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ALLERGOLOGY AND IMMUNOLOGY IN PEDIATRICS

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The aim of this journal is to promote and maintain professional contacts and interactions between basically and clinically oriented allergologists and immunologists. This journal is the official organ of the Association of Pediatric Allergists and Immunologists of Russia (APAIR). «Allergology and Immunology in Pediatrics», founded in 2003, is devoted to the wide spectrum of interests of the pediatricians, allergists and immunologists in clinical practice and related research. As the journal intends promoting productive communication between scientists engaged in the basic research and clinicians working with children, both experimental and clinical research related findings are accepted for publication. The regular format of the Journal includes original articles, concise communications, case reports, discussions, comprehensive reviews, book reviews, correspondence, news, recent advances in clinical research, and selected APAIR proceedings. The Journal also presents Selected Abstracts from other periodicals in related disciplines. Areas of interest also includes but not limited to the evaluation, management and prevention of allergic and other immune-mediated diseases with a special attention to the pediatric allergy and asthma. Furthermore, new sections and activities focusing on the continuing medical education will be introduced shortly. «Allergology and Immunology in Pediatrics»is published quarterly (4 volumes per annum). The journal was founded in 2003. From 2003–2004 it was called Scientific and Practical Journal of Allergology and Immunology in Pediatrics. From 2004 to the present time it is called «Allergology and Immunology in Pediatrics». The journal is published 4 times a year.

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Annotation
The Document contains fundamental provisions regarding allergen -specific immunotherapy in children. International clinical recommendations on the methodology were used, adapted for use in real practice.In the absence of international recommendations, the authors present the consensus opinion of the project participants, based on data from clinical studies in this area. At the moment, we bring to your attention a position paper on allergen-specific immunotherapy in children, created by experts from the Association of Pediatric Allergologists and Immunologists of Russia (APAIR) based on the 2021 consensus document, with the necessary data updates.
Keywords: allergen-specific immunotherapy, children, consensus document.

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Аллерген-специфическая иммунотерапия у детей. Согласительный документ Ассоциации детских аллергологов и иммунологов России (позиционная статья)

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Статья прошла двойное слепое внешнее рецензирование.

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Аннотация

В Документе содержатся принципиальные положения, касающиеся проведения аллерген-специфической иммунотерапии у детей. Использованы международные клинические рекомендации по методике, адаптированные для применения в условиях реальной практики. В случае отсутствия международных рекомендаций авторами представлено консенсусное мнение участников проекта, основанное на данных клинических исследований. В настоящий момент мы предлагаем вашему вниманию позиционный документ по вопросам аллерген-специфической иммунотерапии у детей, созданный экспертами Ассоциации детских аллергологов и иммунологов России (АДАИР) на основе согласительного документа 2021 г., с необходимыми обновлениями данных.

Ключевые слова: аллерген-специфическая иммунотерапия, дети, согласительный документ.

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Allergen-specific immunotherapy (ASIT) was offered more than 100 years ago and showed its effectiveness in the therapy of diseases, mediated by specific class E antibodies (IgE). The evidence base of ASIT efficiency and safety is supported by the results of current research of the highest level and continues to be replenished with. At least one third of reports are dedicated to various aspects of ASIT use at congresses of European and American Academies of Allergy. ASIT is the only method, which can change the course of allergic disease towards remission. Nevertheless, a very small percentage of patients with allergic disease of IgE-dependent type and confirmed sensitization to pollen, household and other kinds of allergens receive this type of treatment.

The benefit of the national allergology is the existence of the school, founded by Academician Andrey Dmitrievich Ado. Our teachers and mentors managed to achieve major breakthrough in the field of allergology and immunology in the 70–80s of XX century. Allergy service was built at a high level in the Soviet Union, and ASIT was applied to a larger number of patients. Nowadays the slow advent of modern allergy vaccine in our market predetermines limited therapeutic options for the allergist-immunologist, not to mention that the process for the creation of own modern allergen drugs is just getting underway in our country.

ASIT HISTORY

ASIT history is 110-year-old way from empirical knowledge to evidence-based medicine. Leonard Noon is called ASIT father, who successfully tested pre-season subcutaneous injections of pollen extracts in increasing doses to treat hay fever, calling the method “preventive vaccination” [1]. R. Cook suggested using extracts of animal dander, food and insects for treatment as well as developed a method used to standardize allergens extracts with the Kejldahl method to determine PNU (protein nitrogen units), which was widely used in the world up to the 1980s, and it is applied in Russia even now [2]. In his works D. Freeman offered expedited ASIT schemes and described adverse local and systematic reactions [3]. Since the beginning of XX century, apart from the classical method of subcutaneous injection, intradermal, intralymphatic, oral, sublingual, nasal, conjunctival methods of ASIT have been actively investigated [4].

Allergen extracts were replaced by allergoids in 1970, improving the efficiency and safety of ASIT. Formaldehyde, glutaraldehyde and polyethylene glycol were used for allergen chemical modification. Physical modification of allergens was carried out using aluminum hydroxide, calcium salts and L-tyrosine. A new milestone in allergology was the creation of recombinant allergens in the late 1980s.

The great merit in forming and developing ASIT method belongs to the USSR allergists. Under the leadership of academician A. D. Ado the production of therapeutic and diagnostic allergens was organized and ASIT methods were developed, being used today [5, 6]. Led by the corresponding member of RAS, Professor I. I. Balabolkin, the school of Pediatric Allergology was established, applying ASIT with non-infectious and infectious allergens in patients with bronchial asthma (BA), allergic rhinitis (AR), atopic dermatitis (AtD) as well as the scheme of sublingual administration of water-salt allergen extracts was developed. The works of Dr. of Sci Yu. S. Smolkin in the 90s of the XX century showed the comparative efficacy of subcutaneous and sublingual methods of ASIT. In current years the evidence base on ASIT efficacy with various allergens is updated, the mechanisms of the method acting and interesting aspects of ASIT effect are investigated, first of all, a disease-modifying prolonged effect and possibility to prevent progression in patients with BA.

MECHANISMS OF ALLERGEN-SPECIFIC IMMUNOTHERAPY

1. ASIT is the method of treating allergic diseases, aimed at building immunological tolerance to certain allergens.
2. The multifaceted mechanism of ASIT action involves humoral (production of blocking antibodies) and cellular (stimulation of cell proliferation and differentiation of regulatory cell subpopulations) mechanisms of the immune response.

ASIT acts as humoral (production of blocking antibodies) and cellular (stimulation of cell proliferation and differentiation of regulatory cell subpopulations) mechanisms of the immune response that provides for the suppression of allergic inflammation in the tissues of target organs. In the first weeks of using ASIT there is a transient increase and then decrease in the level of specific IgE blood serum without any connection with symptoms of the disease. In 4–6 weeks from the start of treatment there is an increase in concentrations of specific blocking antibodies of Class IgA and IgG (subclasses 1–4) [7]; it results in oppression of effector cells (mast cells, basophiles, eosinophils) [8]. Due to deactivation of effector cells, there is a reduction in the secretion of a wide range of mediators and cytokines that prevents further stimulation of type 2 T-helpers, eosinophils, etc. ASIT mechanisms affect both phases of the allergic response — early and late. Tissue specific response to allergen is inhibited, in particular by increasing sensitivity threshold to histamine [9].

The intake of therapeutic allergen suppresses cells, polarizing the immune response towards allergic inflammation, in the part of innate immunity (type 2 innate lymphoid cells (ILC2)) as well as in the adaptive one (Th2 and Th17 cells) and reduces their production of T2 cytokines [8, 10]. ASIT stimulates tolerogenic subpopulations of dendritic and congenital lymphoid cells and also induces allergen-specific regulatory T cells (Treg) and B cells (Breg), whose combined work is most important for creating immunological tolerance, realized through tolerogenic cytokines (interleukin 10 (IL-10)), interleukin 35 (IL-35), transforming growth factor beta (TGF-β) and etc.) [7, 8, 11]. Treg perform early suppression of effector cells, suppression of inflammatory dendritic cells, ILC2, Th1, Th2, Th17, contribute to Breg formation.

ASIT efficiency (formation of tolerance) depends both on endogenous and exogenous factors; the type, method and amount of allergen administered have the greatest impact [12].

IMMUNOLOGICAL FEATURES OF INDUCED TOLERANCE IN CHILDREN

1. ASIT is a generally accepted method of treating IgE-mediated allergic rhinitis and asthma in patients over 5 years; the use of this method at an early age in the conditions of emerging immunity and tendency to Th2 responses is not studied enough yet.
2. Accumulating evidence indicates a relatively high clinical efficacy and safety of subcutaneous and sublingual immunotherapy in AR and BA in pediatric practice, however, there remains the necessity for additional research to confirm the effectiveness and long-term clinical benefits of using ASIT in children, especially at an early age.
3. There is evidence of ASIT preventive effect in children: the possibility to prevent the debut of BA in patients with AR, caused by tree and grass pollen, at least for the first two years after the end of ASIT.

ASIT is widely used in children, though the efficacy of this method in the conditions of the developing immunity and tendency to Th2 responses is being discussed.

Clinical recommendations and consensus documents define the age of 5 years and older as optimal for the possible start of ASIT. This is due,

first of all, to the characteristics of maturating an immune response in young children. It is known that the maturation of the immune system is most active during the early years and directly related to the effects of many infectious and non-infectious factors on the baby's body.

Peculiarities of implementing innate immunity mechanisms and a low functional activity of local immunological reactions in the first years of a child's life might cause not only high susceptibility to infectious diseases, but also imperfection of processes of tolerance formation [13]. The most important features of the immune response in young children are associated with functional immaturity of T cell component, prevalence of Th2 responses and low production of Th1 and Treg cytokines (IL-10, TGF-β), insufficient ability to differentiate B lymphocytes, effective antibody response (in particular, production of IgG and IgA) and the formation of immunological memory.

These features are exacerbated in children with atopic diseases due to further immune polarization towards Th2 response [14].

Nevertheless, a relatively high clinical efficacy and safety of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in AR and BA in children indirectly indicate the identity of immune response mechanisms to ASIT in adults and children. Moreover, only patients under 18 show preventive effect of SCIT and SLIT on BA debut in patients with allergic rhinitis [15].

ALLERGEN STANDARDIZATION

1. There are no common rules of standardizing allergens. There is no correlation and conversion formulas between different units of allergenicity.
2. Allergens, standardized in the biological way, are preferable.
3. The standardized drug must contain the basic major allergen proteins, however, such requirement in Europe should apply only to allergens of birch and timothy grass.
4. Standardized drugs of one manufacturer have a stable composition and reproducibility between series.
5. The result of clinical studies of therapeutic allergen can be fully applied only to a particular drug.

Allergen standardization is the expression of its allergenicity in common units in order to estimate its activity, risk and intended benefit of using as well as to prevent the emergence of drugs of inadequate quality. In contrast to chemotherapy drugs, it is impossible to standardize biological extracts only by their mass as the therapeutic allergen activity strongly depends on usefulness of raw extract and the degree of contamination of other proteins. The control of protein mass does not guarantee the preservation of allergen epitopes and drug immunogenicity [16]. Stages of allergen production are regulated by articles of the State Pharmacopoeia of the Russian Federation. It is easier to get a stable extract from pollen than from epidermal and fungal allergens. Mites require industrial cultivation as making extract from house dust leads to substrate contamination by various impurities [17]. Extracts from animal hair do not contain the whole range of protein molecules that cause symptoms, for instance, it is difficult to reach a stable concentration of prostatic dog arginase in the allergen of its epidermis [18].

Manufactures and regulators could not come to an agreement about using a unified methodology of standardization. In 2001–2008 during the CREATE project there was the study of 9 major allergens (Bet v 1, Phl p 1, Phl p 5a и Phl p 5b, Ole e 1, Der p 1, Der p 2, Der f 1, Der f 2) by which standardization of therapeutic drugs was expected. Nowadays the European Pharmacopoeia regulates the contents of only Bet v 1 and Phl p 5 [19]. The concentration of other major allergens in drugs is controlled by the manufacturer's internal quality standard. Content and activity of allergens in drugs must be in the range of 50–150% of the declared one.

The USA requires to express activity of all drugs in local units. Erythema d = 50 mm after intradermal administration of 0.05 ml of the solution is taken as reference D50 (or 100 000 BAU/ml). 19 allergen extracts have been created, which therapeutic allergens are compared with.

All the designations on medical allergens in the Russian Federation are based on the internal standards of their manufacturers. The vast majority of drugs pass biological tests after laboratory standardization. Stallergenes Greer for 100 IR (IR — standardization

unit, reactivity index) take a positive skin test d = 7 mm. ALK use standardized quality units SQ-U, based on data on the efficacy of the drug in clinical studies [20]. There is no direct comparison of drugs for ASIT as well as "coversine rates". The instructions do not specify the number of major allergens, despite standardization on the content of essential proteins in the production. A domestic producer applies standardization on PNU without the use of biological techniques that may lead to differences in the activity of the drug in each series [21].

Nowadays questions of allergen standardization are not fully solved. It is not clear what dose of the allergen leads to an optimal development of tolerance as standardization units of different manufacturers are not comparable. Standardization on major components should solve some of the problems, however, the protein weight does not indicate its preserved structure and biological effects. The key indicator of the drug suitability for ASIT is sufficient clinical trials on a specific drug in the certain dosage according to the standardization, applied by its manufacturer.

REVIEW AND CLASSIFICATION OF THERAPEUTIC ALLERGENS

Drugs with registration in Russia are recommended for use, and strict adherence to the drug instructions is required.

Drugs, available in Russia, are made from natural raw materials and produced for parenteral (subcutaneous) and sublingual use (see Table 1). In accordance with the legislation, the use of drugs, not registered in the regulatory documents of the Ministry of Health of the Russian Federation, is prohibited.

Therapeutic allergens of mold and epidermis of animals, insect poisons are not registered in Russia.

Allergens are drugs, obtained by extraction and purification of natural raw materials.

Allergoids are drugs from chemically modified protein molecules of the allergen. Allergoids cause fewer adverse reactions which is especially important in parenteral administration, however, there may be severe systemic reactions on allergoids. Allergoids are impossible to use for skin tests with a diagnostic purpose.

Injectable drugs for SCIT are presented in the form of water-salt solutions of allergens, allergoids and allergens, repository on the dosing vehicle. Repository provides a slower allergen release from the injection site, which increases safety; nevertheless, there may be anaphylactic reactions after applying similar allergens. Water-salt extracts are used on preseason scheme, they are prescribed a few months before bloom and canceled not less than 2 weeks before the flowering period of cause significant plant. The indisputable advantage of repository forms is the possibility of their use on a year-round scheme (reducing the dose during the bloom of causal plant) and administration at the stage of maintenance of doses at intervals once in 4–6 weeks that simplifies conducting therapy and has almost no effect on the patient's social activity.

