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Features of Allergy Diagnosis in Children

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Abstract According to the World Health Organization, currently one of the most significant problems, especially in pediatrics, is allergic diseases: in children, this pathology is the second most common. At the same time, there is an increase in the frequency of severe allergic reactions and an increasingly early onset of clinical manifestations. In this regard, timely and qualified diagnostics of allergopathologies becomes the most relevant. This paper examines the current state of the issue of diagnosis of allergic diseases, summarizes world experience and suggests an approach to the diagnosis of allergies based on the use of step-by-step identification of a causally significant factor of allergic reactions.

Keywords: allergy, anti-gene, course, diagnosis**.**

Based on the analysis of the relevance and significance of certain allergens for patients (taking into account the source of allergens and the age of patients), a step-by-step algorithm for allergy diagnosis is proposed. The first step — determining the clinical manifestations of allergies-is direct contact of the allergist with the patient, finding out his complaints, clinical symptoms, and collecting an anamnesis of the disease. The second step — confirmation of the IgE-dependent mechanism of allergy-involves the use of screening tests selected depending on the clinical symptoms of allergy and seasonality of manifestations (screening modules). The third step is to identify the source of allergens that is most significant for the patient, using test panels that combine the most common and clinically significant triggers of allergic reactions. The fourth step is to search for individual causal allergens that are not included in the diagnostic modules. The fifth is to conduct a component-separated diagnosis and identify antibodies to the unique components of causally significant allergens. The developed diagnostic algorithm meets the needs of both adults and children and provides a personalized approach to the patient.

Allergic diseases are a serious public health problem. There is a high prevalence of allergic diseases all over the world, the number of cases of severe allergic reactions increases; this pathology affects patients of any age category and only progresses over time; the quality of life of the patient and his family significantly worsens [1, 2]. Timely clinical diagnosis and the ability to correctly interpret the results of various methods of recognizing allergic diseases are of particular importance and increase the effectiveness of the patient's treatment [3]. In the case of polysensitization, which can occur in a child even at the age of several months of life and further progress, early detection of the disease is especially important [4]. However, the presence of polysensitization or cross-allergic reactions in the patient makes it much more difficult to identify the trigger (s) that initially triggered the immune response cascade when the patient comes into contact with the environment (plant pollen, animal proteins, food, etc .). [5]. Examination of a patient with allergies is a multi-stage process, in which the most detailed clarification and description of the patient's medical history, complaints, and the hereditary nature of the disease is of primary importance. Already at this stage,

