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ABSTRACT
of the dissertation for the degree of Doctor of Philosophy

CLINICAL-IMMUNOLOGICAL FEATURES AND OPTIMIZATION OF COMPLEX TREATMENT ATOPIC DERMATITIS IN CHILDREN

Specialty: 3220.01 – Pediatrics

Field of science: Medicine

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GENERAL DESCRIPTION OF WORK

The actuality of the subject. One of the most common allergic diseases in childhood is atopic dermatitis, which has medical and social significance. The urgency of the problem of diagnosis and treatment of atopic dermatitis (AD) is the steady increase in the spread of the disease, the increase in its severe forms, the chronic relapsing course, the decline in the quality of life of patients, economic costs, side effects associated with pharmacotherapy and the lack of effective anti-relapse therapy [1, 2, 3].

According to modern concepts, AD – is a chronic inflammatory skin disease with hereditary immunodeficiency, characterized by recurrent age and typical clinical and morphological changes in the skin, a certain source of spread and itching of varying intensity of the skin [4, 5, 6].

According to epidemiological studies, the incidence of AD in the world is 5-10% among adults, 20-30% among children and adolescents, and 50-75% in the structure of allergic diseases [7]. To date, there is evidence of a pathophysiological link between severe AD in children and bronchial asthma and allergic rhinitis, and these pathol-

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ogies make up the so-called allergic (atopic) triad [8].

Currently, the pathogenesis of AD is considered as two interrelated links: 1) a defect of the skin barrier and 2) an immune inflammatory reaction that determines the typical symptoms of the disease - itching, edema, redness, immune-inflammatory reaction that determines dryness [9,10]. Disruption of the keratinization process, increased trans epidermal fluid loss, damage to structural proteins and changes in lipid composition weaken foreign substances and bacteria cross the skin barrier and trigger a cascade of immunological reactions. In this regard, the study of the characteristics of the immune mechanisms of the formation of AD in children, in particular, indicators of cellular and humoral immunity, cytokine status remains a promising area of research [11, 12].

Staphylococcus aureus plays a leading role in the pathogenesis of AD, as it is found in more than 90% of children with atopic dermatitis [13].

The gold standard in the treatment of AD is considered to be external therapy [14, 15]. However, the morph functional changes in the

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skin during AD, as well as the age-related anatomical and physiological features of the skin that allow rapid absorption of drugs from the skin in young children, makes it necessary to look for a more reliable external therapy scheme [16, 17].

The above data highlight the medical and social significance of the issue in relation to the high incidence of atopic dermatitis in children, the propensity for recurrence of the process and these factors dictate the need to improve treatments that can improve prognosis and achieve longer-term clinical remission. These define the goals and objectives of the current work.

Object of research. The contingent of the study consisted of 97 children (47 boys and 50 girls) aged 6 months to 17 years and suffering from various degrees of AD and in the period of exacerbation. The duration of the disease ranged from 1.6 months to 16.3 years. Patients in the acute phase were divided into three groups depending on the severity of the course of AD: Group I - mild (n = 23); Group II - moderately severe (n = 54) and group III - severe (n = 20).

The purpose of the research is to determine the characteristics of the course of atopic dermatitis in children based on the study of the dynamics of clinical and laboratory signs and immunological indicators and on this basis to develop optimal therapeutic tactics.

Research objectives:

1. To assess the clinical and anamnestic features of the onset and course of atopic dermatitis in children;

2. To determine the nature of cellular and humoral immune disorders in children with atopic dermatitis during periods of disease exacerbation and clinical remission;

3. To assess the level of integrated hematological indices in chil-

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dren with atopic dermatitis;

4. To determine the effect of the use of anaferon in the complex treatment (basic therapy) on the indicators of the cellular and humoral immune system in children with atopic dermatitis;

5. To assess the state of the microflora of the skin in children with atopic dermatitis during periods of exacerbation and remission;

6. To determine the therapeutic effect of the combined use of Anaferon, an immunomodulation with Pimecrolimus cream (Elidel), in the complex treatment of children with atopic dermatitis.

Research methods. In order to assess the clinical and anamnestic characteristics of children with atopic dermatitis in the study, a family anamnestic and allergological survey, general clinical, biochemical, microbiological, allergological and immunological analysis of blood in all children included in the study, ultrasound examination of the abdominal organs and peritoneal cavity (USI) conducted. In order to detect staphylococcus, general clinical and biochemical examinations of blood, urine and feces were performed using traditional methods of culture of the damaged area of the skin.