Table 1. **Drugs for ASIT registered in Russia***
Таблица 1. **Препараты для АСИТ, зарегистрированные в России****

Group of allergens	Name of drug	Characteristics
Dust mites *Dermatophagoides*	Dust allergen for diagnosis and treatment (FSUC "SIC "Microgen")	SCIT
	Mite allergen *Dermatophagoides pteronyssinus* for diagnosis and treatment (FSUC "SIC "Microgen")	SCIT
	Acarizax® (ALK-Abello A/C)	SLIT (*D. pteronyssinus* et *farinae*)
	LAIS Dermatophagoides (Lofarma S. p. A.)	Allergoid, SLIT (*D. pteronyssinus* et *farinae*)
	Staloral "Mite allergen" (Stallergenes Greer)	SLIT (*D. pteronyssinus* et *farinae*)
	Alustal "Mite allergen" (Stallergenes Greer)	SCIT, repository (*D. pteronyssinus* et *farinae*)
	Allergoid from house dust for treatment (FSUC "SIC "Microgen")	Allergoid

Table 1. **Drugs for ASIT registered in Russia***
Таблица 1. **Препараты для АСИТ, зарегистрированные в России****

Birch and trees of order Fagales	Staloral "Allergen of birch pollen" (Stallergenes Greer)	SLIT
	Fostal "Allergen of tree pollen" (Stallergenes Greer)	SCIT, repository, alder, birch, hornbeam, hazel
	Itulazax® (ALK-Abello A/C)	SLIT
	Mixed allergen from tree pollen for diagnostics and treatment (FSUC "SIC "Microgen")	SCIT
	Mixed allergoid of pollen alder, birch, hazel for treatment (FSUC "SIC "Microgen")	SCIT, allergoid
European ash (Fraxinus excelsior)	Allergen from European ash pollen for diagnostics and treatment (FSUC "SIC "Microgen")	SCIT
(meadow) grasses	Allergen from pollen for diagnostics and treatment (each as a monotherapy): • timothy meadow • herd grass (*Agrostis alba*) • meadow brome (*Bromus erectus*) • bluegrass (*Poa pratensis*) • flint corn • cocksfoot • cereal ruttishness • English ryegrass • common foxtail (FSUC "SIC "Microgen")	SCIT
	Grazax (ALK-Abello A/C)	SLIT, lyophilisate, timothy hay
	LAIS Grass (Lofarma S. p. A.)	Allergoid, SLIT, sift grass, timothy hay, bluegrass
	Oralair (Stallergenes Greer)	SLIT, gramen, spikelet, cockle, bluegrass, timothy hay
	Alustal "Allergen of meadow grass pollen" (Stallergenes Greer)	SCIT, repository, gramen, spikelet, cockle, bluegrass, timothy hay
	Pollen allergoid (each as a monotherapy): • timothy grass • cocksfoot • meadow fescue grass (FSUC "SIC "Microgen")	Allergoid, SCIT
	Mixed allergoid of pollen gramen, fescue grass and timothy hay for treatment (FSUC "SIC "Microgen")	Allergoid, SCIT
Weeds (different families)	Allergen from pollen for diagnostics and treatment (each as a monotherapy): • ragweed • absinth sage • milk-witch gowan • common sunflower (FSUC "SIC "Microgen")	SCIT
	Pollen allergoid (each as a monotherapy): 1. absinth sage 2. ragweed (FSUC "SIC "Microgen")	Allergoid, SCIT
	Ragwizax® (ALK-Abello A/C)	SLIT, lyophilisate, ambrosia
	Mixed allergen from pollen of weeds and sunflower for diagnostics and treatment (FSUC "SIC "Microgen")	SCIT, ambrosia, quinoa, wormwood, sunflower

* https://grls.rosminzdrav.ru, access time 08.06.2023

** https://grls.rosminzdrav.ru, время доступа 08.06.2023

In Russia drugs for SLIT are presented as a solution for sublingual taking, pills with the allergen/allergoid, absorbed on microcrystalline cellulose and lyophilized rapidly dissolving pills. All these dosage forms provide an effective release of the allergen in the oral cavity where it penetrates through the mucous membranes and is captured by macrophages. Drops can be flexibly

dosed in the tolerability, however, they require compliance with the storage conditions and taking is associated with low compliance and failure probability, spontaneous dose change. Pills are more convenient, but indivisible. In case of reactions after taking the allergen, the doctor needs to adjust therapy, constantly assessing the balance of "risks and benefits". The absence of certain "starting" doses with a reduced allergen concentration might increases risks of complications in highly sensitized patients. The advantage of lyophilizates over ordinary pills lies in their faster release [22].

Considering the provisions of EAACI consensus document, when conducting ASIT with pollen, it is possible to use the one of the "main" relevant plant in cases of patient sensitization to many plants of the same family, understanding, pollen will consist of homologous allergens [23]. As a rule, the main plant is most common, produces a large amount of pollen, contains main proteins of its group and causes symptoms in most patients [11, 24].

NEW AND PROMISING APPROACHES TO CONDUCTING ASIT

Approaches to ASIT optimization lie in changing route of allergen administration or changing allergen molecules for a safer and more effective application. It is proposed to use purer and more standardized extracts, recombinant allergens, allergen isoforms, oligopeptides of allergens, chimeras, fusion proteins, certain DNA vaccines, combinations with biological drugs, combinations with viral vaccines [25].

Alternatives routs of allergen administration: intralymphatic, epidermal, intranasal — aimed at improving the convenience of administration or optimization of the course (6–10 injections in intralymphatic route). Despite encouraging data on clinical efficacy, research of their lasting effect is needed [26].

There is promising vector technology of allergen carriage by viruses and the combination of major protein molecules with lipoproteins, boosting immune response. There is development of vaccines, consisting entirely of major recombinant allergens that allows to reach exceptional efficiency and stability of the drug, particularly in the case of difficulty in producing and purifying natural extracts [27].

In the Russian Federation the group of Academician A. V. Karaulov develops a recombinant vaccine to treat cat allergy. It is shown that Fel d 1 cannot adequately bind IgE serums, therefore, there is study of efficacy of recombinant vaccine, containing uteroglobin and lipocalin for a wider coverage of polysensitized patients [28].

Clinical practice uses ASIT in combination with monoclonal drugs to achieve control in patients, who have not got ASIT due to the severity of the condition, and to modify the immune response, when used together. In the first case, any biological drug might be used, however, issues of ASIT efficiency remain open. Data were obtained for dupilumab on the possibility of its combining with ASIT in AtD [29]. Studies of preliminary omalizumab administration at high risk of ASIT anaphylaxis to food allergens have given positive results in the allergen tolerance, possibility to increase its starting dose and to reduce the risk of adverse events (AE) [30].

Insufficient randomized trials have been conducted to say that new allergens or routes of administration have a significant advantage over classical subcutaneous and sublingual ones. ASIT, combined with monoclonal antibodies must have clinical perspectives. Current drugs of monoclonal antibodies do not contain similar indications for the use in the instruction.

ASIT SAFETY, ADVERSE EFFECTS, WAYS TO IMPROVE THE SAFETY

1. ASIT when conducted by a specialist-allergist in accordance with the instruction for the use is a safe method of allergy therapy.
2. The incidence of anaphylactic reactions in ASIT depends on the type of allergen, route and rate of its administration as well as the condition of the patient's body.
3. Severe reactions to the allergen might be delayed, therefore, patients need to be monitored after SCIT up to 60 minutes.
4. Sublingual ASIT is safer than subcutaneous one. Cases of anaphylaxis in ASIT are of a casuistic nature.
5. Patients with systemic responses to SCIT can be successfully transferred to sublingual protocol.

The risk for severe reactions is considered one of the main ASIT drawbacks, especially exacerbations of asthma and anaphylaxis [31].

Adverse events of ASIT can be local and systemic. Local reactions are common both in SCIT (erythema, itching, induration and swelling at the injection site) and SLIT (oropharyngeal itching and (or) edema).

Systemic AE are more commonly associated with SCIT. Systemic adverse events occur less frequently in children than in adults.

AE, requiring discontinuation of therapy or significant dose adjustment, drug change or route of administration, include: anaphylaxis, reactions, requiring the use of epinephrine, severe edema of pharynx and oral cavity, eosinophilic esophagitis, severe exacerbation of BA.

Particular attention should be paid to the fact that 72.4% of all systemic responses are delayed and occur 30 and more minutes later after the allergen administration [32]. It is necessary to review guidelines in the direction of extending the follow-up period after the allergen administration and a mandatory adequate patient instruction.

A favourable safety profile of ASIT is due to the peculiarities of sublingual capture and allergen processing. Allergens penetrate through the mucous membrane, where are captured by tolerogenic antigen-presenting cells, after which there is allergen introduction for recognizing by T lymphocytes [33]. In the absence of damage and inflammatory process, systemic penetration of the allergen and its recognition by mast cell receptors are less probable in the tissues of the oral cavity [33]. Subcutaneous administration route is associated with a greater risk of the allergen contact with circulating pro-inflammatory basophils and Th2 lymphocytes [32–34].

Patients, experiencing serious adverse reactions in SCIT, could potentially be transferred to SLIT [33].

Of particular interest are factors that increase risks of systemic responses and anaphylaxis, first of all, the dose of allergen and dose regimen. A dose-dependent effect is lower in SLIT, but there is a faster dosage adjustment in SCIT than it is recommended by the manufacturer; erroneous administration of increased dose of the allergen is associated with an increase in the frequency of anaphylaxis [11].

S2k guideline for ASIT, accepted by professional allergy associations of Germany, Austria and Switzerland, highlights the factors of developing systematic responses [35]:

1. allergy symptoms at the time of treatment, possible allergen exposure;
2. current infection;
3. mastocytosis; hyperthyroidism;
4. high sensitization rate;
5. inadequate increase in the dose of the drug in the initial phase of treatment; an allergen overdose;
6. administration of certain drugs (beta-blockers, angiotensin-converting enzyme inhibitors (ACE));
7. inadequate circulation load: excessive alcohol consumption, excessive physical exertion, visiting the sauna;
8. violation of the injection technique;
9. non-compliance with the manufacturer recommendations for reducing the dose when transferring to a new batch.

If there are indications, the recommended regimen of SCIT might be changed into a more sparing and cautious [36].

Oropharyngeal injections and lesions (ulcer, gingivitis, stomatitis) might be potential risk factors in SLIT due to possible systematic allergen penetration; on the other hand, it is not clear what effect immune responses have on the course of recurrent stomatitis during the allergen administration. Inflammatory diseases of the oral cavity contraindication for SLIT [11, 33, 35].

Risk patterns of adverse events in ASIT can be traced in connection with the type of therapeutic allergen used. The risk of systemic responses in ASIT is lower in patients with sensitization to dust mites (DM) and higher in pollen polysensitization (more than 3 allergens), higher for extracts of cereal grass pollen, compared to allergoids [31]. Extracts, containing stable proteins — "anaphylaxis molecules", and sensitization to minor proteins (usually coinciding with polysensitization) are associated with a higher risk of anaphylaxis. Such severe reactions are characteristic of immunotherapy with extracts of weeds, nuts and cereals.

AE treatment is carried out on the general principles, according to nosological form. Local AE can disappear on their own or with the use of antihistamines through the mouth. Non-life threatening angioedema can be relieved using systemic steroids once. Symptoms of BA (not as part of anaphylaxis) are relieved with the combination of inhaled bronchodilator and corticosteroid. In the presence of anaphylaxis criteria there is administration of epinephrine and treatment on algorithms of anaphylaxis cupping.

In Russia ASIT is carried out only by doctors allergist-immunologist, experienced in this type of therapy and capable to provide emergency relief with the development of an allergic reaction.

Allergist's offices should be equipped to provide necessary emergency assistance, and patients should be fully informed about the possible risk of adverse reactions, that should be documented. It is unacceptable to delay with epinephrine administration in the development of anaphylaxis [11]. Written informed consent for treatment must be obtained from patients, similar to the one, used for vaccination.

It is recommended to increase follow-up time up to 60 minutes after the allergen administration.

The use of drugs, which have passed biological standardization, safety and efficacy of which are confirmed in clinical studies, allows a relative confidence in the stability of the composition and activity of the allergen in the drug [11, 37]. It is necessary to evaluate the patient's condition before each injection [38].

CONTRAINDICATIONS TO ASIT

1. Conducting ASIT to the patient with relative contraindications justified if the expected benefit of treatment exceeds the possible risk of deterioration.
2. Prior to ASIT there should be spirometry and evaluation of dynamic peakflowmetry results in persons with BA throughout the treatment period.
3. The presence of autoimmune diseases is a relative contraindication to ASIT during remission and an absolute contraindication in the active stage.

Contraindications to ASIT can be absolute and relative. Conducting ASIT to the patient with a relative contraindication is justified if the expected benefit of treatment exceeds the possible risk of patient deterioration [37, 39, 40].

In 2015 EAACI published a position paper, presenting contraindications to ASIT [39]. There was no later revision of this document.

ASIT is not used under 2 years. In children from 2 to 5 years a decision can be taken on an individual basis, based on the child's quality of life and adherence to therapy. However, there are no drugs of therapeutic allergens in Russia, allowed for use in children under 5 years. No other age group is in itself a contraindication to ASIT [11, 39–41].

Absolute contraindications to ASIT [11, 37, 39, 40, 42–44]:

1. Severe or uncontrolled BA, forced expiratory volume in 1 second (FEV_1) is < 80% in children [11],
2. malignant neoplasms in the active stage,
3. autoimmune diseases in the active stage,
4. initiation of treatment during pregnancy,
5. poor compliance with treatment.

Relative contraindications to ASIT:

1. Partially controlled BA.
   Patients, experiencing severe or medically uncontrolled asthma, are at an increased risk of systemic responses by aeroallergens in ASIT (mainly in SCIT) [45]. Spirometry in necessary before starting ASIT. Before each injection patients with BA should be assessed for the disease control rate measured for peak expiratory flow. In the event that lung function has decreased more than 20% of the best individual value, the injection should be postponed even if these indicators meet age and race standards [36, 39]. There is no evidence that ASIT can exacerbate asthma severity or induce it de novo.

2. Immunodeficiency, HIV infection, taking immunosuppressants, anticancer agents, chronic infections.
   Each immunodeficiency has individual pathological mechanism, and in addressing the issue whether the patient should be treated with ASIT, the key feature is evaluating potential efficacy [39].

Some guidelines indicate concomitant treatment of patients with immunosuppressants as the contraindication to ASIT since these drugs might have a significant negative impact on the effectiveness of therapy.

HIV infection is a relative contraindication to ASIT. HIV infected patients, receiving antiretroviral therapy, can take ASIT in the early stages of the disease with the level of CD4 > 400 cells/mm and an undetectable viral load [39, 46]. Any stage C disease (according to CDC-classification of 1993) is considered absolute contraindications to ASIT [46].

Chronic viral infections (hepatitis B or C in remission) as contraindications to ASIT are not listed in the literature [39].

ASIT should be prescribed depending on patients' individual characteristics, considering states of immunodeficiency or the course of chronic infection as relative contraindications.

3. Psychiatric/mental disorder, impairing cooperation between doctors and patients.
   SLIT may be considered in a child with a mental disorder only if it is conducted with a controlling guardian [11, 39].

4. Autoimmune diseases in remission or organ-specific autoimmune diseases.
   Some guidelines consider the presence of autoimmune diseases a relative contraindication to ASIT, others — absolute. Controlled trials haven't identified an increased risk of autoimmune disease manifestation amid ASIT in patients with allergy. In case of developing an autoimmune disease, ASIT should be discontinued, and it shouldn't be prescribed to patients with autoimmune diseases in the active stage [39]. Hashimoto compensated thyroiditis against the background of drug therapy is not a contraindication to ASIT. In multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease the decision on ASIT can be made

on an individual basis in view of no disease activity [11, 40, 43, 47].

5. Chronic diseases.
Some concomitant diseases raise concern when considering the possibility of ASIT due to the lack of any specific information.
Cardiovascular disease in an unstable or progressive stage is a relative contraindication to ASIT with inhalation allergens. Before starting ASIT, there should be a careful evaluation (preferably with a cardiologist) of cardiovascular disease status, its therapy and the risk of anaphylaxis (requiring epinephrine use) [11, 39].

6. Malignant neoplasms.
Malignant neoplasms are considered absolute contraindications to ASIT. Long-term remission and the medical consultation with the oncologist allow to consider ASIT with strict indications and assessment of all risks.

7. Use of drugs.
Drugs of β-blockers, angiotensin-converting enzyme inhibitors and monoamine oxidase can change the effect of epinephrine in the development of anaphylaxis. The use of β-blockers in pediatric practice is limited to rare cases in rhythm disturbances and ophthalmologic pathology. If possible, β-blockers should be replaced by alternative drugs. If replacement is not possible, ASIT is allowed with careful assessment of risks and an individual dosage regimen [38, 40].

8. Severe form of atopic dermatitis.
In European guidelines ASIT might be considered as a potential treatment in patients with severe AtD, associated with other allergic diseases with sensitization to HDM, birch pollen, meadow grasses as well as epidermal allergens if contact with the allergen cannot be avoided [43, 48].

9. Eosinophilic esophagitis (EoE), chronic inflammatory gastrointestinal diseases.
According to statistics, EoE may occur in patients, with pollen allergy with the manifestation of oral allergy syndrome. SLIT is contraindicated in patients with diagnosed EoE [49]. There is increased risk of EoE in patients, receiving SLIT due to ingestion of the allergen and local contact with immune cells of the esophageal mucosa. SCIT prescription is possible in EoE remission [49]. SLIT is not used in patients with chronic inflammatory oral diseases [43].

10. Severe systemic responses to ASIT in anamnesis.
Documented episodes of anaphylaxis during SCIT are its contraindication [33, 43, 50]. Given higher safety of SLIT, there is an opinion that patients with severe adverse responses to SCIT can be shifted to SLIT [33].

11. Pregnancy.
ASIT initiation during pregnancy is contraindicated. If before pregnancy the patient has received and tolerated ASIT well, this type of therapy may be continued during childbearing (following all precautions) [39].

As temporary contraindications to ASIT, most guidelines consider acute infections of the respiratory and gastrointestinal tract, tooth extraction, oral surgery, exacerbation of allergic diseases [39, 40, 37, 43].

EFFICACY OF ALLERGEN-SPECIFIC IMMUNOTHERAPY

1. ASIT efficacy is proven in diseases, causally associated with sensitization to HDM and plant pollen.
2. There is plenty of evidence of ASIT effectiveness in AR, BA.
3. ASIT is not included to the standard of therapy in AtD, however, with a combination of AtD and allergic rhinitis therapy reduces symptoms of both diseases.
4. The minimum duration of therapy is 3 years. There is evidence of maintaining ASIT effect after the end of therapy.

ASIT WITH ALLERGY TO HOUSE DUST MITES

Indication for ASIT with HDM allergen is proven clinically relevant sensitization. The treatment is carried out according to the instructions, dosage depends on the method/form of therapeutic allergen release [51].