allergens or a group of allergens suspected of triggering the formation of class E immunoglobulin (Ig) molecules or triggering a cell-mediated mechanism of allergy development are identified [3, 4]. The next stage of diagnostic search involves the use of instrumental methods and the establishment of both the mechanism of disease development and the true triggers (allergens) [6]. These methods include, in particular, widespread in vivo (for example, skin scarification tests) and in vitro (for example, determination of the concentration of allergen -specific IgE) tests. In addition, an important diagnostic tool, especially in pediatrics, is the assessment of the results of an elimination diet [6]. At the same time, provocative tests with allergens that are widespread abroad are practically not used in pediatrics, which is associated with the risk of developing systemic allergic reactions [7]. In vitro diagnostic methods are primarily used to determine the mechanism of allergy development, in particular, to establish the relationship of clinical symptoms with hyperproduction of IgE, specific for each allergen. At the same time, the revealed hyperproduction of IgE does not always allow us to establish the significance of the allergen in the appearance of clinical symptoms. Many studies emphasize the difference between the concepts of "sensitization" and "allergy". The term "sensitization" refers to the detection of IgE molecules in the patient's blood serum that specifically bind the allergen molecule. At the same time, a number of patients have latent sensitization, i.e. they have allergen-specific IgE, but there are no clinical signs of allergy. At the same time, according to a long-term study on the mechanisms of the Development of Allergy (MeDALL), latent sensitization in many cases precedes the development of symptoms of allergic disease in later life [1, 2]. IgE-key molecules in the pathogenesis of allergic diseasesThe role of total IgE in allergy diagnosis IgE is one of the key molecules in the pathogenesis of allergic diseases, especially in the activation of mast cells and basophils, as well as in the presentation of antigens (allergens) [8]. Allergic reactions can develop outside of the production of IgE molecules: for example, among non-IgE-mediated reactions, cell-mediated reactions are the most significant [9], but it has been shown that IgE-dependent reactions are currently the most common cause of respiratory and food allergies [6]. The discovery of IgE molecules and the subsequent development of test systems that allow determining the total concentration of IgE, as well as detecting allergenic IgE in biological fluids [4], significantly expanded the diagnostic capabilities. Determination of the total level of IgE and the concentration of allergen -specific IgE allowed us to examine patients during the period of exacerbation of the disease, while taking antihistamines, with severe skin damage, low threshold of skin sensitivity, as well as to examine pregnant women with non-specific skin sensitivity and children of any age. At the same time, the diagnostic value of an isolated determination of the total concentration of IgE molecules is ambiguous [10] and differs in its significance from the assessment of the level of specific IgE. Normally, the IgE content in the blood is extremely low: it is lowest in newborns, but it increases with age and reaches a peak in 16-19 years [11]. In patients with atopic bronchial asthma, pollinosis, and allergic rhinitis, the total concentration of IgE is significantly higher than in the general population [12, 13]. An increase in this indicator can confirm that the patient has atopy, but it does not allow us to determine which allergen caused sensitization of the body. In addition, an increase in the total concentration of IgE in patients is not an exclusive characteristic of allergic diseases: parasitic, some viral infections, systemic inflammatory diseases, and tumor diseases can also be combined with hyperproduction of IgE [3]. There is also the problem of determining the reference limit of IgE concentration. On the one hand, many patients with clinical manifestations of allergy show high concentrations of IgE. However, the reference limit (cut-off point), defined in order to divide patients with or without atopy with high accuracy and specificity, is not clearly defined: there is a significant overlap in the ranges of IgE values in healthy individuals and patients with clinical manifestations of allergy [14]. In addition, it is particularly difficult to establish IgE reference intervals for children of different ages. In the works of many authors, there is

evidence that it is necessary to lower the reference limit. So, in the Chen Xin study, the upper limit of the total IgE concentration for children over 11 years of age was taken to be 60 kU/l. However, in the course of the study, it was shown that many children of this age withIn bronchial asthma, the IgE value was lower, and thus the cut-off point was determined to be 47 kU/l [15]. The M. Brauer study also showed that many children (over 4 years of age) with respiratory allergy symptoms rarely have a total IgE concentration above 100 kU/l (no more than 26% of children) [16]. According to foreign literature, the parameter "total IgE concentration" in the blood of patients in isolation, without conducting additional studies, is rarely used for the diagnosis of allergic diseases. At the same time, a complete rejection of this parameter is also impractical: when assessing its diagnostic significance in children, D. Sherrill and Coll. showed that an increase in serum IgE concentration in children of the first year of life is an early marker of the development of an allergic disease in the future [17]. In addition, the significance of determining the total concentration of IgE in different studies varies significantly depending on the manifestation of allergies. Thus, according to the studies of Ahmad Al Obaidi et al. and P. A. Eigenmann et al., observation in the dynamics of this parameter is important: an increase in the total concentration of IgE is associated with an increased risk of allergic diseases, such as bronchial asthma and atopic dermatitis [18, 19]. According to a study by P. A. Eigenmann et al., an increase in the total concentration of IgE in the patient's blood correlates with a worsening of the course of atopic dermatitis, the development of multiple sensitization, and the risk of a severe systemic reaction [19]. However, for patients with pollinosis, there is a lower sensitivity of this diagnostic indicator [10]. Thus, the diagnosis of allergy primarily requires studying the medical history, as well as identifying allergen-specific IgE [20].

