Many anesthesiologists will not ever see such a reaction, and very few will see more than one during their work life. Awareness of allergy in anesthesia is still insufficient.

Key words: anesthesia – anaphylaxis - muscular relaxants

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Introduction

The term anaphylaxis was first used in Paris in 1902 by French researchers Charles Richet and Paul Portie (Ring 2006). About anaphylaxis we talk when a critical blood pressure drop occurs, or there is severe bronchoconstriction, or it is mediated by IgE antibodies, or at least two organic systems are affected by the reaction (Waldhausen 1988, ERC-Guidelines for Resuscitation 2005, Kroigaard 2005, Rajinder 2004, Przybilla 2007). Various symptomatology, rapid onset, and various possible consequences of anaphylactic reactions make it difficult to set up a diagnosis, and in many cases there are many diseases in differential diagnosis (Przybilla 2007, Breckwoldt 2006, Rajinder 2004, Ring 2002). It should be noted that even though anaphylaxis is a serious condition, it is so rare that it can be considered risk for anesthesia.¹² Drugs used for anesthesia and during anesthesia can lead to allergic, pseudoallergic or to reactions of pharmacological intolerance.

Anaphylaxis represents a group of rare reactions, potentially life-threatening and can develop extremely quickly. It is a severe systemic hypersensitivity reaction, it can be allergic and nonallergic. Both images are similar in clinical terms (Breckwoldt 2006).

It is vitally important to recognize the symptoms of anaphylaxis and to know the pathophysiology and anaphylactic shock therapy.

The European Association of Allergologists and Clinical Immunologists has set a task to simplify the description of allergic reactions and in 2001 the nomenclature was revised. It has been suggested that the term anaphylaxis is nowadays also related to immune and nonimmune mediated reactions. These reactions are further divided into allergic and nonallergic anaphylaxis. Allergic anaphylaxis may or may not be IgE mediated. The new classification is shown in Figure 1. The task assignment has determined that the term "anaphylactoid" is no longer used (Johansson 2001).

When a potentially anaphylactic reaction occurs in a patient, only the simultaneous diagnostic approach can be used to determine whether the reaction was immune or nonimmune. Even then, the exact cause can not be found. It is a general assumption that allergic anaphylaxis has more severe effects and that regaining cardiovascular and pulmonary function requires early adrenaline administration. This is not always the case, non-allergic exclusion of histamine and other mast cell mediators can lead to pronounced hypotension and bronchospasm. Unless otherwise indicated, the reaction described as anaphylactic refers to allergic anaphylaxis. There are important limitations for each step in the diagnosis of suspicious reactions, there is no gold standard for anaphylaxis detection and it is not yet, at least today, evidence-based science. This means that the interpretation of the reaction can be difficult and that the exact cause of the reaction can not be determined even if the best procedure is followed (Rajinder 2004).

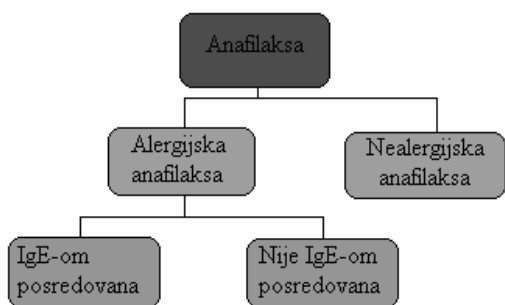


Figure 1. New classification of anaphylaxis

Epidemiology

An anaphylactic reaction can cause many pathogens as shown in Figure 2.

Table 1. Most commonly used agents that cause anaphylactic reactions

Antibiotics
Apoprotin
IV anesthetics, for example thiopental, propofol, midazolam
Latex gum
Local anesthetics
Neuromuscular Blockers (NMBA)
Neopioid analgesics, eg NSAIDs
Opioid analgesics, for example morphine, alfentanyl, fentanyl
Plasma expanders, foe example gelatin
Drugs used in premedication
Preservatives
Protamine
Radio-contrast agents

