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Laboratory diagnosis drug allergy.
Part 1. Methodology for determining the specific immunoglobulins to drugs, mediators and cytokines

Key words: *in vitro-diagnostic medical allergies, total IgE, specific IgE, ELISA, chemiluminescence analysis, multiple alergosorbentny test.*

Allergic reactions to medications the patient encountered in medical practice of any profession. The prevalence is associated with increased consumption of drugs populations and adverse environmental factors that violate the activities of the immune system [1–3]. The risk of drug allergy is generally 1 % in ambulatory practice and 5–10 % in the clinical setting [4]. Hospitals are much more likely to use multiple drugs simultaneously , plus sleeping pills, but they are much higher dose than outpatient treatment , which increases the risk of allergic reactions [5].

The majority of allergic reactions are recorded on antibiotics, local analgesics, non-steroidal anti-inflammatory drugs, heterologous serum, radiographic means, human blood protein drugs, vaccines, enzymes, vitamins, tranquilizers, anti-diabetic drugs, psychotropic drugs, ACE inhibitors, antiarrhythmic agents [11–16]. However, any drug substance may cause drug allergies, antihistamines and even steroides [8]. Allergic reactions can cause conservantes in the composition of many drugs, such as sulfites, complexones and others [17].

The pathogenesis of drug allergy may lie immunological injury, classified by Gell-Coombs, but specificity in the occurrence of a certain type of allergic damage depending on the nature of the drug is not exist (table 1) [23]. Almost any medication can cause one of the 4 types of reactions or more of them [1, 18, 19].

The question of how often the true allergic reactions to medications remains is debated [7]. Pseudoallergic reactions unlike allergic characterized by a lack of true allergic antibody formation and immune T-cells in the body. These reactions are non-specific and induced by various agents in predisposed patients treated long-term therapy [25]. Some medications can cause reactions in primary injected into the body: X-ray contrast agents, local anesthetics, opioids, muscle relaxants, aspirin and others. [26, 27]. Mechanisms of pseudoallergic drug reactions are represented in the table 2.

The most relevant manifestations of drug allergy are anaphylaxis, Kvinkes edema, bronchoobstructive syndrome, acute urticaria and polymorphous rash, including severe manifestations such as toksykodermia, Stevens-Johnson and Lyell syndromes [2, 6, 8, 9]. Drug allergic rhinitis, conjunctivitis, allergic myocarditis, allergic lesions of the gastrointestinal tract and hepatobiliary system, kidney damage and blood system rare apear [1, 2, 10].

Criterias allergy to medicines are: the relationship of clinical symptoms with medication, relief or disappearance of symptoms after discontinuation of the drug, the lack of similarity of symptoms with other forms of medication side effects (toxicity, pharmacological, and oth.); allergy to previous administration of the same drug or chemically similar to their cross-reactants, the presence of the latent period of sensitization during the initial appointment medicament, similar clinical manifestations of symptoms of allergic diseases [4, 5]. Classification of allergic reactions to antibiotics by the time of their development is represented in the table 3.

If the cause of the allergy can not determine on the basis of history, used laboratory methods, skin tests and provocative tests. The reliability of laboratory diagnostics varies from 60–85 % [19–21].

General indications for the use of laboratory methods for detection of drug allergy: patients with intolerance to medication, burdened with allergoanamnesis, with occupational allergy (for diagnosis and placement) diagnostically unclear cases of suspected visceral form of drug allergy, the desire of patients and/or doctor (before administration of drugs operation, etc.) [19].

Obligatory indications for preliminary laboratory testing of patients with drug tolerance include: anaphylaxis, severe toksykodermya, a history of an unknown drug and the need for drug therapy, for large skin lesions (severe toksykodermya) and the need for selection of drugs (antibiotics, etc.) during receiving glucocorticoids, antihistamines, if necessary, the introduction of potentially dangerous drugs, with early childhood, a high degree of sensitization of patients and continuously recurrent disease; polyvalent sensitization,

Table 1

Gell and Coombs classification of allergic reactions on the base of theire mechanism