The role of specific IgE in allergy diagnosis Due to the fact that the use of laboratory methods for allergy diagnosis based only on the assessment of the total concentration of IgE is often insufficient, especially in pediatrics [21], the method for determining the level of allergen-specific IgE is widely used. There are several features of the antibody response to allergens. Thus, in most patients, the presence of allergen-specific IgE precedes the appearance of clinical manifestations of allergy, which can develop after a long time. In one of the largest long-term studies conducted by a group of scientists led by R. J. Settipane, devoted to the study of patient sensitization and its significance, it was shown that if a patient has latent sensitization, the risk of developing allergic rhinitis and asthma in patients increases 2-3 times within 16 years [22]. In the studies of D. Leung et al. It was reported that 80% of children with diagnostically significant levels of IgE to respiratory allergens against the background of clinical symptoms of atopic dermatitis only, later allergic rhinitis and/or bronchial asthma are observed [23]. The current Me DALL study showed similar results [1, 2]. The atopic march — the path from the development of atopic dermatitis at the age of 4 to allergic rhinitis and even asthma at an older age — is quite common in patients. At the same time, in the early stages, antibodies to respiratory allergens may be absent or have a diagnostically insignificant interpretation [24]. Another feature of allergy diagnostics is that examination of patients with atopic dermatitis or food allergies reveals the presence of sensitization not only to food, but also to aeroallergens [25]: on average, up to 50% of children and 35% of adults with atopic dermatitis are also sensitized to respiratory allergens [26]. In addition, allergen-specific IgE can be detected in children immediately after birth [27]. At the same time, in a small number of patients, sensitization occurs only in individual tissues: plasma cells of a limited area of the mucous membrane form allergen-specific IgE, while the systemic level of IgE remains low. This phenomenon of local IgE production is called "entopia" [28]. In patients with "entopia", IgE is not detected either by skin testing or serological studies, but patients give a positive response in provocative tests. Currently, immunochemical testing allows us to determine antibodies to the most important groups of allergens — food products, environmental allergens (allergens of insects, fungi, animals and birds, plants),

some medicines and allergens of the chemical industry. The accuracy of the diagnosis is determined by the sensitivity and specificity of the method, which vary depending on the chosen immunochemical method, the quality of reagents used, as well as the quality of recombinant allergens or allergenic extracts. For all test systems, the sensitivity is determined in the range of 60-95%, and the specificity is determined in the range of 30-95%, which depends on the test systems used [29, 30]. Despite the fact that test systems used in the Russian Federation and abroad allow detecting the trigger factor responsible for triggering IgE hyperproduction, the unjustified appointment of a large number of tests can mislead a specialist, since many allergens cause the development of cross-allergic reactions and, accordingly, distort the patient's sensitization profile. In addition, with an increase in the list of allergens that can lead to the appearance of clinical symptoms of allergies, the cost of research increases [31]. In addition, it should be borne in mind that taking blood from a vein for serological examination is a stressful situation, especially for a child, and may not always be performed or not in full. This determines the need to find effective methods and diagnostic approaches that allow not only to minimize the patient's blood volume required for analysis, but also to reduce the number of tests by identifying prognostic markers that allow us to quantify the level of sensitization of the body to a wide range of allergens.

The role of component-separated diagnosis of allergic diseases in the choice of therapy Component-separated allergodiagnostics appeared relatively recently. The term refers to diagnostic tests that detect antibodies (IgE) to specific allergenic molecules recombinant or isolated from natural sources. Extracts of natural allergen sources contain a large set of proteins with various immunogenic properties. The presence of many proteins with allergenic properties in the composition of an animal or plant product requires an accurate determination of the causal factor both for selecting adequate therapy and for creating a prognosis of the disease and the risk of cross-reactions [4, 6]. Assessment of how primary sensitization is or whether there is a result of cross-reactivity with proteins with a similar structure, helps physicians determine a patient's risk of developing clinical symptoms when exposed to cross-reactive allergens [30] and increase the specificity of testing [32].

Component-separated diagnostics allows you to identify individual proteins that are present in the whole extract of allergens, and determine what exactly they cause sensitization of the patient. Thus, in the work of M. L. Sanz et al. It has been shown that the detection of IgE to casein and ovomucoid in a child, or, conversely, their absence, helps to "predict" whether the patient will develop tolerance to cow's milk or egg consumption in the future [32]. The use of molecular allergology methods allowed us to develop an approach for assessing the risk of severe systemic reactions. If the patient is found to have IgE to plant lipid transport proteins, it may indicate a high risk of anaphylaxis when exposed to food containing these allergens [33]. At the same time, the detection of sensitization to food toxins can determine the risk of developing an allergic reaction in contact with plant pollen (for example, wormwood, timothy, birch) [34]. Work by L. Masthoff et al. It has been demonstrated that sensitization in patients to hazelnut Cor a9 and Cor a14 proteins is a predictor that patients are highly likely to experience severe allergic reactions when eating hazelnuts [35]. In 2010, a group of British researchers reported that the presence of antibodies to Aga h2 in children of the same age is the best marker of persistent peanut allergy and the inability to achieve tolerance to this food product in the future compared to patients who had antibodies to other allergic components of peanuts [36]. In a study by C. Constantin et al. using component-separated diagnostics with recombinant allergens of wheat grains and pollen, it was demonstrated that it is possible to differentiate food allergies to wheat, "baker's asthma" and allergies caused by grass pollen [37]. Cross-reactivity between allergens from different plants contributes to the ability of any single allergen to trigger an IgE-induced response to a range of allergens in one or more different