The main provisions of the dissertation:

1. Atopic dermatitis in children in modern times is accompanied by acute subjective symptoms, significant damage to the skin, an increase in the number of atopic diseases, high colonization of lesions with pathogenic S. aureus strains, increased resistance to standard treatments.

2. In children with atopic dermatitis, persistent changes in the quantitative ratios of different subpopulations of immunoregulatory cells have been identified, leading to impaired immunoregulatory index, synthesis of serum immunoglobulins and predominance of Th2-type cell response. An imbalance in the status of cytokines characterized by an increase in IL-4 and IFN-γ was identified.

3. In children with atopic dermatitis, a high degree of colonization of lesions with pathogenic S. aureus strains is observed in the microflora of the skin.

4. In children with atopic dermatitis, positive dynamics of clinical symptoms, improvement of the state of the immune and cytokine systems during remission under the influence of complex therapy,

including Elidel cream and Anaferon immunomodulator.

Scientific novelty of the research. For the first time in the study, a comprehensive assessment of the clinical status of indicators of the immune status and cytokine profile in children with atopic dermatitis was carried out. Analysis of the research results shows that the structural and functional properties of the skin, which is the primary immunological barrier in atopic dermatitis, are impaired, which leads to a change in all parameters of the immune system.

Based on the data obtained, it was determined that the imbalance of cytokines and regulatory T cells, abrupt changes in humoral immunity and nonspecific resistance are some of the most important factors in the development of the disease, affecting the synthesis of total IgE in the body patients with AD and immunity, IgE - demonstrates the superiority of dependent mechanisms.

As a result of the research, was proved, the effectiveness of complex therapy based on the identified disorders of the immune system which is manifested in the normalization of the immune and cytokine status in children with AD and a reduction in the period of remission of the disease.

Topical therapy, including the use of Elidel cream and the immunomodulatory drug Anaferon, has been shown to allow effective and safe control of allergic skin inflammation.

Practical significance of the research. A set of clinical and laboratory tests has been developed to monitor and predict the effectiveness of treatment, including the determination of the SCORAD index, the study of cellular, humoral and nonspecific immunity and cytokine status, and the state of the skin microflora.

The results of the study showed the appropriateness of assessing the level of cellular, humoral and nonspecific immunity, cytokines and integrated hematological indices of blood in children with AD to determine the severity and effectiveness of treatment. Based on the information obtained, a combination therapy scheme for AD in children has been developed.

Application of scientific research work. The results of the dissertation were applied in the teaching process of the Department of Allergology and Immunology of the Azerbaijan Medical University

and in the practical activities of the Ömür Clinic.

Discussion of the dissertation. The main provisions of the dissertation are presented at the XVII Republican Scientific Conference of Doctoral Students and Young Researchers (2013, Baku), International Journal on Immunorehabilitation, VIII World Congress On Immunopathology, Respiratory Allergy and Asthma, (London - 2012, April 27-30), 100th anniversary of the Medical Faculty Reported and discussed at the International Scientific-Practical Conference (Baku - 2019), at the meeting of the Specialized Approbation Commission (on "Pediatrics") at the Azerbaijan Medical University (June 17, 2011, protocol №10).

Publishing works. On the dissertation were published 7 scientific articles and 3 theses.

Volume and structure of the dissertation. Dissertation introduction (9,900 marks), literature review (46,300 marks), research materials and methods (20,300 marks), three chapters covering personal research (22,300+ 34,100+ 32,300 marks), discussion of the obtained results, summary, conclusions, practical recommendations (49,000 characters), 214,200 characters, consisting of sections of the bibliography, which includes 235 sources (17 Homeland, 218 foreigners). The scientific work is illustrated with 39 tables, 27 graphs and 1 picture.

MATERIALS AND METHODS OF RESEARCH

General characteristics of patients. In the study, 97 children (47 boys and 50 girls) aged 6 months to 17 years and suffering from various degrees of AD were examined in two stages (during exacerbation and clinical remission). The control group consisted of 15 practically healthy children without any allergic pathology.