Type of reaction	Description	Antibodies	Cells	Other factors	Clinical manifestations
I	IgE-dependent / (anaphylactic, reagin)	IgE	Mast cells, basophils		Urticaria, anaphylactic shock, Kvynkes edema, bronchospasm, and others.
II	Cytotoxic / (cyto-lytic)	IgG, IgM	NK, neutrophils, mono-cytes / macrophages	Complement	Hemolytic anemia, cytopenia, nephritis
III	Immunocomplex	Antigen-antibody complex (IgG, IgM)		Complement	Serum sickness-like syndrome, drug fever
IV	Cell-mediated		T-lymphocytes		Contact dermatitis

Table 2

Classification of allergic reactions to antibiotics by the time of their development

Type of reaction	Time of hours	Clinical manifestations	Notes
Immediate	0-1	Urticaria / Kvynkes edema Swelling of the throat Anaphylactic Shock, Hypotension	Often due to pre-existing IgE. If you are allergic to penicillin are often caused by sensitization to their minor determinants
Accelerated	1-48	Urticaria / Kvynkes edema Swelling of the throat	Often caused by newly synthesized IgE. If you are allergic to penicillin are often caused by sensitization to the their main determinants
Slowed	48 h and late	Skin rash, Interstitial nephritis, Hemolytic anemia, Neutropenia, Thrombocytopenia, Serum sick-ness-like syndrome, Drug fever, Toxykodermia, Exudative ery-thema multiforme, Stevens-Johnson syndrome, Layel syn-drome, Exfoliative dermatitis Duhring	Generally, the mechanism of development is not associated with IgE

when there is no possibility of testing in vivo immediately with all the predictable allergens in a limited test period, while dramatically altered reactivity of the skin; false positive or false negative results in skin testing, with urticaria dermographism [19, 21].

Current methods used for in vitro diagnostic allergic diseases are represented in table 4. In order to detect immediate-type hypersensitivity we use the following in vitro tests: determination of tryptaz in serum to determine the presence of mast cells degranulation, determine the concentration of specific immunoglobulin E in serum, the basophil activation test in the presence of potential allergens [19, 23].

For detection of delayed-type hypersensitivity we use the following in vitro tests: lymphocyte transformation test in the presence of a potential allergen, identification of emerging markers CD69 T cells in presence of a potential allergen, the definition of the levels of cytokines in the supernatant of lymphocytes after incubation in presence of a potential allergen, the definition of cytotoxicity (or its products) [22, 24].

Methods fordetermining levels of total IgE in serum

Increase total IgE levels in serum are usually marked in immediate type allergy, but in some cases this figure may correspond to normal. Highly sensitive methods for immunological studies to determine the concentration of IgE les then 50 IU/ml are shown below.

Enzyme immunoassay (EIA). For the quantitative determination of total IgE used solid faze ELISA in which IgE antibodies adsorbed on solid media in wells of polystyrol plate. The complex, which was formed with the introduction of the study show the addition of serum antibodies that correspond to them, conjugated with an enzyme-labeled (horseradish peroxydase, and beta-galactosidase or alkaline phosphatase) [23].

After connecting the enzyme labeled antigen with immune serum is added to the mixture substrate/chromogen.

Table 3

Mechanisms of pseudoallergic drug reactions

Mechanism	Preparation
Release of mediators from mast cells (histamine liberation)	Dextran, polymyxin B, x-reycontrast agents, opiates, tubakuraryn, trymetafan, desferal
Effects on metabolism of arachidonic acid	NSAIDs
Activation of complement	serum γ-globulin (immunization), x-reycontrast agents
Cytotoxic degranulation	quinine
Activation of kinin system	NSAIDs, local anesthetics
Release of neurotransmitters (regulatory peptides)	glutamate
Excitation of autonomic receptors	Metabisulfat, local anesthetics
Malabsorption (recycling)	Lactose, gluten