geographical and / or climatic regions. Patients sensitized to birch pollen, for example, often show a positive response to testing with allergens from other trees of the Betulaceae family (Birch), as well as with allergens from the Fagaceae family (Bucaceae). Such polysensitization is often caused by the body's cross-reaction to Bet v1 family proteins [38]. An important feature of sensitization of patients to pollen allergens is that allergic reactions often develop, including when consuming food products of plant origin [38]. As a rule, food allergies that develop against the background of pollinosis are caused by eating raw fruits, vegetables, nuts, and some spices. IgE-mediated allergic reactions develop due to the existence of cross-reactivity between pollen and food allergens, which are homologs and have a similar protein structure [38]. To determine the probability of a patient developing clinical symptoms of food allergy with pollinosis, the component-divided allergodiagnostics also allows. In some cases, however, there may be latent or clinically insignificant sensitization to plant foods, in which the presence of IgE is not clinically manifested.

Thus, component diagnostics (detection of sensitization to allergicomponents) can identify or establish the mechanism of cross-allergic reactivity between allergens, assess the probability of systemic reactions, tolerance or, conversely, food intolerance, select an adequate elimination diet for the patient, choose treatment tactics and select adequate components for specific immunotherapy.

Development of a diagnostic algorithm In connection with the considered features of allergy diagnostics, our goal was to substantiate an algorithm that would solve the problem of optimizing the diagnosis of allergic diseases and reduce its cost. In other words, it would help the clinician, on the one hand, make a choice about the group of allergens that they suspect as triggers for IgE hyperproduction, and on the other hand, minimize the cost of performing the study. To select the optimal diagnostic algorithm, we analyzed world experience [39, 40], studied and summarized the results of prospective research projects (GALEN, MeDALL) [2, 41], analyzed the results of our own research [42-44], and took into account federal clinical guidelines for allergy diagnosis [40]. Our step-by-step approach includes five stages of research. At each stage, it is expected to conduct an in-depth assessment of the results obtained, analyze them and determine the feasibility of further steps. Each stage implies the possibility of achieving a result sufficient for the patient to make a final diagnosis and identify a causally significant trigger of allergic reactions. The algorithm diagram is shown in Fig. The first step of allergy diagnosis in the proposed algorithm is conservative and involves collecting the patient's medical history. At this stage, the doctor directly conducts a dialogue with the patient, finds out his complaints and clinical symptoms of allergies, collects an anamnesis of the disease, and finds out the hereditary nature of the disease. Further diagnostic steps involve identifying the causal factor that caused the development of allergy symptoms. For this purpose, the patient is assigned testing, which includes certain sets of tests or test panels. The choice of allergens for the test panels was determined based on data on the prevalence of sensitization to a particular allergen, the significance of various allergens as trigger factors for allergic reactions [39-44]. It is suggested that at the second step of the diagnostic search, the doctor selects a specific module, i.e. a set of allergens, and this choice is based on an individual approach to the patient: finding out the nature of symptoms (aeroallergens or allergens associated with food intake, seasonal or year-round). Establishing the presence of respiratory, skin or combined manifestations of allergies determines the direction of further search. Thus, the rationale for choosing test panels for the second stage of diagnosis is based on the doctor's identification of clinical symptoms of allergy and careful collection of the patient's medical history. However, despite the fact that many studies have been published describing the contribution of certain allergens to the development of asthma or pollinosis [26, 27], there are no uniform recommendations prescribing the use of certain sets of allergens. We summarized the accumulated data and came to the conclusion that all allergens have a hierarchical value, i.e. the probability that this particular allergen is causally significant. Thus, among respiratory