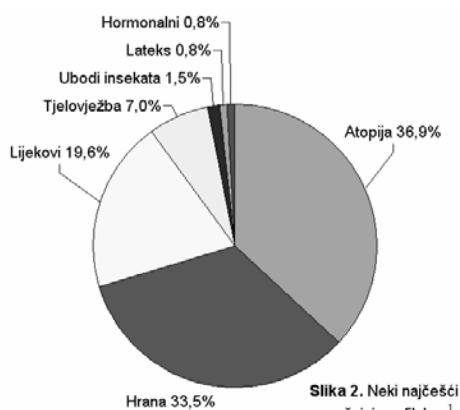


Figure 1. Cause of anaphylaxis

In literature, the incidence varies from 1: 5000 to 1: 25000, with a morbidity of 3.4% to 6%

Awareness of allergy in anesthesia is still insufficient. There are important limitations for each step in the diagnosis of suspicious reactions. Reaction of the reaction may be difficult, until the exact cause of the reaction can be determined even when using the best procedures.

Anaphylaxis during anesthesia

The consequences of anaphylaxis may be serious and potentially life threatening, it is important for anesthesiologists to recognize its clinical manifestations and to know how to suppress it.

Anaphylaxis incidence during general anesthesia was estimated to be very wide ranging from 1 to 950 to 1 in 20,000 anesthetic interventions. Anesthesiologists prevail over the opinion that the latter ratio more realistically describes the situation in practice. This huge incidence range reflects the low risk of developing such reactions (Przybilla 2007).

Though rare, reactions even with the proper treatment can be fatal. The mortality rate in those who developed the anaphylactic reaction was estimated to be from 3 to 6%.

Pathophysiology

Anaphylaxis is induced by the immune response of type I and type III. In allergy with type III reactions, blood-circulating complex antigen-antibody aggregates, including leukocytes and platelets, are deposited in various capillaries of different tissues. Particularly in basal membranes (for example glomerulus), an inflammatory reaction occurs with the activation of the complement system. Capillaries can be blocked by immune complexes. The anticoagulant system releases inflammatory mediators (e.g., histamine) that produce the following effects:

- open the shunts of arterioles;
- contraction of smooth muscles, for example bronchi;
- increase blood vessel permeability;
- increase the chemotaxis of neutrophilic and eosinophilic granulocytes;
- increase production of mucus (for example bronchi) (Przybilla 2007).

In pathophysiology, we distinguish the anaphylactic and anafilactoid reactions.

Released mediators make peripheral vasodilation, increase capillary permeability, and increase mucus secretion. Clinically, there are (Table 2): bronchospasm and laryngeal edema, hypotension, tachycardia, gastrointestinal and cerebral symptoms. A more pronounced course with complete obstruction of the respiratory tract or primary circulatory failure may end up with death (Triggiani 2008).

Depending on the manifestation and symptomatology of anaphylaxis, there are several stages (Table 3).

Table 2. Organ manifestations

Cardiovascular system:	hypovolaemia (tachycardia, hypotension), sometimes angina pectoris
Respiratory tract:	bronchospasm, edema larynx
Gastrointestinal system:	abdominal pain, defect, diarrhea, vomiting, nausea

Table 3. Manifestation and symptomatology of anaphylaxis

0	1	2	3	4
Local	Disseminated		Hypovolemia	
Limited reaction (can be outspred)	cutaneous reaction, uvular edema, mucus edema, nausea, cramps in the abdomen	Circulatory collapse, dyspnoea, prolonged excretion, stool and urine incontinuity	Shock, massive dyspnoea, bronchospasm, Cyanosis, comma	Cardiorespiratory arrest

Causes of Alergic Reactions

The exact order of the challengers is possible for reactions mediated with IgE antibodies, most commonly described in this sense are groups of muscle relaxants. Muscle relaxants can be removed from the mast cells by three mechanisms:

- Antibody mediated release (right anaphylaxis);
- Activation of complement;
- Chemically mediated.

There are frequent reports of life-threatening reactions, mostly bronchospasm as the first symptom of anaphylaxis. Ventilation is temporarily impossible.

Figure 3 shows the causes of anaphylaxis as a percentage of the total number of cases in the two-year study for anaphylaxis during anesthesia conducted in France (Kubitz 2006).

Apart from this study in France, there is very little data on the incidence of anaphylaxis with other drug groups during the surgical procedure.