Table 4

Current methods used for in vitro-diagnosis of allergic diseases

Purpose of test	Principle of the test	Technology	Test systems
Detection of sensitization to specific allergens	Detection of immunoglobulin E, G, G4 to certain allergens	Anti-IgE (G, G4)-antibody adsorbed to the solid phase capture IgE (G, G4) from the serum of the patient. Then captured IgE (G, G4) quantitatively determined by anti-IgE (G, G4)-labeled antibodies with the corresponding	UniCap, ELISA, imunoblot, allergen-mikroarea
Identifying mediators of allergic inflammation	Detection: - histamine; - tryptase; - leukotrienes and prostaglandins; - mediators of eosinophils	The same	UniCap, ELISA
Identification of effector-activating cell immediate type hypersensitivity by neurotransmitter type (late phase of immediate type hypersensitivity)	Production of leukotrienes and prostaglandins. The expression of activation markers.	Same Direct detection of antigens CD63, CD203c antibodies labeled with fluorochrome	CAST Cytofluorymetry

The substrate is cleaved by the enzyme and changes the color of the reaction product, the intensity of color is directly proportional to the number of molecules of antigen and labeled antibody contacted. Chromogen color changes if the result is positive. Each time you add another component reagents are removed from the wells that are not contacted by washing. Accounting for the intensity of the reactions of test and control samples is carried out on a spectrophotometer (ELISA reader) for absorption of light at certain wavelength (for chromogen TMB (tetrametylbenzydyn) it is 450 nm).

Hemiluministsent («sandwich») analysis using paramagnetic label. Anti-IgE-antibodies added to patient serum are labeled with fluorescent (acridine ester) [28]. After washing antibodies are not contacted, adding anti-IgE-antibodies covalently linked to paramagnetic particles. To account for the desired special measuring device that includes a photometer and an electrode with a magnet. Magnet captures paramagnetic particles associated with IgE-konjugates, resulting electrochemical reaction occurs luminescence labels, measured photometrically. The method is highly sensitive and allows you to determine the concentration of total IgE levels in the range 1,5–3000 kIU/l.

Radioimmunoassay analysis (RIA) – a method based on antigen or antibody labeling radionuclide I125. Competitive RIA uses for the quantitative determination of total IgE (on solid phase immobilized antibodies exciting IgE). Patient serum and a certain amount of IgE, labeled with I125, are added in the system. As a result of this reaction is the binding component is inversely proportional to the content of IgE in serum of the patient. The results evaluated by gamma counter for radioactivity immune complexes formed. As RIA requires expensive equipment and reagents, the presence of radionuclides, it is now rarely used [23].

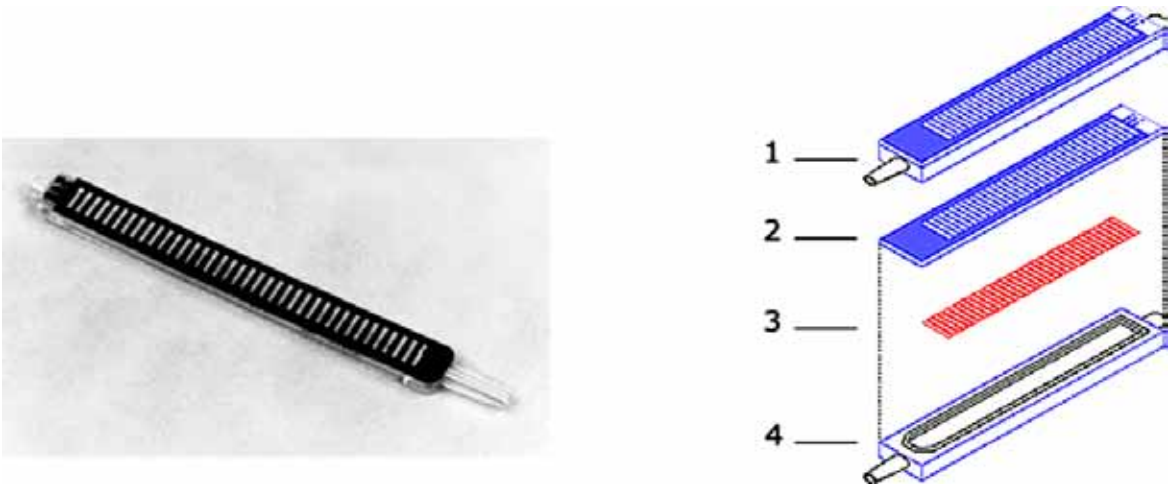


Figure 1. **Device for the production of IDSA,**
where 1 – IDSA panel to collect 2 – Cover 3 – cellulose filaments with adsorbed allergen, 4 – Building.