Admission criteria:

- Clinical signs of atopic dermatitis in the period of exacerbation;
- Severity of atopic dermatitis according to the SCORAD index;
- from 6 months to 17 years;

Removal criteria:

- Atopic dermatitis in remission;
- Erythroderma condition;
- Presence of concomitant diseases during the period of exacerbation;
- Hypersensitivity to the components of the drug;
- Children under 6 months.
- Use of systemic glucocorticoid therapy for 4 weeks and restoring and moisturizing the skin barrier.

The diagnosis of AD was made on the basis of clinical, family and allergy anamnestic data.

The severity of clinical signs of AD and the effectiveness of treatment were assessed using the SCORAD index (Scoring of Atopic Dermatitis), a scale of severity of atopic dermatitis that includes objective (prevalence and intensity of skin damage) and subjective (intensity of skin itching and sleep disturbances) criteria.

The intensity of the clinical signs of AD was assessed based on six symptoms: erythema, edema / papule, aging / watery, excoriation, lichenification, and dry skin.

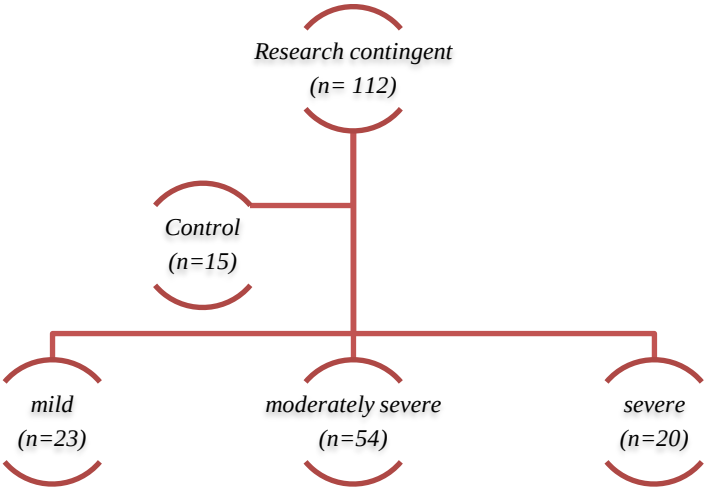
The SCORAD index is calculated according to the following formula:

$$S=A/5+7B/2+C,$$

where *A* – is the sum of the prevalence scores of the skin lesion, *B* – is the sum of the manifestations of the symptoms of atopic dermatitis, and *C* – is the sum of the subjective symptoms (itching, sleep disturbances).

The modified SCORAD index (S = A / 5+ 7B / 2) is calculated in patients younger than 7 years of age who are unable to assess subjective symptoms.

Patients in the acute phase were divided into three groups depending on the severity of the course of AD: group I - mild (n = 23); Group II - moderately severe (n = 54) and III group - severe (n = 20) (graph 1).



Graph 1. Distribution of children depending on the severity of atopic dermatitis.

In accordance with the dynamics of the SCORAD index, the effectiveness of treatment was assessed using the Therapeutic Effect Index (TEI), which was calculated as a percentage according to the following formula:

$$TEI = [(A1-A2)/A1]\times 100\%,$$

here *A1* – is the initial index, *A2* – is the post-treatment index.

Research methods. For all indications, the object of examination is pathological material obtained from venous blood and foci from the peripheral vein from the elbow flexion in the morning on an empty stomach.

Ultrasound investigation (USI) of patients, microbiological culture of washes from damaged areas of the skin to detect the development of staphylococcus, general analysis of blood, urine, feces, biochemical examinations were performed by traditional methods.

All children underwent parasitological examination. Detection of helminth infestation was carried out by standard methods. Lyambli

cyst was determined by microscopy of a thin smear of feces stained with Lugol's solution.

In patients with AD, in a state of complete clinical remission, skin prick test with household, epidermal and plant pollen allergens was performed in accordance with the instructions, and reagents produced by "Allergen" SPA(scientific-production association) were used (Stavropol). At the same time, control tests were performed using histamine and control-negative fluid. 20 minutes after the start of the test, was assessed the local allergic response.

In order to detect changes in cellular immunity, laser flux cytometry was performed on a CoulterEpixXL (USA) cytometer using a monoclonal antibody against peripheral blood lymphocyte differentiating antigens (Becton Dickinson, USA). Quantitative indicators of T (CD3+) and B (CD19+) populations of lymphocytes, T – helper / inducer (CD4+), T – suppressor / cytotoxic (CD8+) subpopulations, T – killers (CD16+) were determined in the examined patients. The immunoregulatory index (CD4+ / CD8+) is the ratio of the percentage of these cells in the blood. The results were expressed as a percentage.