All HDM belong to the same group and have a similar structure. Particles of chitinous cover, faeces and eggs are sources of allergens. The predominant type is mites of the genus *Dermatophagoides* with 39 described allergens. Isolated sensitization to non-dermatoglyphic mites occurs only in 1.5% of cases, in others, it is combined with *Dermatophagoides*. Clinical efficacy and safety of ASIT is shown with the allergen of mites *Dermatophagoides* in children with BA and AR, in the presence of cosensibilization to mites *Blomia*, *Lepidoglyphus* regardless of the therapy method [52]. Apparently, this is due to the fact that despite standardization of therapeutic allergens on Derp (f) 1 and Derp (f) 2, they also contain other proteins, which may serve as a possible reason of efficiency in sensitization to other mite allergens.

ASIT with HDM allergen in BA is the only type of immunotherapy, included in the guidelines of Global initiative for Asthma, GINA. The Cochrane meta-analysis data show ASIT efficacy in children in terms of BA symptoms and a high safety profile of sublingual treatment method [53]. ASIT efficiency in children with AR is confirmed by a decrease in the severity of symptoms and reduced need for drug therapy [54].

Immunotherapy with HDM is an additional method of treatment in children with AtD and (or) combined with BA, AR it is recommended when there is a connection between exacerbations of the disease and allergen exposure [55]. ASIT with HDM drugs improves the course of AtD at any age, especially in monosensitization [56, 57].

According to guidelines, the optimal duration of ASIT is not less than 3 years. The clinical effect of ASIT with HDM allergen, when used in sufficient doses, develops after the first 6 months of therapy. It is possible to trace maintenance of the effect during 5–7 years after the end of ASIT [58].

Therapeutic HDM allergens for SLIT are produced in the form of drops (Stallergenes Greer) and pills, containing the allergen ("ALK-Abello A/C" manufacture) or allergoid ("Lofarma S. p. A." manufacture). Efficacy and safety of these drugs are shown in children of different ages with AR and AR, combined with BA [59–62].

ASIT with HDM allergen is effective against symptoms of BA, AR and AtD, caused by relevant allergens in children with mono- and polysensitization.

ASIT IN POLLEN ALLERGY

Pollen allergy is one of the most widespread types of hypersensitivity in children. The main manifestations of pollen allergy are AR (with conjunctivitis) and BA.

The Cochrane analysis by M. Abramson (2010) was among the first which showed SCIT advantage over placebo (27 studies) in pollen allergy [63]. The meta-analysis by Fortescue R. (2020), studying the effect of SLIT on BA, did not provide the division by the allergen type, however, SLIT had an advantage over placebo in the vast majority of studies [53].

Long-term practice as well as domestic studies have proven that SCIT with pollen allergoids and allergens of the Russian production is effective method of treating children with AR (rhinoconjunctivitis) and BA [64]. Pre-season course is used (the beginning of administration 4 months before flowering) in treatment with subcutaneous drugs of water-salt pollen allergens and allergoids. Allergen mixes are used with allergy to several allergens of the same group. Nevertheless, the dose of each allergen in the mixture is reduced that makes it difficult to reach the optimal dose of the main allergen. The initial course of treatment includes 32 injections for an allergen and 25 for an allergoid. The rhythm of administration is chosen depending on the drug tolerability; the dose is not increased in case of local reactions, the

reduced dose is repeated until satisfactory tolerance is achieved. After reaching maximum dose, injections are repeated with at intervals of 5–7 days prior to the beginning of the pollen season. Accelerated schedules of SCIT with domestic allergens ("fulminant" schedule) is not recommended by APAIR experts for safety reasons.

Deposited allergens "Phostal" — the extract from the mixture of tree pollen and "Alustal" — the allergen of meadow grasses (Stallergenes Greer) are not available for use at the time of the article issue. After increasing a dose for about 4 months, a maintenance dose in administered all year round at intervals of 2–6 weeks during 3–5-year course of therapy; the dose is reduced half or more during the flowering season.

Pollen allergens for SLIT exist in two forms — drip and pill. Staloral "Allergen of birch pollen" is available in the form of drops, used for pre-season-seasonal protocol. The advantage of drops is the possibility of flexible dosing with reaching the maximum maintenance dose of 240 IR daily that is the key to optimal efficacy and implementation of the modern approach of high-dose SLIT. Efficiency of drops with the allergen of birch pollen is proven in a double-blind placebo-controlled trial, using a daily dose of 300 IR in pre-season-seasonal therapy mode (574 patients) [65]. Similar efficacy and safety of SLIT with the allergen of birch pollen is shown in patients with oral syndrome (cross food intolerance) as well as without it.

Sublingual drug of birch pollen in the form of lyophilized pills 12 SQ is registered in Russia for treating AR and (or) rhinoconjunctivitis in children 12 and older. Currently Itulazax drug is passing the final stage of the trial in the population of children aged 5 years in Europe.

In our country drugs in the form of pills are available for SLIT of allergy to cereal grasses: the pollen allergen of 5 herbs ("Oralair"), the allergen of timothy grass in the form of lyophilized pills ("Grazax") and carbamelized allergoid from a mixture of 3 herbs ("LAIS Grass"). Treatment is carried out according to pre-season-seasonal protocol, "Grazax" 75000 SQ-T drug can be used all year round.

Current EAACI guidelines allow to use one allergen for treating diseases, caused by homologous plants. For pollen of cereal herbs the marker major allergen is proteins of timothy grass Phl p 1 and Phl 5 b. The study of antibody neutralizing capacity shows that allergens of major cereal herbs are homologous and bind in vitro by 98–100% [66]. It allowed to use extracts from the allergen of timothy grass for effective immunotherapy for patients with allergy to cereal grains.

In pediatric practice GAP study (n = 712) has shown high efficacy and safety of "Grazax", similar to that in adults, as well as ASIT effect with the pollen of timothy grass on the development and course of allergic asthma. Significant reduction in symptoms of existing asthma, amount of therapy received and improvement in FEV_1 were noted. Effect from ASIT regarding asthma exacerbations, induced by grain pollen, lasted for minimum 2 years after the end of treatment [67].

Treatment protocol of the drug "Oralair", containing 5 herbs (cocksfoot, vernal grass, common ryegrass, bluegrass, timothy grass) involves the use of high maintenance doses of 300 IR/daily. Efficacy and safety of the drug in pediatric practice are shown in a multicentre double-blind placebo-controlled trial (278 children and adolescents aged 5 to 17) with a decline of 28% in the index of nasal and ocular symptoms [66].

Monomeric allergoid of cereals 1000 AU, "LAIS Grass", was studies in several small groups, which results are summarized in the meta-analysis by Mosges R. (2010). The average change in the scale of symptoms and need for medication was compared with placebo and amounted to −34% and −49%, respectively. Serious adverse reactions were not reported, all AE were of a local nature [62].

The standardized drug "Ragvizax" is available in Russia in the form of lyophilized pills 12 SQ with the allergen of ambrosia, registered for patients 5 years. In pediatric practice the drug was studied in the population of 1002 children aged 5–17, having clinical manifestations of AR or AR, combined with BA; there was a decrease of 47.7% in the amount of drug therapy [68].

In clinical trials polysensitized patients noted good tolerability and the possibility to combine the drugs of timothy grass 75000 SQ and ambrosia 12 SQ when taking pills with the difference in 5 minutes [69].

ASIT is the only pathogenetically substantiated method of treating respiratory allergic diseases, associated with sensitization to plant pollen. ASIT gives the patient a chance to prevent the aggravation of the process, expansion of the spectrum of sensitization as well as a chance to achieve a stable remission.

METHOD OF ASIT

The key steps in conducting allergen-specific immunotherapy:

1. Verification of the diagnosis and identification of evidence for ASIT.
2. Identification of a clinically significant allergen via allergological examination.
3. Determination of contraindications to ASIT.
4. Drug selection of therapeutic allergens.
5. Initiation of ASIT during remission of allergic diseases; the first administration of allergy vaccine in the allergist-immunologist's office.
6. Achieving maximum compliance with parents, training the technique of taking the allergen and self-help with the development of adverse reactions, drawing up an individual action plan.
7. Monitoring the efficiency of therapy.

ASIT is indicated in a positive skin test or in identifying an increase in the level of specific IgE (it is believed that sensitization must at least comply with the moderate class) to a suspected allergen. In some cases of polysensitization it is necessary to determine major components of plant pollen to choose an allergen for treatment.

Before ASIT it is necessary to revise the diagnosis, to eliminate the effect of comorbid conditions, occurring with similar symptoms, and to ensure that complaints and symptoms, which disturb the patient, are associated with sensitization.

Remission of the underlying disease is required to start a course of ASIT. It may be spontaneous (for instance, in winter for pollen allergy) or achieved on the basic therapy.

In BA the course of the disease should be monitored for minimum 1 month (it is the minimum period for evaluation of asthma control). By the start of ASIT the patient with asthma should also have acceptable lung function rates, in particular, FEV_1 in children must be at least 80% of the predicted. Low FEV_1 is not only the rate of uncompensated asthma, but also the risk indicator of possible systemic responses to ASIT [11, 70].

SLIT is possible with the oral mucosa integrity and lack of infection foci, therefore, it is crucial to inspect the oral cavity at each visit and train parents to detect trauma, ulcers and erosions. In the event of defects in the mucous membrane, SLIT should be suspended. It is necessary to determine the possibility of having SLIT against the background of orthodontic intervention, implantation, bracket system for the correction of the malocclusion in each specific case.

Before treatment it is required to reveal the patient and their parents the principle of ASIT action, goals of treatment (especially long-term points of efficacy), differences from pharmacotherapy of allergic diseases, peculiarities of treatment regimen, forthcoming labor, time and treatment costs, duration, measure of family responsibility for implementing treatment scheme, precautionary measure, possible AE. Information may be provided both orally and in the form of brochures. The first visit requires signing the informed consent form, training the technique of the drug administration, providing the patient with a written self-help plan in developing AE. The diet should be complete, age-appropriate, but in case of significant food allergy and anaphylaxis in the anamnesis, it is necessary to ensure elimination of the allergen. When conducting ASIT in the flowering season, it is advisable to implement the recommendations on maintaining hypoallergenic household and minimizing contact with pollen. During SLIT it is reasonable not to use food with irritating effects and traumatic for mucous tunic of the mouth.

It is advisable to perform vaccination against infectious disease, according to the vaccination schedule, 1 month and more before the start of ASIT.

The first administration of the allergy vaccine to the patient, regardless of the route and dosage form, is conducted in the allergist-immunologist's office. This also applies to repeated courses, carried out by pre-season-seasonal protocol and to year-round courses, reinitiated after a long break. Before the

first administration, the patient's admission to the beginning of treatment is registered in the patient's medical record: the absence of contraindications, examination data, the lack of data on intercurrent communicable disease. SLIT requires data on the inspection of the mucous membrane of the mouth, the absence of inflammation, lesions. After the first administration of the allergy vaccine, the patient should be monitored at least 30, preferably 60 minutes.

SCIT at home is prohibited both in the dosage phase and conducting maintenance therapy!

Patients, receiving SCIT, follow the injection schedule, indicated in the instructions for the drug. Patients, receiving SLIT, require the follow-up schedule. The critical period of SLIT is the first month of therapy. At this time, as a rule, patients note the emergence of local AE and, due to having no way to contact the attending physician, many parents discontinue treatment because of "intolerable adverse events". Thus, the follow-up of the patient, who has started the course of SLIT, should include:

— availability of the doctor or a competent nurse for the patient, for example, by phone, for quick resolution of emerging issues;

— preliminary explanatory work on the course of treatment before its start;

— follow-up visit during the first month of therapy to assess tolerability of treatment; then — visits to assess the course of treatment, compliance, tolerability of treatment, discussion of the vaccination schedule and etc. — each 3–6 months;

— there may be off-plan visits in case of intercurrent diseases, exacerbations of the underlying disease and questions from patients;

— regular evaluation of ASIT treatment efficacy with HDM is made once a year, with pollen allergens – after the flowering season of plants casual;

— decisions, made on visits: about the possibility of reducing the amount of pharmacotherapy of the underlying disease as well as the moment of discontinuing ASIT [11]. AE are monitored at each patient's visit.

Temporary interruption of ASIT course occurs for various reasons:

— acute intercurrent disease;

— exacerbation of the underlying disease; in patients with BA — decrease in peak expiratory flow up to 80% of the maximum and lower ("yellow zone");

— organizational reasons (departure, untimely purchase of another package of allergy vaccine, etc.).

— in ASIT: a violation of the integrity of the mucous membrane (stomatitis, aphtha, injury, tooth loss/extraction); teething is not a contraindication to continue SLIT if it is not accompanied with bleeding, inflammatory process; acute gastritis, gastroenteritis.

In classical schemes of SCIT with domestic water-salt allergens, in case of the patient's turnout after an approved break, the next dose should be reduced, that is, "to back down" under the scheme of ASIT by 2–4 doses. It is required to "to step back" by 1 dilution when interrupting the course for more than 14 days.

One should be guided by the instructions on resumption of therapy after interruption, given by the manufacturer, during SCIT and SLIT with standardized allergy vaccines. There is no dosage reduction during SLIT with tableted vaccines.

Vaccination against infectious disease in patients, receiving ASIT, should be conducted within periods, as close as possible to the vaccination schedule. Vaccination is not carried out in the stage of building up the dosage of an allergy vaccine (in ASIT with domestic water-salt allergens, parenteral allergens Phostal/Alustal). In treating with sublingual vaccines, which dose build-up stage is 3–9 days or completely absent, we do not recommend to conduct scheduled vaccinations against infectious diseases in the 1st month of SLIT.

In SLIT at the stage of maintenance therapy, vaccination requires a temporary interruption of taking allergenic drug: 3 days before the intended vaccination, on the day of vaccination and for 10–14 days after vaccination [71]. In case of an emergency vaccination or the one for epidemic indication, it is also necessary to check the instruction for the drug.

EVALUATION OF ASIT EFFICACY

1. Biological markers are molecules, cells, receptors, detected in the blood or other biological body fluids and being the measure of the severity of the disease and (or) its response to therapy.
2. Nowadays there are no biomarkers available in clinical practice, reflecting the onset of the therapy effect.
3. Medical practitioner regularly assesses ASIT efficacy, based on changes in symptoms and the amount of drug therapy.
4. There is no standard rating scale, accepted by all communities.

Since ASIT is not fully effective for each patient, the identification of patient's biological markers is of great importance to predict clinical efficacy of immunotherapy and monitor response to treatment.

Of particular importance in predicting ASIT efficacy is specific IgE to the major allergen [41]. Interrelations are described between the profile of molecular sensitization and response to ASIT. Thus, it is shown that sensitization to Der p 1 or Der p 2 might be a good predictor of SLIT efficacy with HDM allergen [72], and combined sensitization to Phl p 5 and Phl p 12 predicts the development of AE [73]. ASIT is not appropriate with no sensitization to the major component of a casually significant allergen.

In 2017 the working group of EAACI, "Biomarkers for monitoring clinical efficacy of allergenic immunotherapy" identified potential biomarkers [74]:

— IgE. There was a demonstrated increase in specific IgE during the first months of ASIT with its subsequent progressive decline after 6 months of therapy. At the same time, there are contradictory data on the significance of the ratio in levels of specific to total IgE as a predictor of clinical response to ASIT [10].

— IgG. Repeated exposure to the allergen induces the formation of allergen-specific IgG4 antibodies, blocking action of which is currently considered one of the main ASIT mechanisms for respiratory allergy. The correlation is shown between the production of specific IgG4 antibodies and clinical outcome of ASIT. Nevertheless, specific IgG4 cannot be currently не могут considered as a reliable biomarker of ASIT efficacy due to the need for long-term studies.

— Inhibitory activity of serum against IgE (IgE-FAB) is regarded as a potential biomarker of ASIT efficacy, but it is not used in practice.

— Basophil activation test has been suggested as a potential biomarker of ASIT efficacy, but the results of the work are contradictory [74, 75].

— There is active discussion of using chemokines, cytokines, cells, participating in an allergic response, for instance, producing IL-10 Treg lymphocytes, molecular markers of dendritic cells, however, they are difficult to use in practice.

— Provocative tests, undertaken in dynamics, are attributed to "Biomarkers in vivo". Thus, endonasal provocative test is used as an indicator of ASIT efficacy in its clinical studies.

Therefore, there is no current validated approach to the use of biological markers to confirm ASIT efficacy in clinical practice.

A the present stage the only possible way to assess ASIT efficacy is the application of clinical efficiency criteria: 1) the reduction in the severity of the disease symptoms, caused an allergen, with which ASIT is carries out, the reduction in the period of exacerbation; 2) the reduction in the need for medication; 3) change in the natural course of allergic disease (stable remission that persists after the end of therapy; prevention of expanding the range of sensitization; prevention of developing new clinical forms of atopic disease).

Satisfaction with treatment is assessed in patient with BA according to the scheme proposed by A. D. Ado [76], and for patients with AR — on a similar principle: 4 points — an excellent effect — disease remission; 3 points — a good effect — very rare and mild symptoms, a sharp decrease in the need for medication; 2 points — a satisfactory effect — exacerbation of the disease is less frequent, symptoms — milder; 1 point — no effect. Scoring is quick, simple and convenient.