The disadvantage of methods for determining total Ig E is nonspecific to the allergen is able to establish only the existence of immediate type allergic reactions for up to 1 month of observation, while we can not specify which allergens cause such serious immune disorders.

The methods used to determine allergenspecific IgE in serum. Highly sensitive and specific/ Methods of determining allergenspecific IgE- antibody tests are allergensorbent - RAST, MAST, immunoblotting, ELISA solid phase, mikroarea.

Radioallergosorbent test (RAST) – a method of determination of specific IgE- antibodies in the serum of the patient to the allergen, preadsorbed on porous media using radioactive labels. In the serum of the patient paid insoluble polymer – allergenic konjuhat containing the drug or its metabolites, which are sorbed in relation to specific allergen antibodies used. Then add antyglobuline serum (against IgE), which marks the radionuclide. After washing agents that are not contacted, the results assessed by gamma counter for radioactivity levels of immune complexes formed in relation to the control and standard curve. Determination of specific IgE to drugs by RAST shown at high risk of anaphylactic reactions, skin lesions and perform a treatment that affects the results of skin tests [16].

Now widespread allergosorbent tests using fluorohrom, enzyme or hemiluminiscent labels that have great sensitivity, specificity and automation.

Definition allergenspecific IgE with alergosorbent method using fluorescent tags

To allergens, such as drugs or their metabolits, adsorbed on cellulose medium, add the patient serum. Then add the labeled enzyme (β-galactosidase) anti-IgE- antibodies that bind to the conjugate formed. After washing antibodies are not contacted, add substrate (4-metylimbeliferil-β-D-halaktozide) in the case of fermentation which formed fluorescent substance whose concentration is detected by reader (FluoroCount). As an example, the method based on the effect of chemiluminescence can lead MAST [28].

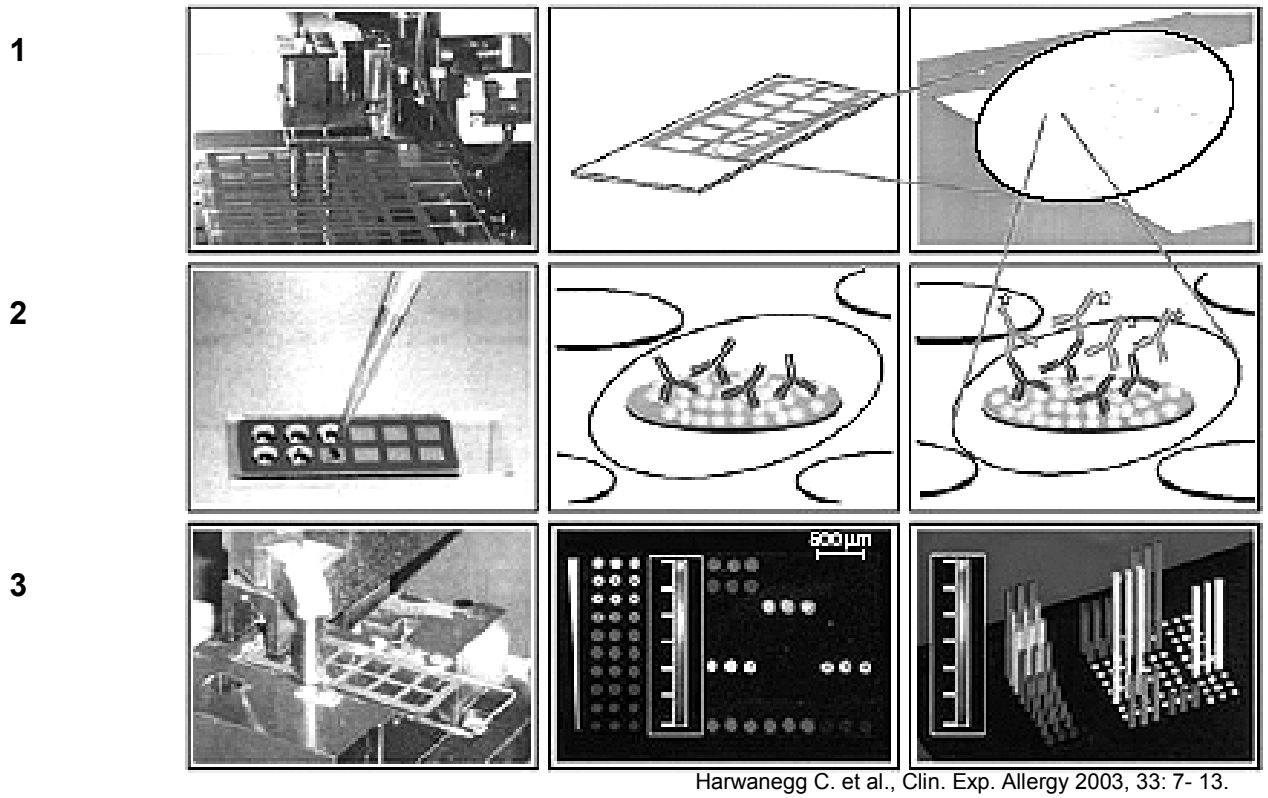
Multiple alergosorbent test (MACT) – a method of determining allergenspecific IgE, where allergen adsorbed on cellulose fibers, as well as the indicator reaction used fotoreagents world are registered in luminometer (fig. 1). The method makes it easier to get the results of the study makes it possible to determine the necessary parameters in one patient without waiting for the storage of samples for use by the whole set.