The concentration of immunoglobulins of class A, M, G and E in the blood serum was determined in accordance with the instructions for use of the solid-phase immunoenzyme analysis method "Vector BEST", a reagent kit belonging to the Russian company.

The amount of circulating immune complexes (CIC) in the blood serum was determinde Grinevich Y.A. and Alfyorova A.K. (1981). The oxygenated activity of neutrophils was assessed by the nitro-blue tetrazole recovery test (NBT-test).

The concentration of cytokines (IL-4 and TNF-α) in the blood serum was determined in accordance with the instructions for use by the method of solid-phase immunoenzyme analysis with the standard reagent kit Vector BEST (Russia). Kinetically analyzed using a jet kit from Diagnosticum RT (Hungary).

Methods of statistical analysis. Statistical analysis was performed in MS EXCEL-2013 and IBM Statistics SPSS-20 package programs using variation (U-Wilcoxon (Mann-Whitney), discriminant (χ2-Pearson), variance and correlation methods.

ANALYSIS OF ANAMNAMIC DATA OF CHILDREN WITH ATOPIC DERMATITIS

Mild degree was determined in 23.7±5.3% (23 children) of the patients with AD we examined (1-2 exacerbations per year, remission period 6–8 months, SCORAD index from 0 to 20 points). The average severity of the disease (frequency of exacerbation 3-4 times a year, remission period 2-3 months, SCORAD index from 21 to 40 points) was recorded in 55.7±5.0% (54 children). Severe course of the disease (at least 5 exacerbations in the last year, short remissions lasting 1–2 months or persistent course of the disease, SCORAD index above 40 points) was observed in 20.6±4.1% (20 children) [10] .

Mild degree was determined in 23.7±5.3% (23 children) of the patients with AD we examined (1-2 exacerbations per year, remission period 6–8 months, SCORAD index from 0 to 20 points). The moderately severity of the disease (frequency of exacerbation 3-4 times a year, remission period 2-3 months, SCORAD index from 21 to 40 points) was recorded in 55.7±5.0% (54 children). Severe course of the disease (at least 5 exacerbations in the last year, short remissions lasting 1–2 months or persistent course of the disease, SCORAD index above 40 points) was observed in 20.6±4.1% (20 children) [10] .

The first symptoms of AD appeared in 20 children (20.6%) for up to 3 months, in 32 children (33.0%) for 3-6 months, and in 17 children (17.5%) for 6-12 months. The development of the disease was detected in 13 people (13.4%) among children aged 1-3 years, 8 people (8.2%) among children aged 3-6 years, and 7 people (7.2%) among children older than 6 years.

Based on the results of the anamnesis, the following results were obtained during the analysis of possible causes of the development of the disease in children observed by us. Analysis of the causes of AD manifestations showed that in most cases, the first manifestations of the disease occurred during the intake of adapted milk formulas and violation of the hypoallergenic diet of the nursing mother - in 40 children (41.2%), and in the second place after supplementation reactions stopped - in 29 children (29.9%). Other factors were as follows:

11.3% (in 11 children) of cow's milk protein; 11.3% - (11 children) hyperallergic foods - citrus, sweets and chocolate; 6.2% - (6 children) reactions to drugs [1, 2, 10].

75 children (77.3%) had a positive family history of AD and atopy in other organs. Living conditions were assessed as adequate in 68.0% of patients, good in 14.4%, and poor in 17.5% ($\chi 2 = 7,510$; $p = 0.023$). According to the results of skin prick tests with non-infectious allergens, positive results were found in 34 (35.1%) out of 97 patients examined. Among them, more food allergens - 16 (47.1%), less pollen - 11 (32.4%) and house dust and bed mite allergens - 7 (20.6%) were important [10].

Of the observed children, 90 (92.78%) were diagnosed with various co-morbidities. Thus, the coexistence of AD with various allergic diseases was observed in 52 (53.6%) children: atopic bronchial asthma - 28 (28.9%), allergic rhinitis - 10 (10.3%), pollinosis - 7(7,2%), urticaria and Quincke's edema-4 (4.1%), allergic conjunctivitis - 3 (3.1%) in children. In addition, 76 (78.4%) children had various infectious and parasitic complications of AD.