Clinical studies of ASIT apply integrated index, addressing symptoms of allergic diseases and the necessary amount of pharmacotherapy, for instance, recommended EAACI scale to determine the average score of nasal and conjunctival symptom severity and the need for drug therapy to relieve symptoms (Table 2) [77].

EAACI clinical guidelines for ASIT in asthma of tick-borne etiology provide "The list of positive changes during AIT with HDM in tick-borne asthma" [42].

It is certainly important to register epicrisis in patients' medical records, where a practical physician reflects the integrated assessment of complaints, symptoms, absences in the child care institution and disability, basic and emergency therapy, antibiotic prescription for respiratory tract infections, an emergency visit to an ENT specialist (with the manipulation), hospitalization and etc.

Table 2. **Index calculation table CSMS (combined symptom and medication score)**
Таблица 2. **Таблица подсчета индекса CSMS (combined symptom and medication score)**

Nasal	Itching in the nose	0–3	0 — No symptoms 1 — Mild, easily tolerated, do not affect the well-being 2 — a clear feeling of a symptom, worries constantly 3 — Intolerable, an impact on sleep, daily activity
	Sneezing	0–3	
	Discharge from the nose	0–3	
	Stuffiness	0–3	
Conjunctival	Itching/redness	0–3	
	tearing	0–3	
Daily symptom score (DSS)*		0–3 (number of symptoms/N signs)	To assess symptoms on HDM eye symptoms are not considered
Assessment of DMS therapy	Antihistamine (locally or systematically)	1	
	Intranasal steroids	2	
	Oral steroids	3	
Overall assessment of daily therapy received (DMS)		0–3	
CSMS — combined assessment of symptoms and therapy	DSS (0–3) + DMS (0–3)	0–6	

The timing of the efficacy assessment are essential. In treating with HDM allergens mandatory cutoff value for initial efficacy assessment is 1 year from the start of therapy. In the absence of effect after the first year/course of ASIT it is necessary to check: the course dose of the allergen by counting PNU when treating with water-soluble allergens or the number of packages of sublingual drugs, patient compliance with a treatment regimen, a break in treatment; re-evaluate the diagnosis, indications for ASIT, the correctness of allergen choice for therapy; make a decision to continue or terminate ASIT [11].

ATOPIC DERMATITIS AND ASIT

1. Atopic dermatitis is not an obstacle to ASIT in patients with AR, BA.
2. In patients with isolated AtD in case of clinically significant sensitization and association of exacerbations with a specific inhaled allergen, ASIT must bring a clinical effect, yet, the indication of AtD is not included in the guidelines to drugs for ASIT, registered in Russia.

ASIT is indicated for patients with an identified cause-significant allergen, responsible for the development of disease exacerbations. In AtD it is often impossible to identify the main cause of exacerbations as xerosis, mechanical damage to epidermis, change in skin microbial combination as well as non-specific triggering play an important role in the deterioration of the skin process [55]. Besides, most patients have non-IgE-mediated phenotype of AtD, in which ASIT will be ineffective.

In Russian clinical guidelines ASIT with pollen and household allergens is recommended to patients with allergic respiratory diseases and concomitant controlled AtD and patients with AtD with no respiratory allergy and proven cause-significant sensitization to HDM allergens [55, 78].

The consensus of the European Association of Dermatovenerologists for treating AtD points that in this pathology ASIT might be considered in patients with severe disease, sensitized to birch pollen, meadow grasses and HDM and the presence of exacerbations in the anamnesis, coinciding with exposure to an allergen [48].

Research findings on efficacy and safety of ASIT with aeroallergens in children with AtD were published in recent years. Systematic reviews and meta-analysis show good efficiency of ASIT with pollen and household allergens in patients with AtD in decreasing SCORAD index and the need for topical glucocorticosteroids [79–81]. There are encouraging trials of ASIT efficacy in adult patients with AtD, sensitized to allergens of cat and dog dandruff.

Thus, after achieving clinical remission, AtD cannot be contraindication for immunotherapy to treat concomitant AR and (or) BA. In patients with

isolated AtD when associating exacerbations with specific inhaled allergens, ASIT should have clinical effect, yet, AtD indication is not included in the instructions of drugs for ASIT, registered in Russia.

ASIT IN FOOD ALLERGIES

1. ASIT is recognized as an effective method to develop tolerance to the allergens of milk, eggs and peanuts in children over 5 years.
2. Standardized drugs of food allergens for treatment, methodologies of a food provocative test and methods of ASIT with food allergens are not presented in Russia.
3. Overall, work on conducting oral immunotherapy in food allergies are experimental.

The standard of food allergy/anaphylaxis treatment remains avoidance of food allergens, however, recently there has been an increase in ASIT studies both to prevent food allergies and to consider as a method of treatment. The first double-blind placebo-controlled trial of SLIT with food allergies was published in 2005. During therapy 45% of patients in the treatment group reached the highest dose of hazelnut (20 g) as compared with 9% in the placebo group [82].

EAACI recommends oral immunotherapy (OIT) as a promising therapeutic method with high short-term efficacy regarding allergy to milk, eggs and peanuts since the age of 4–5 years, however, does not provide recommended schemes of food introduction or the use of standardized drug for OIT. Pharmaceutical companies do not produce therapeutic drugs of food allergens, making it difficult to widespread the method [83, 84].

Anaphylaxis and EoE are referred to possible risks of food ASIT; there is no full information on the duration of maintaining tolerance to food allergen, in other words, on the risk of food allergy relapse after terminating regular intake of a maintenance dose of food allergen. Before wide implementation of food ASIT in practice it is required to find and understand markers, which differentiate desensitization and sustained resistance, and to introduce them for monitoring immunotherapy.

It is necessary to standardize the most important food allergens (anaphylaxis molecules ovomucoid Gal d 1, casein Bos d 8, peanut Ara h 2 и Ara h 6, hazelnut Cor a 9 and Cor a 14, cod parvalbumin Gad c1, shrimp Pen m 1, Pen m 2), with which treatment is justified when symptoms are severe (food anaphylaxis) and the cause is hard to avoid.

With OIT (compared to other forms of immunotherapy) quite large total doses of allergen are used, and thanks to OIT patients can get protection not only from dangerous responses due to accidental exposure of trace amount of allergen, but also from reactions after consuming gram amounts of allergenic products.

In 2020 Food and Drug Administration US (FDA) approved a standardized product for OIT (Palforzia™) to treat food allergy to peanut and also reported on programs for treating allergy on eggs and walnut [85].

Desensitization immunotherapy with food allergens currently includes: oral, sublingual and epicutaneous immunotherapy, using native food allergens or recombinant proteins affected by mutagenesis or over-heated food. Intranasal, intralymphatic and epicutaneous allergen administration is referred to experimental methods of ASIT with food allergy.

The main problem is the lack of consensus regarding doses of the allergen, schemes of its administration, oral provocative testing methods in children as well as failure of reached tolerance after a break/discontinuation of OIT. There is study of conduction OIT combined with anti-IgE monoclonal antibodies to improve safety and tolerability of ASIT. To date, omalizumab is not registered to treat anaphylaxis and food allergy. The earliest age to use is defined as 6 years for allergic asthma.

USE OF SYMPTOMATIC DRUGS AND ASIT

Antihistamines, due to effect on mast cells and reaction of immediate type, as well as glucocorticosteroids, inhibiting the late phase of inflammation, could potentially interfere with efficacy of immunotherapy and incidence of AE.

According to national and international clinical guidelines, ASIT is recommended to children with AR during remission, including drug-induced one, and to patients with a mild and moderate BA, controlled with pharmacotherapy [11, 41]. Most protocols of ASIT studies assumed that during therapy the patient may get symptomatic drugs, if necessary, and under these circumstances immunotherapy appears effective. Inhaled glucocorticosteroids have minimum systemic effect, do not impact on efficacy of immunotherapy and the formation of humoral protection factors [86].

In ASIT antihistamines are used not only to relieve symptoms of AR, but also to monitor AE, induced by administration of therapeutic allergen at the beginning of therapy, being drugs of choice in mild and moderate severity of AE. The use of second generation H1-receptor blockers, not affecting blood pressure indicators and not inhibiting the respiratory centre, is shown. Severe AE may require administration of inhaled and systemic steroids, bronchodilators and epinephrine.

There is no data on negative impact of antihistamines on ASIT efficacy. According to the meta-analysis of 2021, the use of antihistamines as premedication during ASIT significantly reduces the risk of moderate and severe systemic responses and increases the chances of reaching the target maintenance dose of the allergen [87].

Omalizumab allows to reduce to the minimum the incidence of anaphylactic reactions while maintaining efficacy of ASIT [88].

Thus, ASIT is possible with the use of drugs of basic therapy.

ASIT is currently recognized as the only clinically effective, disease-modifying way to treat IgE-mediated allergic diseases (rhinitis, asthma, food allergy), providing the achievement of a long-term effect, ongoing after discontinuation of treatment [8].

In pediatric practice ASIT, according to some reports, reduces the incidence of new sensitization and transformation of rhinitis in asthma.

Specific immunotherapy is most studied and applicable in actual practice in disease, caused by pollen of plants and house dust mites.

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Resume. Multiple sclerosis (MS) is a chronic, demyelinating disease that leads to disability. Understanding the etiology of MS contributes to the development of pathogenetic methods of treatment, and the search for informative biomarkers of the effectiveness of treatment will allow the patient to adjust therapy in time. The aim of this work was to determine informative cytokines and cytokine profiles to predict the effectiveness of IFN-β1a therapy in children with MS.
Materials and methods. 66 children with MS aged 16 [14.2–17.5] years who are on INFß-1a therapy were examined: group 1 — patients with exacerbation of MS (with active foci of demyelination by MRI), n = 34; group 2 — patients in remission of MS (without active foci), n = 32. The content of cytokines in the blood serum of patients was assessed using the multiplex panel Human Th17 Magnetic Bead Panel.
Results: There was a significant increase in cytokine concentrations in patients with exacerbation of MS compared with children in remission: IL5, IL6, IL9, IL12p70, IL17E/IL25, IL21, IL28A, GM-CSF, TNFß. Threshold values for IL9 (AUC = 0,785), IL6 (AUC = 0,750), TNFß

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(0,740), IL28A (AUC=0,744) were obtained above which it is possible to predict an exacerbation of MS in patients: IL9 — 3.9 pg/ml (Sn — 70.6, Sp — 71.9), IL6 — 4.0 pg/ml (Sn — 70.6, Sp — 68.8), TNFß — 6.6 pg/ml (Sn — 70.6, Sp — 71.9), IL28A — 243.0 pg/ml (Sn — 70.6, Sp — 71.9). Cytokine profiles associated with T-lymphocytes and their functions were evaluated using z-score.
Conclusions. For the first time, an increase in cytokine levels was demonstrated in children with active foci of demyelination compared to patients in remission of MS. An increase in proinflammatory cytokines and cytokine profiles associated with Th1 and Th17, as well as with Th2 and Th22 has been shown. The use of threshold values for IL9, IL6, TNFβ, IL28A will help predict the development of exacerbation in patients with MS.
Keywords: cytokines, multiple sclerosis, children, Th1-cytokines, Th2-cytokines, Th17-cytokines, ИНФ-β1a.

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Уровни циркулирующих цитокинов у детей с рассеянным склерозом при разной эффективности интерфероновой терапии

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Аннотация. Рассеянный склероз (РС) — это хроническое, демиелинизирующее заболевание, приводящее к инвалидизации. Понимание этиологии РС способствует разработке патогенетических методов лечения, а поиск информативных биомаркеров эффективности лечения позволит вовремя скорректировать терапию. Целью данной работы было выявить информативные цитокины и цитокиновые профили для прогноза эффективности терапии ИНФ-β1а у детей с РС.
Материалы и методы. Обследовано 66 детей с РС в возрасте 16 [14,2–17,5] лет, находящихся на терапии ИНФ-β1а: 1-я группа — пациенты в обострении РС (с активными очагами демиелинизации, по данным МРТ), n=34; 2-я группа — пациенты в ремиссии РС (без активных очагов), n=32. Содержание цитокинов в сыворотке крови пациентов измеряли с помощью мультиплексной панели Human Th17 Magnetic Bead Panel.
Результаты: у пациентов в обострении РС выявлено достоверное увеличение концентрации цитокинов IL5, IL6, IL9, IL12p70, IL17E/IL25, IL21, IL28A, GM-CSF, TNFβ по сравнению с детьми в ремиссии. Пороговые значения cut-off соста-

вили для IL9 (AUC = 0,785), IL6 (AUC = 0,750), TNFβ (0,740), IL28A (AUC = 0,744), выше которых можно прогнозировать у пациентов обострение РС: IL9 — 3,9 пг/мл (Sn — 70,6, Sp — 71,9), IL6 — 4,0 пг/мл (Sn — 70,6, Sp — 68,8), TNFβ — 6,6 пг/мл (Sn — 70,6, Sp — 71,9), IL28A — 243,0 пг/мл (Sn — 70,6, Sp — 71,9). Проведена оценка уровней цитокиновых профилей, ассоциированных с Т-лимфоцитами, а также с их функциями с использованием метода z-score.

Выводы. Впервые продемонстрировано увеличение уровней цитокинов у детей с активными очагами демиелинизации по сравнению с пациентами, находящимися в ремиссии РС. Обнаружено увеличение провоспалительных цитокинов, ассоциированных с Th1- и Th17-, а также с Th2- и Th22-лимфоцитами. Применение пороговых значений cut-off для IL9, IL6, TNFβ, IL28A позволяет прогнозировать развитие обострения у пациентов с РС.

Ключевые слова: цитокины, рассеянный склероз, дети, Th1-цитокины, Th2-цитокины, Th17-цитокины, ИНФ-β1а.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic, demyelinating disease that occurs in a genetically predisposed individual under the influence of various adverse environmental factors and leads to damage to the central nervous system with subsequent disability. About 2,8 million people suffer from MS worldwide [1]. The prevalence of MS in Russia ranges in different regions from 36 to 79 cases per 100,000 population, while children constitute some 4–5% of all patients [2]. The disease has a remitting course in most children (97–99%), and the average age of the nosology onset is 14,2 ± 1,3 years [2]. Modern drugs allow to reduce the number of exacerbations and the progression of the disease [3]. Patients are prescribed long-term therapy with drugs, changing the course of MS (PITRS). There are 2 approaches of treating MS — escalatory and inductive. Escalatory approach implies prescription of I line PITRS, in case of their inefficiency, drugs of II line are used. Inductive approach uses drugs of II line at the initial stage of therapy that are considered more efficient, but have a large number of adverse reactions [4]. IFN-β1a — I-line drug (allowed from 12 years) and fingolimod (II-line drug, allowed from 10 years) are referred to drugs allowed for MS treatment in children in Russia [5]. The mechanism of IFN-β1a action is to reduce T-cell activation and adhesiveness, the inhibition of matrix metalloproteinases and the loss of the ability for lymphocytes to pass through the blood-brain barrier. The effect of fingolimod is aimed at suppressing lymphocyte release from the lymph nodes [4].

The main mechanism of MS pathogenesis is immune system dysfunction [6]: particularly, the prevalence of T-helpers type 1 (Th1) over T-helpers type 2 (Th2) during an exacerbation and the production of increased levels of such pro-inflammatory cytokines as IFNγ and IL-12 [7]. There is also the critical role of T-helpers 17 (Th17) in the pathogenesis of MS, producing IL-17 and IL-23 [8]. Adults with MS showed an increase in the cytokine concentration of both Th1- (IL-1β, IL-2 и TNFα) and Th17-lymphocites (IL-17A, IL-21 and IL-22) that confirms both populations of T-lymphocytes to be involved in the pathogenesis of MS [9]. The inflammatory response and impaired interaction of immune cells with MS, mediated by cytokines, constitute an attractive target for MS immunotherapy [10]. Over the last decade there has been an increase in the number of studies, dedicated to the search for predictive biomarkers of disease progression and response to drug treatment [11, 12]. It has been shown in adult patients with MS that an increase in concentration of cytokines IL-1α, IL-4, IL-18, CCL7 CCL27, INFγ, LIF, M-CSF, SCF and TNFα allows to differentiate the phase of MS with a high degree of accuracy [13]. There are very few works on studies of the levels of cytokines with MS in children. An increase in the number of cytokines (IL-10, IL-21, IL-23, IL-27) was shown in children with MS both in an exacerbation state and in remission, compared to the group of healthy children [14]. Understanding of the pathogenesis of MS will contribute to the development of treatments, modifying the course of the disease, and the search for predictors of inefficiency of drugs used will allow to adjust therapy on time.

The purpose of this work was to identify the main cytokines and cytokine profiles to prognose the efficacy of INF-β1a therapy in children with multiple sclerosis.