Immunoblotting used in the presence of the on-causal allergen (data history, elimination test) and negative results of testing for specific IgE majeure components of this allergen. In such cases, allergen extract (including preparation) use blots and conduct an analysis of patient sera for the presence of IgE, specific to not described (minor) component allergen. Such a test is designed to diagnose the presence of specific IgE to penicillin minor determinants (penycylloat and penylloat), other beta-lactams. Positive results immunobloting of minor determinants indicate a high risk of anaphylactic reactions [28].

Pseudoimunobloting – method to simultaneously detect specific IgE- antibodies to various allergens in serum. Pseudoimmunoblot based on solid-phase ELISA, has a higher specificity (but less sensitive), execution speed, minimal blood volume (less than 0,5 ml), simultaneous testing of a large number of allergens (20 in each panel).

Mikroarea is based on DNA-olygonuceotides but develops microerrey using monoclonal antibodies and recombinant antigens. In particular, this technology is used to diagnose and optimize the treatment of allergies, including drug allergy (fig. 2) [29].

Research carried out in two stages. 1). Preparation microchip: recombinant allergens addes to the surface of glass. One glass contains 12 cells. Each cell contains a variety of allergens and calibration curve (increasing the number of IgE) in triplets. So, while you can examine up to 12 patients. 2). Progress test: a) deturmen patient sera (15 ml); b) incubation (IgE patient connectes to allergens); c) addition of monoclonal antibodies against IgE, which are presented fluorochrome; d) microchip scan. In fig. 2 shows the option scans the microchip. The first three rows – calibration curve (intensity proportional to the amount of the world IgE); further – sensitization patient profile (type and quantity of specific IgE in serum of patients).



Harwanegg C. et al., Clin. Exp. Allergy 2003, 33: 7- 13.

Figure 2. **The scheme of mikroarea method to diagnose of allergy. Determination of specific IgE levels using biochip.**

Detection of specific immunoglobulin E in serum is highly specific and sensitive, but their use is possible only in cases where potential allergens are those kits for the determination of which are in the laboratory. Methods for determining cell activation in presents of allergen can use as positive control standard antigens.