In the US, the main causes of anaphylactic reactions are associated with medical intervention of penicillin, radiosuppressive agents, protamine and latex. NMBAs are not mentioned in this extensive study and appear to have no major role in the emergence of anaphylaxis in the US (Breckwoldt 2006).

Compared to this, a smaller Denmark study showed that opioids, chlorhexidine and latex were responsible for the emergence of more anaphylactic reactions than NMBAs (Figure 4) (Kenneth 2007). Serious and mild reactions were investigated in this study, all drugs and all substances given to the patient before the reaction were tested and all patients were tested on latex and chlorhexidine. The performed tests included the measurement of mast cell triptazes, specific release of IgE antibodies and basophilic histamine, prick skin test, intradermal test, oral test provocation and test flask.

Although allergies and anaphylactic reactions to chlorhexidine are well described in the literature, there is rarely a risk of hypersensitivity in France. Chlorhexidine is an important anaphylaxis agent during anesthesia because it is widely used, especially as a sterilizing agent and as a catheter coating. The staff should not be obvious that the patient was in contact with chlorhexidine.

Although between different centers and states, a parallel incidence may vary, it is generally accepted that NMBAs are the most common cause of anaphylaxis during anesthesia (Kubitz 2006) (Table 4).

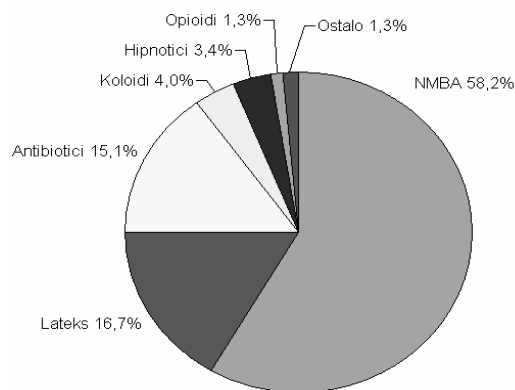


Figure 3. Cause of anaphylaxis (in France)

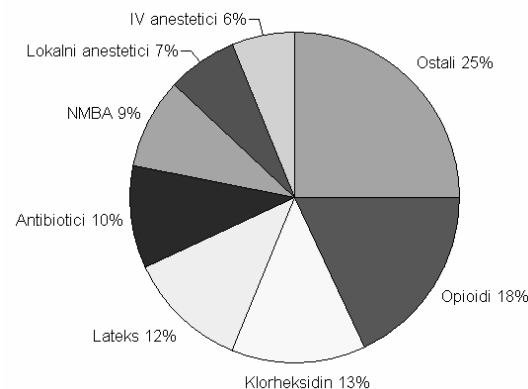


Figure 4. Cause of anaphylaxis

The incidence of anaphylactic reaction, according to the French study, caused by some NMB. As is shown in Table 5 (Przybilla 2007).

Risk factors for the development of anaphylaxis

Predisposing factors for the intolerance reactions for the substances used in the introduction to anesthesia can not be identified. Exceptions are atopy (as a predisposing latex allergy factor) and gender (80% of patients with muscular relaxation are women) (Przybilla 2007, Johansson 2001, Kroigaard 2005, Pühringer 2003).

Latex: Allergy to natural rubber gets in the last years in significance. In addition, type 1 allergies with proven IgE antibodies are rare (Johansson 2001).

English research for 10 years has not registered any deaths due to latex allergies. Due to the necessity of known latex allergy, the environment should be free from triggers (Rajinder 2004).

It is believed that several factors affect the incidence of anaphylaxis.

Table 4. Possible causes of anaphylactic reactions in the current literature described according to the degree of dilution for intracutaneous testing

Groups	Substances	The incidence of anaphylaxis %	Dilution for intradermal testing µg/ml
Miorelaxants	58.2-59		
	Rocuronium	43.1	100
	Suxamethonium	22.6	20-100
	Vecuronium	8.5	40
	Atracurium	22.6	10
	Pancuronium		2-200
	Mivacurium		2
Latex	Alcuronium		5-50
		16.7 3.4	
Anesthetics	Thiopental		200-250
	Methohexital		100
	Propofol		
	Etomidate		
	Midazolam		
Opiates	Fentanil	1.3	
	Morphium		
Colids		4	
Antibiotics		15.1	
Contrast media			
Blood products			