MATERIALS AND METHODS

66 children with MS, aged 14,2-17,5 years (average age — 16 years) were examined, undergoing ING-β1α therapy. The patients were divided into groups based on clinical anamnestic and the presence of active foci of demyelination by the results of magnetic resonance analysis (MRA): group 1 contained patients with exacerbation of MS (with active foci) (n = 34); group 2 — patients in remission of MS (without active foci) (n = 32). The groups were compared by duration of the disease: exacerbation — [Me 1,2 (0,6–2,2)], remission — [Me 1,5 (0,7–3,4)], p = 0,545 — and by the duration of INF-β1a therapy: exacerbation — [Me 67,4 (14,8–95,7)], remission — [Me 41,4 (4,9–138,0)], p = 0,498.

All children were examined according to regulatory documents of the Russian Federation after receiving approval from the local ethics committee FSAI "NMRC for Children's Health", the Health Ministry of the Russian Federation (protocol № 6 of 11 June, 2019) and informed consent of parents and children over 14 in accordance with the Declaration of Helsinki.

Venous blood samples for the study were obtained from the cubital vein on an empty stomach in BD Vacutainer® clot activator test tubes. The test tubes with blood were centrifuged at 1500 rpm for 10 min, the resulting serum was stored at −80 °C until analysis.

The measurement of cytokine concentration in samples was performed using multiplex analysis (xMAP-technology) with MILLIPLEXMAP Human Th17 Magnetic Bead Panel (EMD Millipore Corporation, USA). The analysis made was according to the manufacturer's instruction, followed by analysis on Bio-Plex™ 200 Assay System (Bio-Rad, США) flow fluorometer using xPONENT 4.2 and Milliplex Analyst 5.1 software. The panel of the studied cytokines included: IL-17F, GM-CSF, IFN-γ, IL10, CCL20/MIP3α, IL12p70, IL13, IL15, IL17A, IL22, IL9, IL1β, IL33, IL2, IL21, IL4, IL23, IL5, IL6, IL17E/IL25, IL27, IL31, TNFa, TNFβ, IL28A. The results of cytokines were obtained in pg/ml. Differences between the groups of patients in exacerbation and remission of MS were analyzed on separate cytokines as well as on the complex of cytokines, associated with different cells and their functions: macrophage M (IL-1+IL-6+TNF-α), regulatory Reg (IL4+IL5+IL10+IL13+IL33), associated with particular cells (c), cell functions (f): Th1-assoiciated (cTh1) — (IFN-γ+IL12p70+TNF-β+IL2); Th2-associated (cTh2) — (IL4+IL5+IL10+IL13+IL17E/IL25+IL33), Th17-associated (cTh17) — (IL1β+IL6+IL17A+IL17F+IL21+IL22+IL23), fTh2+mast-associated fTh2+mast) — (IL4+IL5+IL31+IL13); family IL-12 (fIL12) — (IL12+IL23+IL27); fTh17 — (IL17A+IL17F); fTh2 (IL4+IL5+IL13); fTh22 (IL13+IL22) [14, 15, 16, 17].

To analyze and normalize data for cytokine profiles, we have implemented the approached, described in Cataldi C. work [18]. Z-standardization (z-score) was conducted for cytokines, using the following formula: $z = (x_i - \mu)/\sigma$, where z — standardized score, x_i — initial sampling unit, μ — arithmetic mean, σ — standard deviation. Z of separate cytokines was summed up to define z-score of cytokine complexes.

Statistical processing of the data obtained was carried out using Statistica 10.0 (StatSoft, USA) programs. Descriptive statistics of quantitative trait are presented in the format: median (lower and upper quartiles) — Me ($Q_{0,25}$–$Q_{0,75}$). Significance of differences between groups in the condition of exacerbation and remission was evaluated using nonparametric the Mann-Whitney U-test. Differences were considered statistically significant at $p < 0,05$. ROC-analysis was used to identify thresholds of cytokines in exacerbation and remission, the area under the curve, sensitivity and specificity were determined (SPSS, version 25, USA). Spearman correlation analysis was carried out to evaluate the effect of disease and therapy duration on the level of cytokines in patients with MS.

RESULTS AND DISCUSSION

The content of cytokines in the blood serum in patients with MS in groups with and without active foci of demyelination is presented in the table 1. In particular, significant differences for 9 pro-inflammatory cytokines out of 25 studied ones (IL5, IL6, IL9, IL12p70, IL17E/IL25, IL21, IL28A, GM-CSF, TNFβ) were found when comparing two groups. Concentrations of all the above cytokines were higher as well in the group of patients with active foci, compared to the group of patients without active foci (table 1).

Table 1. **Cytokine content in groups of MS patients with active foci and without active foci**
Таблица 1. **Содержание цитокинов в группах пациентов с РС с активными очагами и без активных очагов**

Cytokine name	Group 1 Me ($Q_{0,25}$–$Q_{0,75}$), pg/ml N = 34	Group 2 Me ($Q_{0,25}$–$Q_{0,75}$), pg/ml N = 32	p_{12}
IL1β	1,7 (0,3–2,0)	1,7 (0,5–2,0)	0,084
IL2	6,3 (4,3–10,8)	5,2 (2,5–10,8)	0,237
IL4	95,2 (27,6–130,4)	38,6 (4–124,2)	0,165
IL5	5,3 (3,7–6,5)	1,9 (0,1–4,1)	**0,013**
IL6	11,7 (0,9–30,2)	1,5 (0,3–5,4)	**<0,001**
IL9	8,5 (1,8–25,5)	0,2 (0,2–4,9)	**<0,001**
IL10	2,6 (0,1–5,1)	2,4 (0,1–5,1)	0,814
IL12p70	2,2 (1,9–2,6)	1,7 (0,2–2,0)	**0,021**
IL13	198,2 (101,7–313,1)	133,9 (57,4–235,7)	0,092
IL15	5,5 (3,9–9,2)	5,5 (1,9–10,8)	0,784
IL17A	0,5 (0,3–0,8)	0,3 (0,2–1,2)	0,0985
IL17E/IL25	25,6 (10,5–33,4)	7,7 (2,0–29,9)	**0,049**
IL17F	45,6 (9,7–55,9)	16,8 (2,2–39,6)	0,062
IL21	7,5 (5,3–8,8)	5,3 (0,9–7,7)	**0,031**
IL22	709,3 (36,0–1444,0)	36,0 (36,0–797,8)	0,146
IL23	928,9 (8,0–1343,0)	83,6 (8,0–1025,0)	0,185
IL27	518,7 (394,5–745,5)	558,6 (334,5–860,9)	0,924
IL28A	369,9 (45,0–808,9)	45,0 (45,0–255,1)	<0,001
IL31	35,1 (18,2–66,3)	4,2 (0,7–50,5)	0,098
IL33	20,9 (6,2–28,2)	2,4 (0,1–22,1)	0,105
CCL20	21,5 (16,9–25,6)	20,1 (8,5–32,0)	0,579
GM-CSF	212,4 (148,1–255,0)	12,4 (2,0–217,2)	0,019
IFNɣ	3,8 (3,0–9,0)	3,3 (0,9–8,3)	0,495
TNFa	15,0 (9,7–16,8)	11,1 (7,4–30,7)	0,479
TNFβ	71,9 (3,0–149,0)	3,0 (3,0–7,9)	**<0,001**

Note: group 1 — with active foci, group 2 — without active foci.

Примечание: группа 1 — с активными очагами, группа 2 — без активных очагов.

A weak inverse correlation is revealed between disease duration in children with MS and the level of cytokines: IL33 (R = −0,26); IL23 (R = −0,27); IL6 (R = −0,32); IL31 (R = −0,27); IL28A (R = −0,25). A similar correlation is found between therapy duration in children with MS and the level of cytokines: IL17F (R = −0,38); IL10 (R = −0,48); IL12p70 (R = −0,49); IL2 (R = −0,37); IL4 (R = −0,40); IL5 (R = −0,34); IL6 (R = −0,34); IL17E/IL25 (R = −0,33); TNFβ (R = −0,33); IL28A (R = −0,37). Thus, there was reduced level of cytokines in the blood serum in children with MS with an increase in duration of the disease and INF-β1a therapy. ROC-analysis showed a good quality of the separation model for exacerbation/remission conditions for the following cytokines: IL9 (AUC = 0,785), IL6 (AUC = 0,750), TNFβ (0,740), IL28A (AUC = 0,744) (fig. 1).

Threshold cut-off values are obtained, above which it is possible to prognose exacerbations of MS in patients (table 2.)

There was evaluation of cytokine complexes on z-score in groups of patients with MS. Analysis of the results showed that cytokine profiles M and with Th1 on z-score were significantly different in patients with active foci, compared to patients in remission, whereas cytokine profiles, associated with Th2 and Th17 cells, между группами did not differ significantly between groups (fig. 2A). Meanwhile, difference between groups of patients with MS for

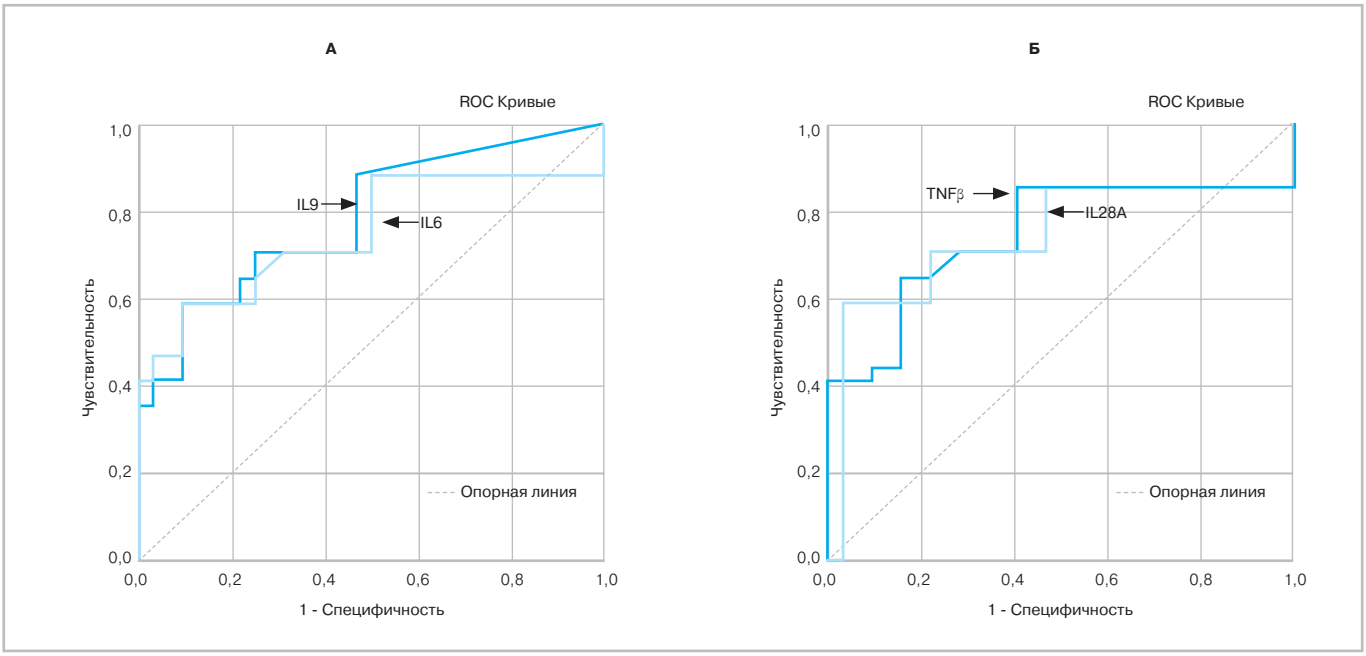

Fig. 1. **ROC curves for serum cytokines in children with MS. A — IL9, IL6; B — TNFβ, IL28A**
Рис. 1. **ROC-кривые для цитокинов сыворотки крови у детей с РС. А — IL9, IL6; Б — TNFβ, IL28A**

Reg, fTh22 and fTh2 cytokine profiles were reliable (fig. 2Б).

Thus, patients with MS exacerbation showed a significant increase in pro-inflammatory cytokines, involved in the differentiation and activation of different types of Th-cells, compared to patients in remission of the disease. It has been also found that patients in MS exacerbation experience a significant increase in cytokine production, necessary for differentiation from naive $CD4^+$-cells in Th1-cells and a significant increase in cytokine profile, characteristic of M1-macrophages as well as levels of cytokines, associated with the activation and function of Th2-cells: IL5, IL17E/IL25, IL13, IL33. It is interesting to note that patients in exacerbation showed a significant increase in cytokines of the regulatory profile (IL4, IL6, IL10, IL11 и IL13, IL33). It is known that, on the one hand, these cytokines play a neuroprotective role, and on the over hand, may be involved in the damage to the brain tissues, activating Th2-cells with subsequent stimulation of B-cells and complement activation [19]. We have shown previously that patients with active foci of demyelination have a significantly lower number of T-regulatory lymphocytes, compared to the group in MS remission, which might be explained by the compensatory response of T-cells [20]. Recently there have been studies on Th22 role in autoimmune diseases that produce IL22 and IL13 [21, 22].

It is known that, depending on the microenvironment, Th22 may differentiate into Th1- and Th2-cells. Besides, IL22 can play synergistic role with IL17, damaging the integrity of blood-brain barrier [21]. As our study has shown, patients in exacerbation of MS have a significantly increased profile of cytokines, synthesized by Th22-cells.

Table 2. **Cytokine thresholds for exacerbation/remission conditions in children with MS**
Таблица 2. **Пороговые значения цитокинов для состояний обострение/ремиссия у детей с РС**

Cytokine	Sensitivity (Sn), %	Specificity (Sp), %	cut-off, pg/ml
IL9	70,6	71,9	3,9
IL6	70,6	68,8	4,0
TNFβ	70,6	71,9	6,6
IL28A	70,6	71,9	243,0

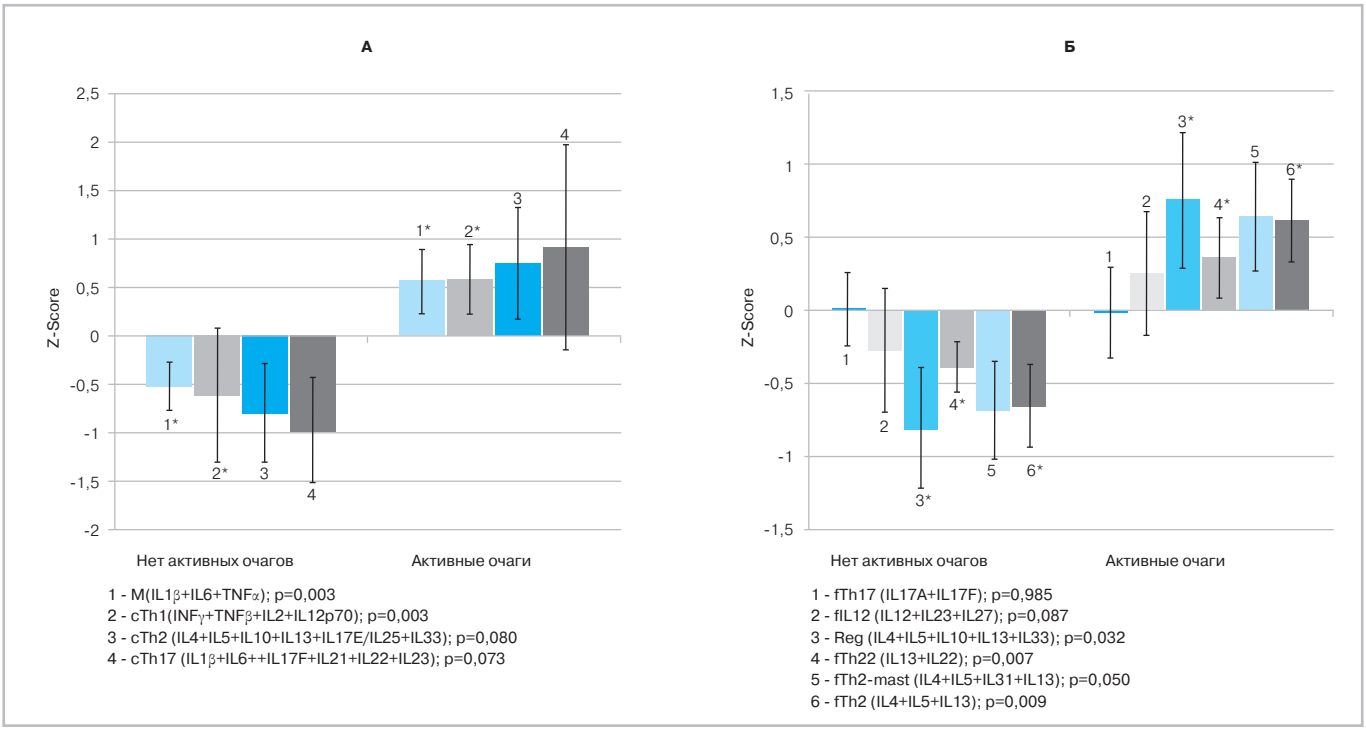

Fig. 2. **Z-score of cytokine profiles. A — M, cTh1, cTh2, cTh17. B — cytokine profiles associated with the function: fTh17, fIl12, Reg, fTh22, fTh2-mast, fTh2**

Рис. 2. **Z-score профилей цитокинов у пациентов с активными очагами и без активных очагов. А — M, cTh1, cTh2, cTh17. Б — профили цитокинов, ассоциированные с функцией: fTh17, fIl12, Reg, fTh22, fTh2-mast, fTh2**

Примечание: * отмечены достоверные результаты (p < 0,05); по оси OY — отложены средние значения в z-трансформации с указанием стандартной ошибки.