allergens, the most relevant allergens are tree pollen (primarily birch, alder, hazel) [48], grasses (primarily hedgehog, meadow timothy) [42], weeds (most often allergens of wormwood, ragweed, dandelion) [31], cat and dog epidermal proteins, and mold fungi (Cladosporium herbarum, Alternaria alternata). An important role in the selection of allergens for testing is played by the presence of seasonality of clinical symptoms in the patient. It is shown that the most significant allergens responsible for the development of symptoms of allergic rhinitis, rhinoconjunctivitis, and bronchial asthma, which are seasonal in nature, are the allergens of birch (t3), meadow timothy (g6), wormwood (w6), and mold fungi — C. herbarum (m2) and A. alternata (m6). These allergens in combination with the determination of the total IgE level formed a screening set of the second step of diagnostic search for patients with signs of seasonal respiratory allergies. The third step of diagnosis for patients of this group involves an in-depth examination of them with allergens that are predominant in a certain period of the year-in spring or summer. At the same time, for the diagnosis of allergies in patients with respiratory symptoms, but with no pronounced seasonality of the disease manifestations, an approach was proposed that takes into account the determination of antibodies to both pollen plant allergens and mold fungi, as well as household and animal allergens. Considering the importance of respiratory allergens in the development of sensitization, it should be noted the extreme importance of allergens from house dust mites, mold fungi and animals in the development of allergic diseases in both children and adults. Allergens of house dust mites are among the most important causal factors in the development of bronchial asthma [42], and also in some cases play a role in the development of atopic dermatitis [33], with D. farinae (d2) and D. pteronyssinus (d1) being the most significant. Among patients with allergies, from 5 to 30% are sensitized C. herbarum and A. alternata are most important in the development of moderate and severe forms of bronchial asthma, and depending on the region of residence, from 30 to 80% of patients with bronchial asthma are sensitized to at least one type of mold [54]. Allergens of animals, especially cats and dogs, are also among the most important in human life: sensitization to them is most often expressed in the form of symptoms of rhinitis, conjunctivitis, and asthma [55]. About 60-70% of patients with pet allergies are cosensitized to several animals: the presence of common antigenic determinants of the main allergens of cats and dogs explains the frequent association of allergies to these animals [56]. Due to the high frequency of allergic reactions caused by these allergens, it is extremely important to include them in test panels at an early stage of diagnosis in order to be able to detect sensitization of the patient and prevent further progression of the disease and expand the spectrum of trigger allergens. As a module (set of allergens) for the second step of diagnosis of patients with respiratory allergies that do not haveThe module "inhalation screening" in combination with the determination of the total IgE concentration is proposed. This screening module is not limited to pollen and fungal allergens, but also includes household and epidermal antigens. If further examination is necessary, extended allergen kits are offered for the third diagnostic step. A different picture is observed for patients with food allergies or atopic dermatitis. If patients have symptoms of allergies caused by the ingestion of allergens through the gastrointestinal tract, the question becomes relevant, which allergens from the number of people used by the patient are suspected as triggers of an allergic reaction. Various studies have shown that food allergies and atopic dermatitis are most often caused by sensitization to allergens of the so — called Big Eight-cow's milk proteins, egg white, peanuts and nuts, fish and seafood, soy, cereals. According to various publications, the prevalence of food allergies to food products in children in the general population ranged from 1.2 to 17% for milk, from 0.2 to 7% for eggs, and 0-2% for peanuts and fish [39, 40, 57]. In this regard, after the first diagnostic step, when the doctor detects skin symptoms of allergies or suspects a link between gastrointestinal disorders and food consumption, the following set of tests was proposed for the second step of allergy diagnosis: determination of the total IgE concentration together with a

diagnostic screening module, which includes the following allergens: f2 — milk,f2-milk, f2-milk, f2-milk, f2-milk, f2-milk, f2-milk, f2-milk, f2-milk, f2-milk, f2-milk, f2-milk, f2-milk, f2-milk, f2-milk, f2-milk, f1 — egg white, f3-fish, f27-beef, f4-wheat, f7 — oats, f14-soy, f92-banana, f49-apple. In addition to the previously mentioned important allergens of cow's milk, egg, fish, wheat, soy, the module is supplemented with allergens of beef, banana, and apple. Their inclusion in the diagnostic screening panel is due to the high frequency of sensitization to these allergens in the population, their significance in the development of cross-allergic reactions [39, 42]. At the same time, as a child grows up, they are exposed to a wide range of proteins, many of which also play an important role as triggers of allergic reactions. According to the works of J. Kwon et al. and R. Kumar et al., the number of foods that trigger allergic reactions increases in older children [39, 40], and it has also been shown that the frequency of allergic reactions to vegetables and fruits, fish, and seafood increases with age. As a result of the analysis of available foreign and own data, for patients with clinical symptoms that develop after contact with food, five test panels with food allergens were proposed, selected depending on the patient's age, which formed the third step of diagnosis.