Table 5. NMBA causes of anaphylactic reactions during anesthesia (n=306)

NMBA	No. (%)	Contribution in anesthesia %
Rokuronium	132 (43.1)	8.8
Succinylcholine	69 (22.6)	6.7
Atracurium	58 (19.0)	54.1
Vecuronium	26 (8.5)	11.3
Pancuronium	10 (3.3)	9.5
Mivacurium	8 (2.6)	5.5
Cisatracurium	2 (0.6)	4.1

Atopy

Atopy is an important variable if the antigen is applied over the skin or mucosa (e.g., orally), but not when parenterally administered. Anaphylaxis is generally more common in atopic patients, but the opinion on the relative importance of atopy as a predisposition for anaphylaxis caused by succinylcholine is divided.

Method of application

Anaphylaxis may develop in any mode of antigen use. However, it is more common and more serious if the antigen is injected intravenously. In addition, the emergence is much faster after the injection.

Age

Reactions are rare in children, probably due to lack of previous exposure and lower sensitivity to the effects of anaphylactic reaction. It is thought that reactions are

more common in adults and it seems that the peak of the occurrence is in the fourth decade. Exceptions are children who have been subjected to numerous operations, such as those with spinal bifid, considered to be risky for latex allergy.

Previous anesthetics

It has long been considered that the number of local anesthetics has increased and therefore more exposure to agents is also a risk factor. However, this is not supported by solid evidence.

Previous Allergy to Drugs

It has been observed that the reaction during earlier anesthetic procedures is also a risk factor. Any unexplained reaction during the previous anesthesia may be an allergic reaction and should be considered a risk factor.

Sex

Anaphylactic reactions to latex and NMBA are more common in women than in men (ratio 3: 1) (Raulf 2004). This difference may be due to exposure or cross reaction. For example, women are the majority of health care professionals and therefore are more likely to be exposed to latex, which is conducive to the onset of allergies. They are also more often exposed to chemicals (eg, cosmetics, soaps, detergents) that can lead to cross reactivity with other agents, including NMBAs. This does not mean that pre-anesthetic testing is required or recommended in women.

Diagnosis of anaphylaxis

When symptoms and signs occur after several drugs are administered, one after the other, as usually occurs during anesthesia, does not mean that the last drug used is anaphylaxis causative.

Clinical Symptoms

Signs of anaphylaxis according to body systems are shown in Table 6 and clinical symptoms of anaphylaxis are shown in Table 7.

Table 6. Signs of anaphylaxis according to body systems

Cardiovascular system:	hypovolemia (tachycardia, hypotensia), sometimes pectoral angina
Respiratory tract:	bronchospasm, laryngeal edema
Gastrointestinal system:	abdominal pain, defecation, diarrhea, vomiting, nausea

Table 7. Clinical symptoms of anaphylaxis

Symptom	Frequency
Cardiovascular	74.70%
Skin	71.90%
Cardiovascular collapse	50.80%
Bronchospasm	39.80%
Hypotension	17.30%
Angioedeme	12.30%
Cardiac arrest	5.90%
Bradycardia	1.30%

Clinical manifestations of anaphylaxis vary greatly from patient to patient, from mild to severe shock. Anaphylaxis may occur at anytime during anesthesia and slowly until very rapid progression. In most cases, making the symptoms faster, the reaction is more serious.

Clinical symptoms and signs of anaphylaxis usually begin within 5 to 30 minutes after the injecting the antigen, but may develop within a matter of seconds. If signs appear later, during anesthesia, indicate allergies caused by latex or plasma expansions.

Serious cases are often the first affected respiratory and cardiovascular system. It is important to note that hypotension in about 10% of cases is the only sign of allergic anaphylaxis.

One of the most common early signs of anaphylaxis caused by anesthetics is the difficulty of pulmonary inflation prior to tracheal intubation. Serious obstruction of the upper respiratory tract caused by angioedema can lead to asphyxia. Lower respiratory tract obstruction caused by bronchospasm may result in wheezing and chest compression. Serious hypotension causes massive fluid transfer from intravascular to extravascular space as a result of increased vascular permeability. Venous return to the heart is dramatically reduced and hypotension occurs. Intravascular volume loss can be fast and enormous: up to 50% can be lost within 10 minutes.

Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal pain. Skin marks include redness, urticaria and angioedema. Heart symptoms are varied and can be expressed. Characteristic compensatory tachycardia is the response to reduced effective vascular volume or vasodilation. Bradycardia, as a result of increased vagal tone, may also occur.

Anafilactic reactions to premedication substances are extremely rare.

Intravenous anesthetics: Anaphylaxis in very rare cases is observed after thiopental administration, manifested with type 1 reaction with urticaria and angioedema, however, in rare cases, pseudoallergic reactions may occur due to the release of histamine and serum disease (Type III)- Propofol rarely causes maculopapular exanthema. Systemic reactions to etomidate are extremely rare, so far only a few cases of vague mechanism have been described, and activation of complement appears to be involved.

Inhalational anesthetics: Angular reactions to inhaled anesthetics are extremely rare, skin testing on inhaled anesthetics due to the volatile character is remarkably difficult. Opiates are also extremely rare causes of anaphylactic reactions, regardless of what they are characterized as potent non-specific histamine-blockers. Frequent use of opiates causes pruritus. Skin tests on opiates have little power of expression.

Anafilactoid reactions are due to direct histamine release by some drugs. Thus, it is known that morphine causes direct release of histamine from the fatty cells in the skin, but not from the fat cells of the lungs, the gastrointestinal tract and the heart. Other drugs, atracurium, vecuronium, and propofol, on the other hand, lead to the direct release of histamine from the lung mast cells. These differences lead to anaphylactoid reactions with different clinical images and with the help of these knowledge their symptoms are explained.

Anaphylactic reactions are mediated by antigens, usually by mediation of IgE, secretion of mediators from mastocytes and many other mediators and basophilic granulocytes IgE presence. Implies an earlier exposition, which is often unknown. In 1999. and 2000. in France, a total of 789 patients who responded to anesthesia were summed up in one multicentre study and investigated. The reactions were divided into clinics, skin testing and specific IgE antibody. It has been shown in 51 cases that this is an anaphylactic reaction and in the case of an anaphylactoid reaction. Muscle relaxants cause IgE antibody mediated delivery and through non-immunologically mediated stimulation of basophilic granulocytes and mast cells release mediators. Specific IgE is directed at the anaphylactic reaction first against a quaternary ammonium group of muscle relaxants which leads to translocation of the cell surface and specific IgE. This leads to the bridging of the necessary divalent ammonium gorous structure,

specific IgE is present directly or after in vivo of the protonation of the substance, as is the case for veku-ronium.

Activation of complement: Activated immune complex of antigen-IgE or IgM antibody on cell surface. Activation leads to the formation of anaphylotoxins, which release histamine and other substances. The significance of complement activation with muscular relaxants is still not completely clear.

Chronic release of histamine: This is the most common mechanism; histamine is liberated by the direct action of NMBA with a bezilylococaine structure on the surface of mast cells. An antigen-antibody reaction is not involved. The measure of chemical release of histamine depends on the dose of muscle relaxants and the rate of injection. For atracurium, the histamine release thresholds were 0.5 mg/kg (frequency 30%), for mivacurium at 0.2 mg/kg (frequency 40%).

Cross reaction

The cross-reaction in muscle relaxants was observed in 75.1% of anaphylaxis. The highest incidence of cross reactions is rocuronium 80.6%, vevuronium 87.5%, atracurium 76.8%, succinylcholine 54.3%. Responsible for cross reactivity is considered to be ammonia. Approximately 70% of patients showing muscle relaxant reactions had no prior contact with this drug group. There has probably been previous sensitization of quaternary ammonia found in everyday use substances such as hair care products. Normal skin population skin tests on muscular relaxants show positive responses at 9.4%, the number that is higher than the number of anaphylaxis after the administration of these medications. Oxygen group drugs are potential histamine-blockers, mainly related to anaphylactoid reactions. Allergen morphine structures are the cyclohexene ring with hydroxylation at the C6 atom and the most important methyl structure on the N atom.