Note: * — reliable results are marked (p < 0,05); on the OY axis — the average values in the z-transformation are postponed, indicating the standard deviation.

CONCLUSION

For the first time, we obtained the data that demonstrate an increase in cytokine levels in patients with active foci of demyelination compared to patients in remission of MS. There is an increase in proinflammatory cytokines, necessary for differentiation of naïve $CD4^+$ T-cells into effector cells and activation of not only Th1 and Th17, but also Th2 and Th22-helper populations. Most significant differences were noted for cytokines, associated with Th1-cells. Levels of pro-inflammatory IL10 and IL13 cytokines did not differ between patient group. However, the profile of regulator cytokines was higher in patients in exacerbation, which may indicate the compensatory cell response to inflammation. Threshold cut-off values, obtained for IL9, IL6, TNFβ, IL28A, will help predict the development of exacerbation in patients with MS.

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Tatiana V. Radygina — collection of material, conduct of study, text writing, statistical analysis, text editing.
Svetlana V. Petrichuk — text writing, statistical analysis, text editing.
Olga V. Kurbatova, Daria G. Kuptsova — text writing, text editing.
Andrei P. Fisenko, Elena L. Semikina, Luizat M. Abdullaeva, Bella I. Bursagova — text editing.
Ekaterina V. Freydlin — processing and preparation of biological material for research.

ВКЛАД АВТОРОВ В РАБОТУ

Радыгина Т. В. — сбор материала, проведение исследования, написание текста, статистическая обработка, редактирование текста.
Петричук С. В. — написание текста, статистическая обработка, редактирование текста.
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Фрейдлин Е. В. — обработка и подготовка биологического материала к исследованию.

Features of the clinical course and treatment of anaphylaxis in children in the Ryazan region according to survey data

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Annotation

Anaphylaxis is a life-threatening systemic hypersensitivity reaction with the rapid development of critical changes in hemodynamics and /or disorders of the respiratory system, which can lead to death. Despite the trend towards the spread of anaphylaxis among children, there are difficulties in monitoring statistical data, since there is no generally accepted cipher "Anaphylaxis" in the ICD-10, and designations from allergic urticaria to anaphylactic shock appear as a diagnosis. Epidemiological studies on anaphylaxis in the Russian Federation are isolated, so the assessment of data from each region is relevant.

Objective: to study the clinical features and medical care for anaphylaxis in children of the Ryazan region in real clinical practice.

Materials and methods: A retrospective analysis of medical documentation was carried out in 300 children who had suffered an "acute allergic reaction" over the past 5 years, followed by a telephone survey of patients' parents about the disease, and based on the clinical criteria for the diagnosis of anaphylaxis presented by the World Organization of Allergists (WAO) in 2020 and in the Federal Clinical Guidelines for the Diagnosis and Treatment of anaphylaxis, 57 patients were selected for anaphylactic shock of the Russian Federation in 2022, whose data were compared in a spreadsheet and analyzed using SPSS V24.0, including descriptive statistics.

Results: It was revealed that the average age of first—time anaphylaxis is 3.5 years. Clinical manifestations from the skin and mucous membranes were present in 67.2% of patients, symptoms from the respiratory system in 11.8% of cases. The leading trigger for the occurrence of anaphylaxis in children is the nutritional factor (n = 27 (40%), ($\chi^2 = 4.56$; p = 0.033)). In 29% of cases, the causally significant allergen remained unknown. The most common drugs in the treatment of anaphylaxis in real clinical practice were glucocorticosteroids (n = 48 (84.2%)) and antihistamines of the first and second generation (n = 47 (82.5%)). The frequency of epinephrine use was only 3 cases (5%).

Conclusion: The epidemiological study of anaphylaxis in the Ryazan region was a pilot project for our region. It showed difficulties both in the organization and in the interpretation of the data obtained. According to preliminary results, food allergy is a frequent trigger of anaphylaxis in children of the Ryazan region. Regional studies of anaphylaxis in children in real clinical practice make it possible to identify not only the features of this urgent pathology, but also to note the problems of providing primary medical care in order to improve it. Further study of population models of anaphylaxis, apparently, should be based on the creation of a unified questionnaire of the pediatric community, following the example of the ISAAC questionnaires or the creation of registers, which will more accurately help determine the true prevalence of anaphylaxis, determine the need to identify anaphylactogenic relevant molecules in the pediatric population, and improve the provision of assistance to children with these conditions.

Keywords: anaphylaxis, allergic reaction, children, adrenaline, food allergy.

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Особенности клинического течения и терапии анафилаксии у детей в Рязанской области по данным опроса

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Аннотация

Анафилаксия — это жизнеугрожающая системная реакция гиперчувствительности с быстрым развитием критических изменений гемодинамики и (или) нарушениями со стороны дыхательной системы, которая может привести к летальному исходу. Несмотря на тенденцию к распространению анафилаксии среди детей, существуют затруднения в мониторинге статистических данных, так как в МКБ-10 нет общепринятого шифра «Анафилаксия», а в качестве диагноза фигурируют обозначения от аллергической крапивницы до анафилактического шока. Эпидемиологические исследования по анафилаксии в Российской Федерации единичные, поэтому оценка данных каждого региона является актуальным.

Цель работы: изучить клинические особенности и оказание медицинской помощи при анафилаксии у детей Рязанской области в реальной клинической практике.

Материалы и методы. Проведен ретроспективный анализ медицинской документации у 300 детей перенесших «острую аллергическую реакцию» за последние 5 лет с последующим телефонным опросом родителей пациентов о перенесенном заболевании с помощью адаптированной анкеты, и на основании клинических критериев диагностики анафилаксии, представленных Всемирной организацией аллергологов (WAO) в 2020 году и в Федеральных клинических рекомендациях по диагностике и лечению анафилаксии, анафилактического шока РФ 2022 года, отобрано 57 пациентов.

Результаты. Было выявлено, что средний возраст впервые возникшей анафилаксии у детей от 2 до 6 лет составляет 3,5 года. Клинические проявления со стороны кожи и слизистых оболочек присутствовали у 67,2% пациентов, симптомы со стороны дыхательной системы в 11,8% случаев. Ведущим триггером возникновения анафилаксии у детей является пищевой фактор (n = 27 (40%), ($\chi^2 = 4{,}56$; p = 0,033)). В 29% случаев причинно-значимый аллерген остался неизвестным. Наиболее распространенными препаратами в лечении анафилаксии в реальной клинической практике оказались глюкокортикостероиды (n = 48, (84,2%)) и антигистаминные препаратов первого и второго поколения (n = 47 (82,5%)). Частота применения адреналина составила всего 3 случая (5%).

Заключение. Проведенное эпидемиологическое исследование анафилаксии в Рязанской области явилось пилотным проектом для нашего региона. Оно показало сложности как в организации, так и в трактовке полученных данных. По предварительным результатам пищевая аллергия является частым триггером анафилаксии у детей Рязанской области. Региональные исследования анафилаксии у детей в реальной клинической практике позволяют выявить не только особенности этой ургентной патологии, но и отметить проблемы оказания первичной медицинской помощи с целью ее совершенствования. Дальнейшее изучение популяционных моделей анафилаксии, по-видимому, должно строиться на создании единой анкеты педиатрического сообщества, по примеру опросников ISAAC или создания регистров, что более точно поможет определить

истинную распространенность анафилаксии, определить потребность в определении анафилактогенных релевантных молекул в детской популяции, улучшить оказание помощи детям при этих состояниях.
Ключевые слова: анафилаксия, аллергическая реакция, дети, адреналин, пищевая аллергия.

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Anaphylaxis is defined as a severe life-threatening systemic immediate hypersensitivity reaction with a rapid onset and life-threatening airway and circulation problems usually but not always associated with skin and mucosal changes. These are the most commonly used definitions, presented in national clinical guidelines and positional articles of EAACI (European Academy of Allergy and Clinical Immunology) and WAO (World Allergy Organization) [1, 2].

The diagnosis of anaphylaxis is based primarily on a detailed episode history, including information on all exposures and events in the hours leading up to onset of symptoms, for instance, physical activity, taking drugs, infectious disease, stress, journey or other violations of the daily routine. The key to diagnosis is pattern recognition: the sudden appearance of characteristic symptoms and signs within a few minutes or hours after exposure to known or potential triggers, often followed by their rapid progression within a few hours.

Clinical criteria for diagnosing anaphylaxis are currently used to make a diagnosis, proposed and recommended by the World Allergy Organization (WAO) in 2020 [3]. Based on them, anaphylaxis if highly probable under any of the following two criteria (Table 1).

The absence of generally accepted encryption for this nosology introduces a certain level of complexity in evaluating real epidemiological indicators of anaphylaxis. The identification of cases using systems of medical coding, such as ICD-10, is a common general methodological approach, though is prone to misclassification as there is no generally accepted code for anaphylaxis, which can appear under other diagnoses: allergic urticaria (L50.0), unspecified

Table 1. **Clinical criteria for anaphylaxis (World allergy organization anaphylaxis guidance, 2020)**
Таблица 1. **Клинические критерии анафилаксии (World allergy organization anaphylaxis guidance, 2020 г.)**

Criterion	Characteristics of symptoms
1	Acute onset of the disease (from a few minutes to a few hours) with simultaneous lesion of the skin, mucous membrane or both (e.g., generalized urticaria, itching and hyperemia, swelling of the lips, tongue, uvula) and combined with one of the following symptoms: A. Respiratory disorders (e.g., shortness of breath, rales-bronchospasm, stridor, PEF decrease, hypoxemia); B. Blood pressure reduction or accompanying symptoms of target organ dysfunction (e.g., hypotension (collapse), fainting, urinary incontinence); C. Severe gastrointestinal symptoms (e.g., severe spastic abdominal pain, repeated vomiting), especially after exposure to non-food allergens.
2	Acute onset of the disease in the form of hypotension* or bronchospasm or a lesion of the larynx** after exposure to a known or highly suspected allergen*** for this patient (from a minute to a few hours****), even in the absence of typical skin lesions.

* Hypotension is defined as a decrease in systolic blood pressure more than 30 % of this person's baseline (infants and children under 10: systolic BP less than (70 mmHg + [2 × age in years]), adults and children over 10: systolic BP less than < 90 mmHg).

** Larynx-related symptoms include stridor, voice changes, odynophagia, symptoms of lower respiratory tract, should not be caused by common inhalant allergens or food allergens, which are believed to cause "inhaled" reactions in no ingestion.

*** An allergen is defined as a substance (usually protein), capable of triggering an immune response that may lead to an allergic reaction. Most allergens act via IgE-mediated pathways or by direct activation of mast cells.

**** Most allergic reactions develop rapidly, however, delayed response with onset from 10 hours after ingestion may occur for some food allergens (e.g., alfa-Gal) or be secondary to immunotherapy.

urticaria (L50.9), angioedema (T78.3), unspecified anaphylactic shock (T78.2), anaphylactic shock due to adverse food reaction (T78.0), anaphylactic shock due to adverse exposure to the right medication or the drug, administered properly (T88.6) that leads to difficulty in monitoring epidemiological data on anaphylaxis [4].

Therefore, unlike most allergic or hypersensitive states, such as asthma or rhinitis, epidemiological data on anaphylaxis worldwide remain scarce, which makes it difficult for comparable morbidity statistics [5, 6]. They can vary greatly, depending on information gathering and statistical processing, but in general demonstrate increased incidence of anaphylaxis [5, 7, 8, 9].

In recent years there has been an increasing interest in epidemiology of anaphylaxis due to a growth trend in this pathology in most developed countries all over the world over the past three decades. According to published data, the number of hospitalizations for anaphylaxis have increased in Great Britain, the USA, Canada and Australia. For instance, European data point to incidence rates of anaphylaxis from all causes in the range from 1,5 to 7,9 per 100 000 people a year, however, 0,3 % (95 % CI 0,1–0,5) of population are estimated to experience anaphylaxis at some point in life [10, 11, 12]. In Great Britain the number of hospitalizations for anaphylaxis has increased by 615 % over the 20-year period; similar data were provided by Australian researches [13]. According to emergency inpatient evaluation in hospitals of the USA, 1 in 3000 people suffers from anaphylactic reaction [14, 15]. American research for the period 2005– 2014 describes an increased incidence of anaphylaxis in all age groups, while the maximum increase was in a patient group aged 5–17 [14, 12]. A recent systematic review Wang et al shows an increase incidence of anaphylaxis among children, noting that the morbidity rate of anaphylaxis varies around the world from 1 to 761 incidents per 100 000 children a year [16].

Mortality from anaphylactic reactions in all age groups is from 0,5 to 1 % of cases per 1 million people a year [18]. Food anaphylaxis is the cause of death in 0,06 % of cases per 100 000 children aged 0–15 years a year [19].

There are currently several studies on epidemiology of anaphylaxis in the regions, published in the Russian Federation, but there are no presented systematic data on the incidence of anaphylaxis in the country [2, 10, 20, 14]. The most known ones, which are given in updated Federal clinical guidelines of the Russian Federation, show that the incidence of AS in Kazan in 2012 was 0,37 per 10 000 people and mortality was up to 1 % [10].

Therefore, the study of regional particularities of anaphylaxis in the Russian Federation is relevant.

OBJECTIVE OF OUR STUDY: to study clinical features and provide medical care for anaphylaxis in children of the Ryazan region in real clinical practice.

MATERIALS AND METHODS

It was an open retrospective study.

The first stage included a retrospective analysis of medical records: the history of a child development (112/y form) and discharge summary (027/y form) of children aged 0-18, living in the territory of the Ryazan region and undergoing “an acute allergic reaction with the code МКБ-10 (allergic urticaria (L50.0), unspecified urticaria (L50.9), angioedema (T78.3), unspecified anaphylactic shock (T78.2), anaphylactic shock due to an adverse food reaction (T78.0), anaphylactic shock due to adverse exposure to the right medication or a drug, administered properly (T88.6)) in the anamnesis from January, 2017 to December, 2022. For collecting documentation and identifying incidence, we contacted City Children’s Clinics № 1, 2, 3, 6, 7 in Ryazan and the Ryazan regions via regional pediatricians.

The data were collected with oral voluntary consent from children and their legal representatives. In all the tables of statistical processing, except the primary one, the interviewees are presented under serial numbers. The telephone survey was carried out on the basic questions to determine compliance with the clinical criteria for anaphylaxis diagnosis if at least one of the two criteria coincided, provided by the World Allergy Organization (WAO) in 2020, the child was chosen for further participation in the study [3]. The survey was conducted in the form of a telephone questionnaire based on the adapted one (Appendix 1).

SPSS V24.0 package was used for statistical processing, including descriptive statistics. To describe quantitative indicators of the studied data Me median was used in the range, the lower boundary of which is the first quartile Q_1, and the upper boundary — the third quartile Q_3 in the Me format [Q_1; Q_3]. The study considered only independent data

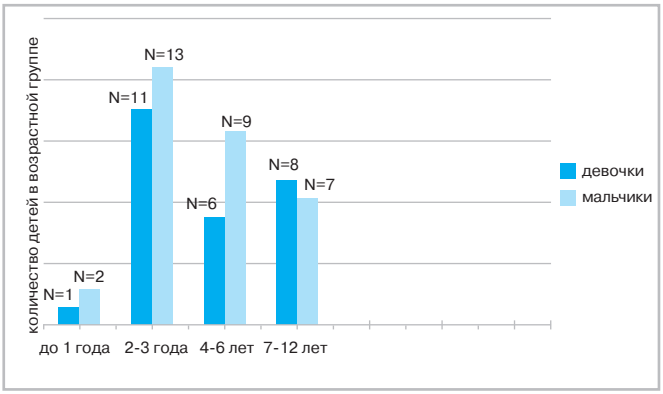

Fig. 1. **Age and sex structure of children in the Ryazan region**
Рис. 1. **Возрастно-половая структура детей Рязанской области**

groups. The statistical significance of different values for binary and nominal indicators were determined using parametric criterion χ_2. The level of statistical significance was $p < 0,05$.

RESULTS AND DISCUSSION

The Ryazan region consists of 4 city districts and 25 municipal regions [21]. The study involved all city children's clinics of Ryazan city and areas of the Ryazan region. According to preliminary estimates as of January, 1, 2022 the child population under 18 was 194,400 people.

The vast majority of children live in Ryazan city — 73,3 %, in rural areas— 26,7 % [22].