In the acute phase, all patients (97 children) had skin rashes, 80.4% (78 children) had itchy skin, and 50.5% (49 children) had sleep disorders.

Virtually all patients with moderate to severe AD had severe dryness, flour, and fine-grained peeling in both the damaged and healthy areas of the skin.

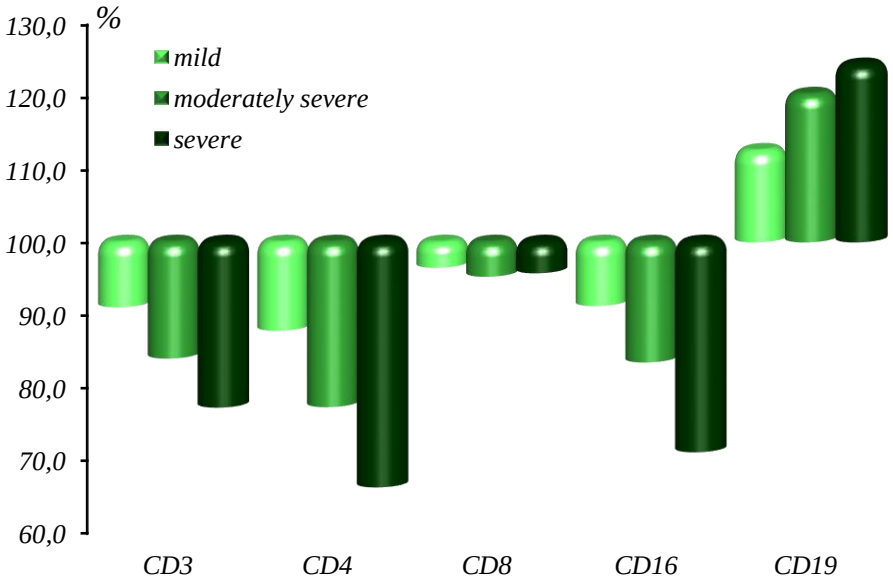
Among patients with AD observed, the mean score on the SCORAD scale was 36.88±2.65 for patients over 7 years of age, and 27.52±1.84 for patients under 7 years of age.

Among the patients we observed, there were more children with erythematous-squamous disease (28.4%), erythematous-squamous with lichenification (31.1%) and lichenoid forms (23.0%). The morphology of skin manifestations during AD exacerbation was as follows: popular rash 97 (100%), erythema 94 (96.9±1.8%), irrigations 17 (17.5±3.9%), areas of lichenification 18 (18.6±3.9%) and excoriation in 49 (50.5±5.1%) children [3, 5, 10].

IMMUNOLOGICAL PROFILE OF CHILDREN WITH ATOPIC DERMATITIS

During the analysis of cellular immunity, it was found that according to the SCORAD index of AD, the amount of leukocytes in children with mild gait was within the norm, with an average of 8.3±0.3 × 10^9/l (5.3-11 × 10^9/l; r = 0.145). The amount of leukocytes was 9.2±0.4 × 10^9/l in the moderately severe course (5.4-14.6 × 10^9/l; p = 0.022) and 10.8±0.7 × 10^9/l in the severe course (7), 0-16.8 × 10^9/l; p<0.001) and their amount increases statistically significantly compared to the control group of 24.0% and 44.7%, respectively.

A comparative analysis of changes in immunograms showed that children with AD had moderately severe (38.0±0.9%, p = 0.004) and severe (33.0±1.2%, p<0.001) acute lymphopenia. This decrease was 12.3% and 23.8%, respectively, compared to the control group. No significant changes were observed in the mild course of the disease (40.0±1.2%; p = 0.114) (graph 2).



Graph 2. Indicators of cellular immunity variation of AD by severity.

Analysis of T-cell immunity showed a statistically significant decrease in the relative number of CD+ 3 lymphocytes in all groups of patients compared to the control group, and the accuracy factor was calculated as $p<0.001$ for each of the 3 groups. Thus, the relative number of CD+ 3 lymphocytes in children with mild AD is 60.2±0.7% (56-66%), in moderately severe course is 55.6±1.1% (42-67%), in severe cases it is 51.1±1.3% (40-61%) and this indicator relative to the control group, 8.9%, 16.0% and 23.7% respectively tends to decrease [6].