Clinical differences between the analfloxioid and anaphylactic reactions can not be attributed solely to the clinical picture. The anaphylactic reaction is usually more difficult than anaphylactoid. Cervical symptoms are more common in anaphylactoid than in an analgesic reaction. Reactions (93.7 at 71.9% and 86% respectively), blood collapse (50.8 versus 11.1%, respectively 49 versus 12%) and bronchospasm (39.8% versus 19.2% or 41.9% to 25%) is more frequent in anaphylaxis. Cardiovascular collapse may be a sign of reaction. After each allergic reaction, a diagnostic study should be performed. Anamnesis, documentation, and time sequence after drug administration provide guidance on possible reaction. It is important to understand that a single test does not give us a clear picture of what has happened. There is no gold standard. Therefore, more tests have to be done to obtain a more accurate diagnosis and determine the

agents or agents most likely to cause an anaphylactic reaction. Determination of the value of degranulated mastocytic tryptase is a diagnostic sign, followed by unfortunately only in a small number of patients. The top of the tryptase concentration is 30-60 minutes after the blood reaction, the biological half-breakdown of the mast cell release protease is 2 hours. Up to 6 hours after stimulation, an increase in serum tryptase can be demonstrated, optimal re-measurements for the assessment of the course of the event. To differentiate from other diseases in the early stages of the reaction (up to 60 minutes), increased serum histamine can be measured. A blood sample should be taken as soon as possible after the reaction (stage I 5-15 minutes, stage 2 <30 minutes, stage III 10-120 minutes). In one study of 158 patients with elevated triptaze values in anesthesia incidents, only 33 patients demonstrate unspecific IgE.

The determination of IgE antibodies should be made, and it has also proved useful for years after death. It has even been found that the determination should be done 4 to 6 weeks after the reaction. However, it would be argued that the determination should be made much earlier, if possible, 2 to 3 days after the reaction. Previously performed determination would undoubtedly demonstrate the antibodies generated during the reaction, while later detection of the detected antibody does not have to be caused by reaction, but by some later stimulus.

Unfortunately, only a few tests for the determination of IgE antibody-specific antibodies are available commercially (see below) and this fact limits the practical blending of these tests. Several specialized centers have developed their own specific IgE tests. The only NMBA for which there is a commercially available test is succinylcholine. However, specific IgE determination is an integral part of determining possible reaction to latex.

The results of the IgE test will be negative or positive, indicating whether the antibodies specific to the serum test substance are found or not. Although a positive IgE test does not prove an anaphylactic reaction, the IgE antibody determination gives us more data than tryptase determination. The results of the IgE antibody and tryptase determination and the skin test should be used together to determine the probable cause of the reaction.

In the second place, tryptase increased in 20.7% of anaphylactoid reactions, and in 64% of anaphylactic reactions. The positive finding of tryptophan for anaphylaxis has been calculated from 92.6%, negative values from 54.3%, sensitivity 64%, specificity 89.3%.

In the study by Renza an anaphylactoid reaction was tested when, vancomycin was rapidly infused, after which plasma histamine increases, but not up to triptase. These studies underline the diagnostic determination of tryptase as evidence of the anaphylactic character of the anesthetic incident.

Skin tests (Pinprick, intradermal tests): They have an advantage because they can be carried out anywhere without special laboratories. In the study involving 1200 respondents, there were no serious incidents during testing. Performing a skin test is recommended at the earliest 4-6 weeks after the reaction, because they were again filled with the intracellular supply of histamine. Testing can be done earlier, but the risk of false positive findings is higher. After three months the skin reactivity decreases. The prick test is carried out on untreated original medications with the exception of atracurium, mivacurium and cisatracurium, diluting 1:10. After the prick test is carried out, the intracutaneous test is added. The indications of dilutions of muscle relaxants for intracutaneous testing listed in the table result from minor irritation reactions.