The scope of the study amounted to 300 children with a diagnosed acute allergic reaction from January 2017 to December 2022, of which 57 children aged 7 months — 12 years (19 %) met the clinical criteria of anaphylaxis by phone survey. Of these, 48 children (84,2 %) were city dwellers, 9 (15,8 %) lived in rural areas. The answers of children's parents to the telephone survey were analyzed statistically.

Evaluating regional epidemiology of anaphylaxis in the age aspect, it is possible to note the minimum age of the onset of anaphylaxis, which is 7 months, the maximum one is 12 years. Median (Me) age of anaphylaxis onset is 3,5 [2; 6] years. Gender has no impact on the onset of anaphylaxis symptom as there are 29 boys (50,9 %) and 28 girls (49,1 %), though, according to published data, a higher incidence of anaphylaxis can be traced among male patients aged 10 that disappears after this age [4, 14, 23]. However, there are very few works on the assessment of gender differences in the onset and development of anaphylactic reactions (Fig. 1).

Evaluating clinical syndromes of anaphylaxis by the description in medical records and the answers, given by our patient, we identified lesions of skin and mucous membranes (n = 45) in 67,2 %. Disorders of the respiratory system were the next in the incidence (n = 8 (11,8 %), ($\chi_2 = 38,2$; $p < 0,001$)), followed by gastrointestinal (n = 7 (10,3 %) and cardiovascular (n = 2 (2,9 %)) manifestations. Urticaria was the most common symptom (n = 47 (69,1 %) from the skin, laryngospasm and bronchospasm — from the respiratory system (n = 7 (10,8 %)). Combination of signs of skin and respiratory system lesion prevailed (n = 5 (7,5 %)).

Analyzing comorbidity of allergic diseases in children, undergoing anaphylaxis, we noted that it was a debut of clinical manifestations (n = 39,

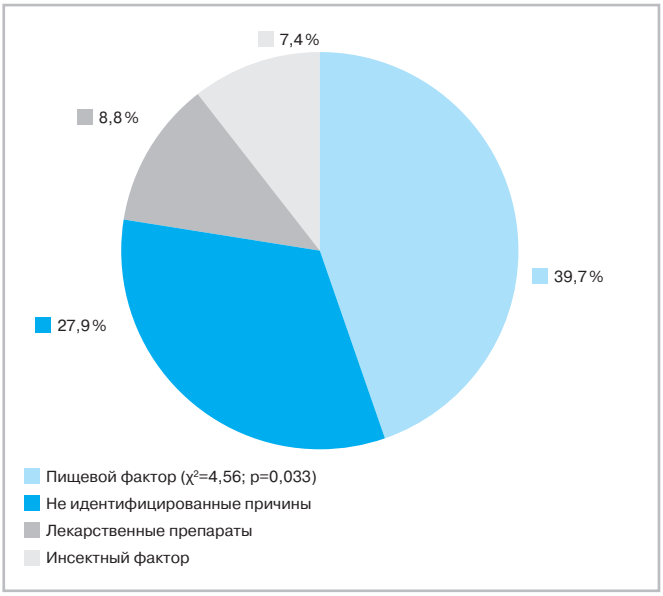

Fig. 2. **A causally significant factor in the development of anaphylaxis in children of the Ryazan region**
Рис. 2. **Причинно-значимый фактор в развитии анафилаксии у детей Рязанской области**

(57,4 %)). Atopic dermatitis was found in 8 children (11,85 %), allergic rhinitis (n = 5 (7,4 %), bronchial asthma (n = 1 (1,5 %), gastrointestinal diseases (n = 1 (1,5 %), chronic urticaria (n = 1 (1,5 %)).

The prevalence of anaphylaxis in children depends on a causally significant trigger and the age of patients under consideration. According to published data, food allergy is one of the most common causes of anaphylaxis in general and in the pediatric population in particular, it is the cause of 30–50 % of all cases of anaphylactic reactions in the general population and 81 % of cases of anaphylaxis in children [17, 24, 25, 26]. According to Russian authors, patients die from anaphylaxis on food allergens 6-7 times as often as from insect bites. In about one-third of cases among hospitalized with anaphylaxis, the reason of severe reactions is food products [2, 10, 20, 27]. Our work evaluated triggers of anaphylaxis according to anamnestic data in the medical records, parents' responses to the telephone survey and recorded the predominance of anaphylactic reactions, associated with food (n = 27 (39,7 %), (χ_2 = 4,56; p = 0,033)). Drugs take the second place after food among the known causes in children (n = 6 (8,8 %)). This trigger plays a leading role by the adolescent period that correlates with the literature data [24]. Following are insect bites — about 7,4 % of polled. And the survey method could not identify a provoking factor in 27,9 % of cases (Fig. 2).

The most common food triggers of anaphylaxis were presumably products, containing cow's milk protein (63 %), followed by fish or seafood (21 %) and nuts (7 %). Food triggers were most widespread in children under 6 (83 %), while drugs (30 %) and insect bites (28 %) were more common in the age group of 7-12 years.

According to modern care protocols and guidelines in anaphylaxis, adrenaline is the first line drug treatment [1, 2, 3]. However, according to our data, its use was recorded only in 5 % of cases in real clinic practice, and according to the literature, the use of adrenaline is described in 25 % of cases of acute allergic reactions in Europe, 44 % in Japan, 49,6 % in the USA, 46 % in Portugal and 9,3 % in Beijing [28]. In most cases glucocorticoids were used — 48 patients

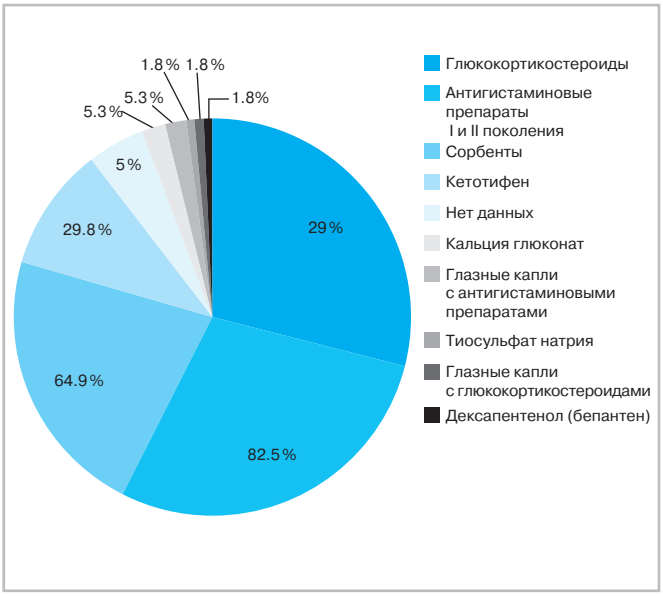

Fig. 3. **The volume of therapy when providing care to children with anaphylaxis in real clinical practice**
Рис. 3. **Объем терапии при оказании помощи детям с анафилаксией в реальной клинической практике**

(84,2 %) that is much higher than the use of adrenaline, followed by antihistamines of I and II generation and drugs, which are not listed in the FCG of the Russian Federation in assisting children with acute allergic reactions and anaphylaxis in general (Fig. 3).

Analyzing the scope of the therapy, it can be assumed that adrenaline administration might have been delayed due to the absence of signs of hypotension as many histories did not provide data of blood pressure monitoring. Besides, an accurate blood pressure measurement in young children is challenging in real clinical practice. Prospective study, carried out by Chinese researchers, showed that blood pressure measurement in children under 5 in the emergency room may be inaccurate due to the effect of fear and anxiety [28]. Literary sources name three main causes of low use of adrenaline. First, it is failure to recognize and diagnose anaphylaxis. Online survey of 7822 Medscape users showed that only 49 % of doctors were able to properly identify and diagnose food anaphylaxis, suggesting that inadequate identification and diagnostics affects the use of adrenaline [29]. Second, spontaneous anaphylaxis remission also influences on the rate of adrenaline administration [28]. Third, there is a lack of knowledge about adrenaline that further affects its use [30]. Since the delay or failure of adrenaline administration might be associated with a fatal reaction, medical personnel should certainly receive further training in recognizing and treating anaphylaxis.

CONCLUSION. The epidemiological study of anaphylaxis in the Ryazan region was a pilot project for our region. It showed difficulties both in the organization and interpretation of the data obtained. According to preliminary results, food allergy is a frequent trigger of anaphylaxis in children of the Ryazan region. Regional studies of anaphylaxis in children in real clinical practice make it possible to identify not only the features of this urgent pathology, but also to note the problems of providing primary medical care in order to improve it. Further study of population models of anaphylaxis, apparently, should be based on the creation of a unified questionnaire of the pediatric community, following the example of the ISAAC questionnaire or the creation of registers, which will help more accurately determine the true prevalence of anaphylaxis, determine the need to identify anaphylactogenic relevant molecules in the pediatric population, and improve the provision of assistance to children with these conditions.

APPENDIX 1

Anaphylaxis is a severe acute allergic reaction, including manifestations on the part of 2 or more systems and leading to a life-threatening condition. For studying the incidence of anaphylaxis in the Ryazan region, please fill out your doctor's questionnaire.

1) How old are you? (your child)

2) Gender of your child:
   - o Male
   - o Female

3) The name of the school/ preschool institution, which your child attends?

4) Does your child suffer from anaphylaxis (allergic shock)?

5) Do you know if there are other children, suffering from anaphylaxis, in the school/ kindergarten, which your child attends?

6) If yes: who gave you information about the other children, suffering from anaphylaxis?
   - o Teacher
   - o Parent Committee
   - o Headmaster
   - o Own child
   - o Other parents

7) When did your child experience anaphylactic reaction for the first time?
   - o 6
   - o 12
   - o 18
   - o More than 24 months ago

8) How often does your child experience anaphylactic reactions?
   - o once
   - o 5–2 times
   - o More than 5 times

9) Where does your child have anaphylactic reactions? (more than one answer is possible)
   - o At home
   - o In the kindergarten/school
   - o At the restaurant/cafe
   - o At friends'/relatives'
   - o On vacation
   - o In public places
   - o In the hospital (except diagnostic provocations)
   - o Other_____

10) What are the first symptoms of anaphylactic reactions (multiple choice is possible):
   - o Headache
   - o Fever
   - o Tingling in the mouth
   - o Abdominal pain
   - o Diarrhea
   - o Cough
   - o Dizziness
   - o Fainting
   - o Itching
   - o Urticaria
   - o Swelling of the throat (larynx, neck)
   - o Vomiting
   - o Feeling short of breath/dyspnea
   - o Difficulty breathing
   - o Chills/trembling in the body
   - o Cardiac arrest
   - o Swollen face
   - o Redness
   - o Nausea
   - o Abdominal cramps
   - o Trips
   - o Apnea
   - o Sleepiness
   - o Fear/ panic
   - o Other_____

11) What was the reason?
   - o Food (which?)
   - o Peanut
   - o Wheat
   - o Soy
   - o Egg
   - o Nuts
   - o Milk
   - o Fruits
   - o Other _____

12) Who was the first one to face/treat anaphylactic reaction?
   - o Parent
   - o Family doctor
   - o Outpatient treatment in a polyclinic
   - o Teacher

- Pediatrician
- Hospital
- Emergency doctor
- Accident and Emergency

13) Which type of treatment was administered?
- Prescription of emergency drugs
- Call of a doctor
- Intravenous drip
- Call for ambulance
- Oxygen insufflation
- Lying position
- Nothing

14) What treatment was prescribed?
- Administration of adrenaline
- Antihistamines
- Glucocorticosteroids
- Inhaled salbutamol/Berodual/ Pulmicort
- Other _____

15) Did your child get the emergency kit?
- Yes
- No

16) If yeas, what did the kit contain?
- Administration of adrenaline
- Antihistamines, which ones?
- Glucocorticosteroids, which ones?
- Inhaler, used in asthma (β_2-agonist), which one?
- I don't know
- Other _____

17) Were you taught how to use the emergency kit?
- Yes, I was
- Yes, I was shown how to use the kit
- Yes, we were trained on a mannequin; by the video; visually
- No

18) Have you ever had to use the kit to assist in an emergency situation?
- Yes
- No

19) If you were taught, who provided training?
- Ambulance doctor
- Pharmacist
- Nutritionist
- By myself (how?)
- Doctor in a hospital
- Friends/family
- Allergist
- Nurse
- Patient organization
- Other _____

20) Did your child receive a special emergency document/certificate?
- Yes (Who gave it?)
- No

21) Does your child wear a medical alert bracelet?
- Yes
- No
- Other _____

22) Have you informed the school/kindergarten about allergy?
- Yes, the teacher
- Headmaster
- No, nobody

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Стежкина Е. В., Агапова А. И. — разработка дизайна исследования, участие в проведении исследования, анализ результатов, статистическая обработка и интерпретация данных, написание статьи.

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A clinical case of autosomal recessive agammaglobulinemia with B-cell deficiency

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Annotation

Background. Primary agammaglobulinemia is the result of specific changes in B-cells that lead to low antibody production. A preliminary diagnosis is established if there is a history of frequent bacterial infections (otitis media, sinusitis, skin abscesses), including severe course, in some cases caused by opportunistic flora and atypical mycobacteria; low levels of immunoglobulins. The main symptoms of primary immunodeficiency in a child from this clinical example were frequent recidivating bronchial obstruction with the development of pneumonia.

Presentation of the clinical case. The publication presents a clinical case of autosomal recessive agammaglobulinemia with B-cell deficiency in a child of 2 years, 7 months. During the follow-up period from 4 months to 2 months, 7 months, the child had 3 episodes of pneumonia, 3 episodes of purulent otitis media. The child repeatedly underwent inpatient treatment, where he received broad-spectrum antibiotics as treatment. Based on the examination (IgA (0.02 g/l), IgG (0.3 g/l), IgM (0.07 g/l) and the absence of $CD19^+$ cells), the diagnosis of "Primary immunodeficiency, agammaglobulinemia" was made, which was subsequently confirmed by the RDC of Moscow. From the moment of diagnosis, the child receives intravenous immunoglobulins at a dose of 7.5 g. and antibacterial therapy.

Conclusion. Early recognition and diagnosis of these conditions is crucial to improve outcomes and prevent complications.

Keywords: Primary immunodeficiency, agammaglobulinemia, autosomal recessive form, children, clinical case.

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Клинический случай аутосомно-рецессивной агаммаглобулинемии с дефицитом В-клеток

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Аннотация

Введение. Первичная агаммаглобулинемия является результатом специфических изменений в В-клетках, которые приводят к низкой выработке антител. Предварительный диагноз устанавливается при наличии в анамнезе частых бактериальных инфекций (отиты, синуситы, абсцессы кожи), в том числе тяжелого течения, в некоторых случаях вызванных условно-патогенной флорой и атипичными микобактериями; низкого уровня иммуноглобулинов. Основными симптомами первичного иммунодефицита у ребенка из данного клинического примера являлись частые рецидивирующие бронхообструкции с развитием пневмонии.

Изложение клинического случая. В публикации представлен клинический случай аутосомно-рецессивной агаммаглобулинемии с дефицитом В-клеток у ребенка 2 лет 7 мес. В период наблюдения с 4 мес. до 2 лет 7 мес. у ребенка наблюдались 3 эпизода пневмонии, 3 эпизода гнойного среднего отита. Ребенок неоднократно проходил стационарное лечение, где в качестве лечения получал антибиотики широкого спектра действия. На основании обследования (IgA (0,02 г/л), IgG (0,3 г/л), IgM (0,07 г/л) и отсутствие $CD19^+$-клеток) был выставлен диагноз «Первичный иммунодефицит, агаммаглобулинемия», который в последующем был подтвержден в Российской детской клинической больнице (РДКБ) г. Москвы. С момента постановки диагноза ребенок получает ВВИГ в дозе 7,5 г и антибактериальную терапию.

Заключение. Раннее распознавание и диагностика этих состояний имеют решающее значение для улучшения результатов и предотвращения осложнений.

Ключевые слова: первичный иммунодефицит, агаммаглобулинемия, аутосомно-рецессивная форма, дефицит В-клеток.