Determination of the relative amount of CD4+ lymphocytes / helpers showed that in children with mild, moderate severe and severe AD, a significant decrease in this indicator ($p<0.001$) is observed, which reflects the depression of T-cell indicators of the immune system. Thus, the relative amount of CD4+ lymphocytes decreased by 12.2% in the mild walk to 36.6±0.6%, in the moderate heavy walk by 22.7% to 32.1±0.8% and in the heavy walk by 33.7%. 27.6±0.8%.

Acute imbalance between CD4+ and CD8+ lymphocytes leads to an increase in the severity of AD, as in the group of sick children with moderately severe (1.39±0.04 u.) and severe (1.19±0.05 u.) compared with the control group, a decrease in the immunoregulatory index (IRI) by 19.1% ($p<0.001$) and 30.7% ($p<0.001$), respectively.

In the mild course of AD there was no difference reliability for this indicator (1.57±0.05 u., $P = 0.235$).

In the group of severe patients, decrease in reliability in the relative amount of CD16+-lymphocytes (8.4±0.5%) was observed in 28.8% ($p<0.001$). A similar tendency was observed in the group of moderately severe children, as the relative amount of CD16+-lymphocytes in this group (9.9±0.5%) decreased by 16.5% ($p = 0.028$) compared to the control group. The relative amount of CD19+ - lymphocytes, in moderately severe and severe, respectively 20,4% (p=0,009) and 24,4% (p=0,005) is observed increasing statistical reliability(respectively 26.7±0.8% and 27.5±1.1%).

A comparative analysis of cellular immunity was accompanied by a decrease in adult CD3+ lymphocytes and a decrease in CD4+

lymphocytes / helpers in all patients with AD, regardless of the severity of the disease [6].

The results show that the total IgE titer is 9.2 times in mild course (37.8±8.0 IU/ml; p<0.001) and 19.2 times in moderately severe course (78.9±10.1 IU/ml; p <0,001), and in severe course 53.2 times (218,4±27,5 IU/ml; p <0,001) increases statistically significantly compared to the control group (Table 1).

Table 1

Humoral-type immunity in children with atopic dermatitis, depending on the severity of the disease, indicators of non-specific resistance and cytokines

	Mild grade (n=23)	Moderately severe grade (n=32)	Severe grade (n=18)	control (n=15)
General İgE, IU/ml	37,8±8,0 (1-110) p<0,001	78,9±10,1 (4-200) p<0,001	218,4±27,5 (80-500) p<0,001	4,1±0,9 (0,1-10,2)
İgA, mq/ml	0,730±0,045 (0,3-1,2) p=0,014	1,341±0,040 (1,1-1,9) p<0,001	2,050±0,079 (1,5-2,7) p<0,001	0,547±0,055 (0,2-0,9)
İgM, mg/ml	1,543±0,112 (0,9-3,1) p<0,001	1,803±0,077 (1,1-2,9) p<0,001	2,089±0,085 (1,4-2,6) p<0,001	0,847±0,077 (0,4-1,5)
İgG, mg/ml	7,34±0,33 (4,4-11,6) p=0,033	10,63±0,73 (4,1-19,9) p<0,001	12,26±1,08 (7,5-22,2) p<0,001	6,15±0,38 (3,9-9,2)
CIC, conventional unit.	62,7±4,3 (37-109) p=0,003	74,7±4,2 (36-120) p<0,001	81,0±6,1 (38-123) p<0,001	44,8±1,9 (35-59)
NBT-test, unit.	57,4±2,2 (40-72) p<0,001	55,6±2,0 (40-88) p<0,001	49,7±2,9 (33-70) p<0,001	76,6±1,5 (69-89)
İFN-γ, pg/ml	24,35±0,65 (18,6-29,3) p<0,001	33,50±1,58 (19,8-52,7) p<0,001	39,15±2,77 (26,2-58,8) p<0,001	1,47±0,37 (0-5)
İL-4, pg/ml	2,222±0,064 (1,6-2,9) p<0,001	2,794±0,119 (1,7-5) p<0,001	3,639±0,191 (2,5-5,5) p<0,001	0,520±0,125 (0-1,5)

Note: - p - statistical accuracy with control group indicators.

In children with mild AD, there is a significant increase in serum IgA levels (0.730±0.045 mg/ml), which is responsible for the local immune response, by 33.6% ($p = 0.014$) compared with the control group. IgM and IgG levels also increased by 82.1% (1,543±0.112 mg/ml; $p<0.001$) and 19.3% (7.34±0.33 mg/ml; $p = 0.033$), respectively.