Activation of basophilic granulocytes was determined by means of histamine measurements in the histamine release assay, sulphoicutriene and cellular antigen stimulation test or by marking the labeled surface (CD63 and CD203). It is often used to measure CD63 expression in basotest or FLOW-CAST. In post-anesthesiological incidence studies, the sensitivity of CD63 measurements after activation of basophilic granulocytes with muscular relaxants ranges from 54 to 65%, with specificity of 93% and correlation of $r=0.53$ with the success of skin testing. Kvedariene also argues that the sensitivity of basotest for muscle relaxants varies depending on the reaction time after testing. The sensitivity of the test 4-8 years after the reaction was 47.6% and consumed the last 3 years 85.7%. Comparative sensitivity analysis of CD63 compared to CD203 that performed Sudheer and sur showed for sensory muscle relaxants 79%, CD 63 and 36% sensitivity to CD203c. The dilution of the following commercial muscle relaxant preparations is described in the following

manner: atracurium 10 mg/ml, mivururum 2 mg/ml, rocuronium 10 mg/ml, suxamethonium 11 mg/ml and veuronium 4 mg/ml: 1/100, 1/500; 1/1000 <, 1/5000; 1/10000, 1/50000.

Exposure test

It is not recommended for suspicious medications due to the reactions that may occur, with the exception of local anesthetics.

Therapy

Anaphylactic reaction therapy algorithm are shown in Figure 5 and Table 8.

Intravenous adrenaline use in anaphylactic shock is disputed. Some authors argue that adrenaline closes open arterial shunts, thereby slowing blood flow. Adrenaline, even at minimal doses, overcomes an empty heartbeat into fibrillation that is very difficult to cure and induces heart infarction. The most important measure here is the infusion of 500 -1500 ml of colloids (Dextran, HAES, Gelatine). With rheological and oncotic effects, the blood that stagnates in the capillaries begins to circulate again and the bloodstream is established.

When undesirable adrenaline effects and volume of substitution, dopamine can be used instead of or together with adrenaline i.v. Noradrenaline can be used with insufficient adrenaline / dopamine action, cut off. As an infusion, in some cases, a combination of arginine vasopressin is also desirable.

Prophylaxis: Cardiovascular reactions can be avoided by combined injection of the H1 and H2 receptor antagonists 15 minutes before giving muscle relaxants.

The effect of the histamine receptor antagonists occurs after the latency time of 5-10 minutes.

Table 8. Anaphylactic reaction therapy algorithm

The measure	Conduction
Position	Depending on the patient's wish: the shock position (in case of hypotension) lying or the upper part of the body too (with dyspnoea)
Oxygen	10-15 l/min
Allergen	Remove/stop administration
Adrenalin	0.5 ml i.m. at a dilution of 1: 1000 for every 5 minutes, administration may be repeated every 10 minutes, depending on the pressure and pulse recovery. Alternatively, 50-100 µg i.v. during 1 minute (about 5-1.0 ml at 1.10000) is recommended for hypotension titration of further doses p.p. Never give unillute adrenaline i.v.
Antihistaminics	H1 antagonists (e.g. Clemastin, evt.-H2 antagonists (ranitidine)
Glucocorticoids	Eg. 1 g of prednisolone, or 100-500mg of hydrocortisone
Volume	When adrenaline is inefficient: 1-2 liters fast (crystalloids and colloids)
β2 mimetics	When it persists bronchospasm regardless of adrenaline administration
Intubation	Early when it is indicated
Reanimation	ERC Reanimation Standards, Massive volume algorithm (4-8 liters)
Save any blood samples collected before or during the procedure. It may be necessary to test	