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INTRODUCTION. Agammaglobulinemia is a type of primary immunodeficiency, characterized by severe forms of decrease in the level of all types of immunoglobulins in the blood serum and the absence of B-cells in the blood [1, 2, 3, 4]. Prevalence of agammaglobulinemia range from 1:100000 to 1:200000 [5]. Agammaglobulinemia should be considered in detail, paying special attention to the study of life and the disease history. The patient has frequent recidivating bronchial infections at the age of 5, severe bacterial infections, such as meningitis and septicemia, aplasia of lymphoid tissue [3, 6]. Laboratory evaluation includes the analysis of leukocyte formula, the state of the cellular component of immune system (immunophenotyping of B- and T-cells), levels of ɣ-globulins, quantitative levels of immunoglobulins in the serum (IgM, IgG, IgA, IgE) and specific antibody responses to both protein and polysaccharide antigens,

as well as whole-exome genome sequencing [3]. In the immunological study agammaglobulinemia is manifested in the form of IgG level decline in the blood below 1,0 g/l in combination with the decrease in IgM concentration below 0,2 g/l and IgA level below 0,1 g/l with a normal or reduced level of peripheral B-cells [5]. Nowadays there are several reported genes, defect in which might be the cause of agammaglobulinemia: BTK, IGHM, IGLL1, CD79A, CD79B, BLNK and PIK3R1 [7]. The diagnosis is confirmed by genetic analysis and the detection of mutations, associated with X- and autosomal recessive or dominant chromosome. X-linked form (XLA) is characterized by the absence of circulating B cells and a pronounced decrease in all serum immunoglobulins due to mutations in the BTK gene [2]. The only difference between autosomal recessive and XLA-agammaglobulinemia is that the former occurs in females. The incidence: 1:100000–1:500000 population [2, 5]. Inherited immune system disorders, XLA, or Bruton disease affects only men [2]. Autosomal recessive agammaglobulinemia is a rare type of primary immunodeficiency, characterized by mutations in genes, responsible for early differentiation and B-cell function [8]. These are mostly related to defects in the components of BCR complex. Transition from pro-B-cells to pre-B-cells, along with the consistent rearrangement of immunoglobulin genes and a normal development of B-cells, requires surface expression of pre-BCR functional complex. As a result, defects of the very BCR structure, including μ heavy chain, surrogate light chains (VpreB and λ5), Igα (CD79) and Igβ (CD79B) genes, which form heterodimeric transmembrane signal transduction elements, lead to autosomal forms of agammaglobulinemia. After BTK gene, encoding μ heavy chain, IGHM (located on chromosome 14q32.33) is the second most frequently mutated gene in patients with agammaglobulinemia, but it is still about 5% of patients [3, 9].

CLINICAL CASE REPORT

The girl A., at the age of 2 years and 7 months, was admitted to the emergency room of Pediatric Republican Clinical Hospital (PRCH), Saransk, December, 10, 2018 at 11:05 with complaints about an increase in body temperature to 38,0 °C, unproductive cough with sparse serous sputum, shortness of breath at rest, using accessory muscles, weakness and loss of appetite.

Life history. The child from the 2nd pregnancy, occurring against the background of mild iron-deficiency anemia, exacerbation of bronchial asthma, the presence of antibodies to herpes simplex virus in the blood, cytomegalovirus, toxoplasma, 2 births at 39 weeks. Natural delivery. The condition at birth is severe due to reduced neuro-reflex excitability. Birth weight is 3250 g, height is 50 cm. APGAR score is 7/7.

Disease history: the parents noted increased body temperature to 38 °C, productive cough, lethargy and loss of appetite for the first time at the age of 4 months. The child was hospitalized with the above described complaints, where, according to the results of physical (fine moist rales on the right side during auscultation), laboratory (leukocytosis with a shift of the leukocyte formula to the left and a moderate increase in the number of neutrophils) and hardware examination (low-intensity infiltration is determined in the lower lobe of the right lung on the radiograph of the thoracic organs in direct projection against increased pulmonary pattern) she was diagnosed with "Community-acquired right-sided lower lobe pneumonia of moderate severity. RF 0 degree". Against the background of antibiotic treatment (ceftriaxone solutions, 130 mg + NaCl 0,9 % 100 ml iv once per day for 7 days; azithromycin suspension 1,5 ml orally once per day for 5 day): there is a positive dynamic in the form of normalization of body temperature on the 4th day of hospital stay. With repeated radiographic examination on the 14th day: pulmonary pattern is enhanced, enriched, radiological signs of infiltrative changes in lung have not been defined.

At the age of 7 moths there was an episode of an increase in body temperature to 39 °C, tearfulness, irritability, abundant discharge of pus; examined by an otorhinolaryngologist at the place of residence, diagnosed with "Acute purulent otitis media", and symptomatic therapy and broad-spectrum antibiotic are prescribed as treatment— cefixime suspension, 3 ml orally, once per day for 7 days.

At the age of 11months (according to the parents, without documentary proof) there was hospitalization with the diagnosis "Left-sided bronchopneumonia".

According to the discharge summary, there was hospitalization to PRCH, Saransk, since the age of 1 year 5 months and for 2 months with the diagnosis "Obstructive bronchitis, acute laryngotracheitis, laryngeal stenosis of III degree, pseudomembranous candidiasis, immune thrombocytopenic, purpura complicated by intestinal bleeding and anemia of moderate severity. Immunodeficiency

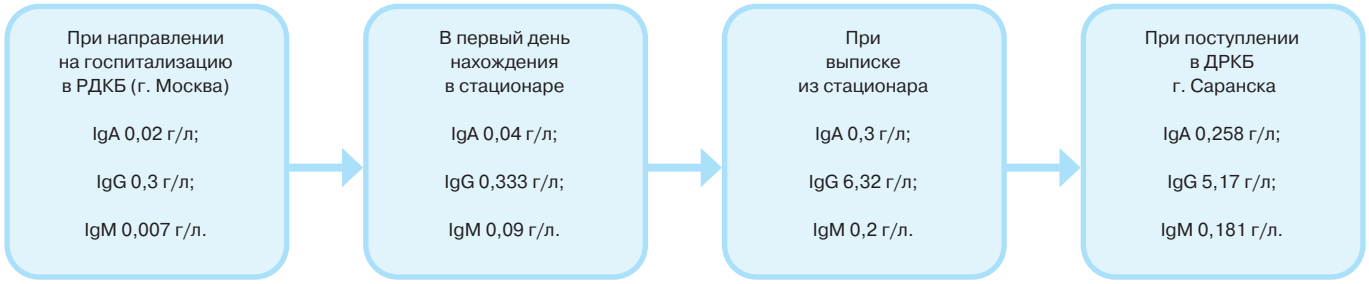

Fig. 1. **Immunoglobulin levels in the patient's blood serum**
Рис. 1. **Уровни иммуноглобулинов в сыворотке крови пациентки**

state is unspecified". There was red blood cell transfusion, replacement therapy with normal human immunoglobulin 5 g intravenous drip, antibiotic therapy in the form: ceftriaxone solution 200 mg + NaCl 0,9 % 200 ml IV once per day for 10 days; antifungal drug was prescribed: fluconazole suspension 3 ml orally once per day for 3 days.

Over the next4 months (according to the parents) she suffered from acute tracheitis and purulent otitis media. Follow-up and treatment were carried out on an outpatient basis.

According to the parents, there was an increase in temperature up to 38,5 °C, productive cough with purulent sputum discharge, tearfulness and irritability at the age of 2 years and 2 months. The radiograph of thoracic organs determines intensive infiltration on the left in the direct projection against the backdrop of increased pulmonary pattern. Hospitalized with the diagnosis "Community-acquired left-sided pneumonia of moderate severity. RF 0 degree". The child was first consulted by an allergist-immunologist, and immunological examination was recommended, according to which there was a significant decrease in the concentration of serum IgA (0,02 g/l), IgG (0,3 g/l), IgM (0,07 g/l) and lack of $CD19^+$ cells.

Due to the deterioration and reduction in serum immunoglobulins, the child was diagnosed with "Primary immunodeficiency, agammaglobulinemia" and sent to the Department of Clinical Immunology and Rheumatology of RPCH, Moscow. On admission there were complaints of cough and mucous discharge from the nose. According to x-ray data, signs of right-sided polysegmental pneumonia were visualized in the lungs. Data of immunological examination revealed a decrease in serum immunoglobulins: IgA to 0,04 g/l (1–3,5 g/l), IgM to 0,09 g/l (0,8–2,5 g/l), IgG to 0,33 g/l (9–18 g/l) and reduction in $CD19^+$ cells to 1% (5–19%). According to screening there was the clinical diagnosis of "Primary immunodeficiency with B-cell deficiency". By using a genetic research method, the child was diagnosed with autosomal recessive form of agammaglobulinemia. Replacement therapy was carried out during hospitalization — human normal immunoglobulin 7,5 r IV drops, antibiotic therapy in the form: cefepime solution 750 mg + NaCl 0,9 % 200 ml IV twice a day for 10 days, symptomatic therapy. There was positive dynamics during treatment in the form of improved overall well-being and increased concentration of serum immunoglobulins: IgA 0,3 g/l (1–3,5 g/l), IgG 6,32 g/l (9–18 g/l), IgM 0,2 g/l (0,8–2,5 g/l). In the future life-long replacement therapy with IVIG is recommended.

At the age of 2 years and 7 months the parents noted an increase in body temperature to 38 °C, the appearance of cough, nasal discharge of greenish colour, nasal congestion. Physical examination data: difficulty in nasal breathing, puromucous discharge from the nose, auscultatory puerile respiration, in all pulmonary fields, wheezing is not heard. Radiography of the thoracic organs identified: pulmonary pattern is enhanced, low-intensity infiltration is detected on the right. RT 24 per minute. According to immunological laboratory data: humoral immunity — IgA 0,258 g/l (1–3,5 g/l), IgM 0,181 g/l (0,8–2,5 g/l), IgG 5,17 g/l (9–18 g/l). There was an increase in the content of $CD4^+$- (46% (55–80%)) and $CD8^+$-lymphocytes (16% (31–51%)), single $CD19^+$-lymphocytes (2% (5–19%)). Broad-spectrum antibiotics were prescribed

— ceftriaxone solution 200 mg + NaCl 0,9 % 200 ml IV once per day for 10 days, symptomatic therapy; due to exacerbation of chronic foci of infection, it was decided to complement the planed course with IV administration of 5 g of normal human immunoglobulin.

CONCLUSION

Primary immunodeficiency and autosomal recessive agammaglobulinemia with B-cell deficiency were diagnosed in this clinical case. PID are severe life-threatening diseases in young children. Timely diagnosis before developing severe infectious processes in the patient significantly improves the prognosis for survival of this group of patients. Neonatal screening (TREC и KREC) is an important measure for early diagnosis of patients with PID.

INFORMED CONSENT

The legal representative of the patient provided voluntary informed consent for publishing the description of the clinical case in the journal "Allergology and Immunology in Paediatrics": the date of signing the document by the legal representative of the patient— 01.02.2018.

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Evgenia N. Tyagusheva — preparation of a draft article.
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ВКЛАД АВТОРОВ В РАБОТУ

Негоднова Е. В., Искандярова М. С. — концепция исследования.
Тягушева Е. Н. — подготовка черновика рукописи.
Радаева О. А., Фоминова Г. В. — доработка и редактирование рукописи.

Oral manifestations and dental considerations of hereditary haemorrhagic telangiectasia in paediatric population — a systematic review

SCO — краткое сообщение

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Симптомы в полости рта и стоматологические аспекты наследственной геморрагической телеангиоэктазии у детей — систематический анализ

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INTRODUCTION:

One in 5000-8000 affected individuals in the population in general, is due to autosomal dominant hereditary disorder such as Osler-Weber-Rendu syndrome like Hereditary Haemorrhagic Telangiectasia, (HHT). Malformed vascular networks and endothelial cells are due to mutations in genes such as endoglin or ACVR1 which might affect the TGF-beta superfamily. Right-to left shunts are caused by lack of capillaries intervening the veins and arteries in case of arteriovenous malformations in HHT. Severity of HHT increases with the age. After removal of the pressure, refill occurs in which, might come before pressure blanching in relation to Telangiectasias in oral cavity and nasal cavity. Minimal trauma may result in tearing of lesions which are usually seen in superficially in relation to mucosal surface. Repeated bleeding from nasal areas is most common clinical presentation of HHT[1,2,3,4,5]. Arteriovenous malformations may occur in lungs, hepatic region or cerebral system such as PAVM,and CAVM. Bacteraemia might result due to performance of dental procedures such as removal of tooth, cleaning of teeth and root canal therapy. Presence of anaerobic bacteria is seen more than the aerobic bacteria. There is a relationship between the per iodontal abscess and brain abscess. Curaçao criteria consists of repeated bleeding from nasal region, occurrence of Telangiectasias in relation to oral cavity, labial mucosa, fingers, nasal mucosa and mucosa of gastro intestinal tract, AVM in brain, spinal cord, liver and the lungs and the first-degree relative with HHT[6,7,8,9,10].

The main objective of this study was to determine the oral manifestations of Hereditary Haemorrhagic Telangiectasia in paediatric patients and fill the gap between the paediatrics and dentistry.

MATERIALS AND METHODS:

This systematic review was followed as per the PRISMA guidelines.

ELIGIBILITY CRITERIA:

Research articles conducted in English such as randomised controlled trials, cohort trials, case control trials, cross sectional studies, opinion articles and case reports pertaining to paediatric population in relation to HHT were considered.

SEARCH STRATEGY:

Detailed and relevant documents search was conducted in the following databases such as MEDLINE. Duplicate records were removed to improve the accuracy. All the 5 articles were identified and screened. The search strategy included names such as Rendu, Osler, Weber syndrome, Hereditary, Haemorrhagic, Telangiectasia, paediatric population, oral and dental. The selected articles were read fully and summarised in following text.

RESULTS:

The findings of this review were based on 6 full text articles pertaining to oral manifestations of Hereditary Haemorrhagic Telangiectesia in paediatric population only. The article selection includes reviews, narrative reviews and original research. Dental professions are the first persons

Table 1. **Genes involved in HHT**
Таблица 1. **Гены, участвующие в развитии НГТ**

Gene	Chromosome Locus	Protein
ACVRL1	12q13.13	Serine/threonine-protein kinase receptor R3
ENG	9q34.11	Endoglobin
SMAD4	18q21.2	Mothers against decapentaplegic homolog 4

to come across to identify the oral manifestations of Hereditary Haemorrhagic Telangiectesia in paediatric population. The most commonly affected sites are the oral mucosa, gingiva, palate, tongue, nasal mucosa, etc.

General practitioner:

There is a link between PAVM and brain abscess. Bacteraemia can be formed even though regular tooth brushing is done. Dental procedures for the patients with PAVM and HHT should get the written consent for receiving the antibiotic prophylaxis prior to the dental treatments[11,12,13,14,15].

Oral Medicine:

Malformed capillary beds which blanch upon application of pressure are known as Telangiectasias. Specifically, Telangiectasias do not need any treatments.

Oral and maxillofacial surgery:

If we need any medical intervention, it can be managed by convention method, laser and electron usage[16,17,18,19,20].

Endodontics:

Endodontic therapy can be done in paediatric patients with HHT after getting proper informed consent.

Periodontology:

The periodontal prophylaxis includes oral hygienic instructions, rules and regulations, plaque control and scaling[21,22,23,24,25].

In summary, this systematic review highlights the gaps of knowledge in dental and oral considerations

Table 2. **Methods of treatment of hereditary hemorrhagic telangiectasia**
Таблица 2. **Методы лечения наследственной геморрагической телеангиоэктазии**

Author	Year	Article type	Main Field	No. patients	Treatment modalities/ Clinical relevance
Meir Mei-Zahav et al	2006	Cross-sectional study	OM	14	Cauterization and laser ablation
Jamie Mc Donald and David Stevenson	2006	Review	OM	-	Humidification, topical moisturizing therapy, haemostatic products, antifibrinolytic therapy, ablation therapy, systemic antiangiogenic agents, septodermoplasty, and nasal closure.
Cesare Danesino et al	2023	Review	OM	-	Argon plasma coagulation Embolization, Stereotactic radio surgery, and surgery.
Priya Verma	2022	Review	OM	-	Teeth cleaning, tooth extraction, orthodontic treatment, endodontics, clotting factor replacement, fluoride supplements, oral hygiene instructions, pit and fissure sealants, twice daily tooth brushing, mouth wash, dietary advice, haematologist opinion, prophylactic antibiotic therapy, and anti fibrinolytics
Vanishree Halasagundhi Shivakumar et al	2022	Review	OM	-	Tooth extraction, teeth cleaning, fluoride supplements, oral hygiene instructions, tooth brushing twice daily, mouth wash, endodontics, clotting factor replacement, dietery advice, prophylactic antibiotic therapy, haematologist opinion and anti fibrinolytic agent.
Ennio Bramanti et al	2014	Cross-sectional study	OM	116	Correction of coeliac disease, and paediatric dental treatment procedures.

of paediatric patients with Hereditary Haemorrhagic Telangiectasia and emphasises the importance of more studies in the particular field which includes case reports, original researches, etc. This may act as a reliable evidence and guide in clinical decision-making[26,27,28,29,30].

CONCLUSION:

This systematic review has the limitation in the research mainly in the field of paediatric oral and maxillofacial manifestations in relation to Hereditary Haemorrhagic Telangiectasia. This article might impart consciousness among the dental professionals to identify the disease since they are the first line of people who come across the condition. Future research relies on the oral and maxillofacial pathology mainly with HHT focusing on the paediatric, emphasising on the antibiotic prophylaxis, dental treatment procedures to be done and prognosis of the patients for the long-term follow-up.

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АЛЛЕРГОЛОГИЯ И ИММУНОЛОГИЯ
В ПЕДИАТРИИ
ALLERGOLOGY AND IMMUNOLOGY
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