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If the patient has symptoms of both respiratory and food allergies, for the second step of diagnosis, the joint use of the screening modules "food allergens screening" and "inhalation screening", as well as the determination of the total level of IgE, was proposed. If there is a need for further diagnostic search in the case of a positive response to screening or the need for an extended examination at the third stage of diagnosis for mixed symptoms, it will be relevant to use both types of test panels: panels of inhaled allergens (plant, household, animal) and panels of food allergens that are most relevant for each age range. At the same time, the allergen sets offered in the modules and panels certainly do not reflect the entire spectrum of allergenic proteins found in nature. Despite the fact that the proposed panels take into account possible cross-reactions to various allergens, such allergenic molecules remain, the frequency of sensitization to which among the population, including children, is low. Thus, in the absence of detection of an obvious trigger of an allergy or if it is necessary to determine not only a group of cross-reactive allergens, but also each individual protein separately, there is a need for the fourth step of diagnosis. The fourth step involves performing serological tests using those allergens that were not previously included in the test panels (depending on the selected search direction). Thus, sensitization to rare allergens or allergens that are not typical for the patient's region of residence is detected. However, in addition to the obvious diagnostic role of tests that determine IgE concentrations to whole allergenic extracts, world researchers emphasize the role of component-separated diagnostics. Thus, the determination of the level of antibodies to the main birch allergen in early childhood allows us to determine the probability of developing sensitization to birch pollen in adulthood [58], and the detection of IgE to the cat's Fel d1 and dog's Can f1 allergocomponents is an important predictor of cross-reactivity [41]. Thus, with the proper technology and equipment of the laboratory department, the fifth stage of the study is possible, during which molecular diagnostics is performed, i.e. the determination of IgE not to whole allergenic extracts, but to its individual components. This approach is relevant for detecting cross-allergic reactions in a patient, selecting therapy, including allergen-specific immunotherapy, and evaluating its effectiveness.

Conclusion The generally accepted algorithm of diagnostic search for the subsequent appointment of adequate therapy currently consists in collecting a medical history of the disease, a patient's life history, a physical examination, establishing the patient's genetic predisposition to allergies, as well as conducting laboratory and instrumental examination methods [4, 6].

Identification of allergen-specific IgE in a patient and establishing a link between their presence and clinical symptoms are among the key iv vitro diagnostic methods.

Many current clinical guidelines regulate the activities of doctors working with patients with allergic diseases, in most cases accompanied by the appearance of specific IgE to a causally significant allergen/allergens. Most of these recommendations focus on the interaction between the doctor and the patient. At the same time, the procedure for applying instrumental diagnostic methods and the approach to choosing these methods are much less described. However, it is noted that the presence or absence of a reaction to a particular allergen (or the detection of a corresponding SiGe) can only be interpreted in the context of anamnestic data. At the same time, the decision on which laboratory tests should be prescribed to the patient, which allergens should be considered the most priority, remains at the discretion of the doctor. At the same time, the list of allergens to which it is possible to determine the level of SiGe is extremely large and continues to expand, there are new unique tests that allow detecting antibodies to individual components of the allergenic extract. The proposed algorithm takes into account both the age-related characteristics of patient sensitization and relies on a detailed study of the patient's medical history and clinical symptoms of allergy. Step-by-step testing allows you to exclude an excessive number of assigned tests and leave the most relevant ones with the greatest predictive significance. Each diagnostic step requires a thorough analysis of the results obtained, and the transition to the next step requires justification for such a decision. Knowing the cross-reactivity between allergens allows you to minimize the number of tests prescribed. This approach is most relevant for patients with multiple allergy symptoms that affect more than one system, but several, when identifying a causal trigger is particularly difficult. The principles of allergen selection for each step of the developed algorithm are consistent with the results of international research, in particular, on the relevance of different allergens in different age periods, the expansion of the spectrum of sensitization with age, and the significance of sensitization to respiratory allergens in food allergies.

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