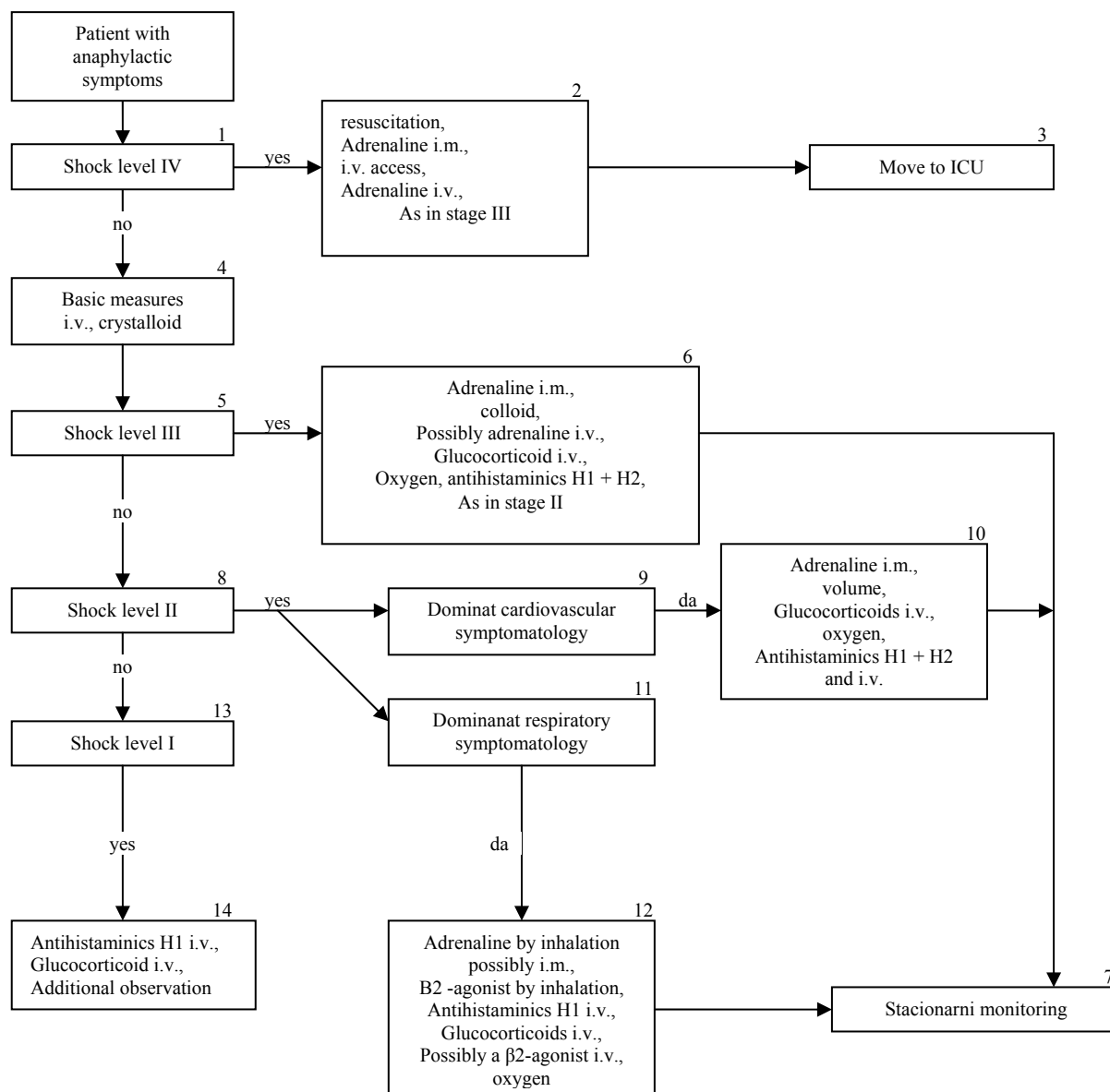


Figure 5. Anaphylactic reaction therapy algorithm

In fulminant anaphylactic and anaphylactoid reactions, the first symptom may be instability of the bloodstream or bronchospasm. Allergic reactions to muscle relaxants can lead to multiple organ failure and to death of the patient.

During anesthesia, to reduce the likelihood of unwanted reactions, circumstances can be adjusted as follows:

- Slow drug delivery;
- Reduction of the dose of the drug;
- Avoiding giving multiple medications in the short term;
- Avoiding fast spinal anesthesia;
- Careful monitoring of patients with oral antihypertensive therapy;
- Avoiding hypovolemia;

- Using preoperative H1 and H2 blockers and / or corticosteroids in susceptible patients and atopic individuals. Yet, this is still controversial.

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Danijela Glibo Bevanda, Marko Čačić & Slobodan Mihaljević: conception and design of the publication, literature searches and analyses, writing the first draft participate in drafting the article, execution of tables, approval of the final version;

Mateo Bevanda, Ante Bogut & Maja Karin: participate in revising it critically for important intellectual content, revising the manuscript, approval of the final version.

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