Nephelometric reaction of microprecipitation by Uane used for the detection of IgG-, IgM- antibodies haptenes (drugs) in serum. Prepare two-fold dilutions of allergen and serum of the patient. In one cell of photoelectric or strypphotometer make 150–180 mcl or 1,5–1,8 mL studied serum (starting dilution 1:2) pursuant to another – control solution or blood serum of healthy people. Measure the initial absorbance (at 500 nm wave and litefilter number 4). Then in each cuvette is added 100 mcl or 0,1 ml according to the type of instrumentation diluted allergen from the minimum concentration and mix. Again determine the optical density of the mixture in the cuvette after 2 min. The reaction is conducted first with various dilutions of allergen, then when it determined the minimum concentration – with serum (to determine its titer). The optimum concentration of hapten – is the one that causes a delay reduction or even an increase in the optical density of the mixture. When testing the drug concentration is estimated dose, dissolved in 1 liter of distilled water. The reaction is considered positive if the optical density of the mixture serum + allergen adding in certain concentrations (as with a negative result) does not decrease or even increases [3].

The reaction of passive hemagglutination (RPHA) based on the agglutination of red blood cells or particles of latex, etc.), loaded allergen. The method can detect full antibodies can cause agglutination (antibodies of IgG or IgM). The critical point of this reaction - making diagnosticum. Often this is used erythrocytes (sheep, rabbit, human, etc.). Their surface is activated by various chemicals (formalin, tannin, etc.). Red blood cells, treated with 0,25 % glutaraldehyde solution [6], a well- bind different proteins, and 0,1 % solution of chromium chloride precipitate on the surface of their red blood cells, which increases the density of allergenic determinants on the surface of red blood cells.

Identification of mediators and cytokines in the systemic circulation (usually by solid phase ELISA):

1. *Detection of histamine* extremely difficult at high speed its inactivation (minutes), so to identify its presence in the systemic circulation (anaphylactic shock) often used definition methylhistamin in urine (high level persists for several hours after the disappearance of symptoms of systemic anaphylaxis) [28].

Method for determination of histamine in the blood. Blood with heparin volume in 25 ml placed in fybrogass holes, where preadd 25 ml PIPES-buffer. Next plates incubated for 1 h at 37° C and after washing with distilled water further incubated for 30 min at 37° C with 0,04 % solution of sodium dodecyl sulfate. After washing with distilled water to each well plate added a solution of orthophtalic dialdehyde to condense histamine sorbed on fibroglass matrix. The reaction was stopped after 10 min by adding 0,59 % solution of $HClO_4$. Results obtained by automated analysis spectrofluorymetry, expressed in ng/ml of histamine in the blood.

2. *Definition tryptase in serum.* Tryptase found in mast cells and granules for several hours kept in circulation. Mast cells are activated during IgE-dependent immediate type reaction,

release into the surrounding tissue proteases deposited histamine, and again formed vasoactive mediators. Tryptase is a neutral serine trypsinlike esterase. It is stored in the secretory granules of mast cells in an active state in combination with heparin and is a marker of activation. Tryptase immunoreactive levels in serum of healthy people is less than 5 mg/l. Increased serum tryptase more than 10 mg/l is observed within 4 h from the start of anaphylactic reactions, tryptase half-life is 2 hours. Recommended time taking blood serum to determine the level tryptase is from 30 minutes to 4 hours after the onset of a severe allergic reaction. Like tryptase histamine released from mast cells after degranulation in vitro. Currently developed sets of reagents for quantitative determination tryptase in serum by ELISA method [30].

3. *Determining cytokine status of peripheral blood* (IL -4, IFN -γ, IFN-γ/IL-4) provides an overview of the nature of the type of immune response at the time of the test. In recent years Th1/Th2 model gave way to study the role of the T-regulators in allergy.

4. *Determination of cells that secrete cytokines.* Now it is possible to determine these parameters for allergenspecific cells (tetramer technology). Most often used for these purposes flowing cytofluorymetry and elispot.

Therefore, laboratory methods for detection of allergy, based on the determination of immunoglobulin specific to particular drugs, neurotransmitters (tryptase) and cytokines (IL -4, IFN -γ, IFN-γ/IL-4) safety and possible use in any one period of the disease are preferred. However, the main drawback of these methods for the determination of specific antibodies to drugs is the need to have a lab kits for all possible drug allergens, indeed, even to their metabolites, which considering the availability of modern medical arsenal of more than 1000 drugs impede the process of in vitro drug diagnosis of allergies.

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LABORATORY DIAGNOSIS DRUG ALLERGY. PART 1. METHODOLOGY FOR DETERMINING THE SPECIFIC IMMUNOGLOBULINS TO DRUGS, MEDIATORS AND CYTOKINES

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Summary

Allergic inflammation of the skin is the basis of drug allergies, mucous membranes and other tissues and organs damage, it is due to the synthesis of immune factors in the body that can interact with drugs or their metabolites. The vast majority of allergic reactions is registered on antibiotics, local analgetics, nonsteroidal antiinflammatory drugs, heterologous serums, radiopaque agents, protein drugs of human blood, vaccines, enzymes, vitamins, tranquilizers, antidiabetic preparations, psychoactive preparations, ACE inhibitors, antiarrhythmic drugs. However any medicinal substance can cause drug allergy.

The indications for laboratory examination of patients with drug intolerance are: anaphylactic shock, severe toxikodermia in anamnesis of an unknown drug and the need for drug therapy, significant lesions of the skin and the need of a medication; during using of glucocorticoids, antihistamines, necessary the introduction of potentially harmful drugs, in the early childhood, a high level of sensitization of patients, continuously relapsing course of disease; polyvalent sensitization, where there is no possibility of testing in vivo directly with all potential allergens in a limited period of examination; dramatically altered reactivity of the skin; false-positive or false-negative result in skin testing, urticaria autographism.

In order to identify immediate hypersensitivity use the following in vitro tests: determination of the activity of tryptase in the serum in order to determine the presence of mast cell degranulation, the definition of the concentration of specific IgE in serum, holding basophil activation test in the presence of a potential allergen.

Key words: *in vitro-diagnostic medical allergies, total IgE, specific IgE, ELISA, chemiluminescence analysis, multiple alergosorbent test.*

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ЛАБОРАТОРНАЯ ДИАГНОСТИКА МЕДИКАМЕНТОЗНОЙ АЛЛЕРГИИ. ЧАСТЬ 1. МЕТОДИКИ ОПРЕДЕЛЕНИЯ СПЕЦИФИЧЕСКИХ ИММУНОГЛОБУЛИНОВ К ЛЕКАРСТВАМ, МЕДИАТОРАМ И ЦИТОКИНАМ

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Резюме

В основе медикаментозной аллергии лежит аллергическое воспаление кожи, слизистой оболочки и других тканей и органов, обусловленное синтезом в организме факторов иммунной системы, способных взаимодействовать с лекарственными веществами или их метаболитами. Подавляющее большинство аллергических реакций регистрируются на антибиотики, местные анальгетики, нестероидные противовоспалительные препараты, гетерологические сыворотки, рентгенконтрастные средства, белковые препараты крови человека, вакцины, ферменты, витамины, транквилизаторы, противодиабетические препараты, психотропные препараты, ингибиторы АПФ, антиаритмичные средства. Однако любое лекарственное вещество может стать причиной медикаментозной аллергии.

Показаниями для лабораторного обследования больных с лекарственной непереносимостью являются: анафилактический шок, тяжелые токсикодермии в анамнезе на неизвестный препарат и необходимость медикаментозной терапии; при значительных поражениях кожи и необходимости подбора препаратов; в период приема глюкокортикоидов, антигистаминов, при необходимости введения потенциально опасных препаратов; в раннем детском возрасте; при высоком уровне сенсибилизации пациентов; при непрерывно рецидивирующем течении заболевания; поливалентной сенсибилизации, когда отсутствует возможность проведения тестирования in vivo сразу со всеми потенциальными аллергенами в ограниченный срок обследования; резко измененная реактивность кожи; ложноположительный или ложноотрицательный результат при кожном тестировании; уртикарный дермографизм.

С целью выявления гиперчувствительности немедленного типа используют следующие in vitro тесты: определение активности триптазы в сыворотке крови с целью установления наличия дегрануляции мастоцитов; определение концентрации специфических иммуноглобулинов Е в сыворотке крови; проведение теста активации базофилов в присутствии потенциального аллергена.

Ключевые слова: *in vitro-диагностика медикаментозной аллергии, общий IgE, специфический IgE, иммуноферментный анализ, хемилюминесцентный анализ, множественный аллергосорбентный тест.*

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