The moderate course of atopic dermatitis was characterized by changes in the humoral immunological response [3, 4]. Compared with the control group, the level of IgA, IgM and IgG fractions was 2.5 times ($p<0.001$), 2.1 times ($p<0.001$) and 72.8% (1.7 times; $p<0.001$), respectively. a significant increase was observed and the results were as follows: IgA - 1,341±0.040 mg / ml; IgM - 1,803±0.077 mg / ml; IgG - 10.63±0.73 mg / ml.

In children with severe AD, the immunogram showed a significant difference in humoral immunity compared with the control group and included IgA (2,050±0.070 mg / ml), IgM (2,089±0.085 mg / ml), and IgG (12.26±1.08) mg / ml) of the concentration of immunoglobulins, respectively, 3.8 times ($p<0.001$); An increase of 2.5 times ($p<0.001$) and 2.0 times ($p<0.001$) was observed.

In the group with a mild degree of the disease, a significant increase of 19.9% ($p = 0.033$) was observed compared to the control group (62.7±4.3 c.u). In children with mild disease, the results of the spontaneous NBT test were significantly lower than in the control group (76.6±1.5 u.) (57.4±2.2 u .; $p<0.001$).

In moderately severe patients, 66.8% ($p<0.001$) increase in CIC concentration was observed compared with the control group (74.7±4.2 c.u.). The value of the spontaneous NBT test decreased by 27.4% ($p<0.001$) compared to the control group and was 76.6±1.5 u.

In the group with a severe degree of the disease, a significant increase in the level of CIC in the blood serum of patients was noted by 80.8% ($p<0.001$) and averaged 81.0±6.1c.u. Evaluation of the spontaneous NBT test showed a statistically significant decrease of 35.2% ($p<0.001$) compared with the control group, and the average result of this indicator was 49.7±2.9 u. calculated.

Thus, studies show that the functional-metabolic activity of neutrophils is significantly reduced in children with AD. This reflects the

invaluable contribution of non-specific mechanisms in the development and formation of AD in children.

The concentration of IL-4 and IFN-γ in the blood serum of children with a mild course of the disease was 4.3 times (0.222±0.064 pg/ml; p<0.001) and 16.6 times (24.35±0.65 pg/ml; p <0,001) increases statistically significantly compared with the control group.

In children with moderately severe AD, the concentration of IL-4 and IFN-γ was 5.4 times (2,794±0.119 pg / ml; p<0.001) and 22.8 times (33.50±1.58 pg/ml; p<0.001) increased significantly compared with the control group.

Increased levels of IL-4 and IFN-γ cytokines in the clinically severe course of the disease accurately reflected the degree of skin damage. In this group, the concentrations of IL-4 and IFN-γ were 7.0 times (3,639±0.191 pq / ml; p<0.001) and 26.7 times (39.15±2.27 pg / ml; p<0.001). 0.001) recorded a statistically significant increase [9].

The correlation analysis revealed that between CD3+ CD4+ (ρ = 0.826; p<0.001), between CD8+ (ρ = 0.555; p<0.001), CD19+ (ρ = 0.352; p = 0.002), CD16+ (ρ = 0.255); p = 0.029), as well as a positive direct correlation between leukocytes (ρ = 0.373; p = 0.001) and lymphocytes (ρ = 0.237; p = 0.044). In addition, a positive correlation is observed between CD4+ and CD16+ (ρ = 0.232; p = 0.048) between IRI (ρ = 0.680; p<0.001) and lymphocytes (ρ = 0.336; p = 0.004).

Thus, in children with AD, specific disorders of both cell-type and humoral-type immunity have been observed. The changes found by us affect the increase in total IgE synthesis and indicate the activation of immune, especially IgE-dependent mechanisms, mainly in patients with AD. The results obtained indicate the presence of immune compromises in patients with AD, which should be taken into account in future pathogenetic immunocorrection [6, 9, 10].

FUNCTIONAL SITUATION OF THE HEPATOBILIAR SYSTEM IN CHILDREN WITH ATOPIC DERMATITIS

An assessment of the functional status of the hepatobiliary system and pancreas in children with AD examined showed that 43.5%

of children had positive gallbladder symptoms and pain in the right subcostal region. In the mild course of AD, the mean values of alkaline phosphatase(APH) in the blood serum of patients increased almost 3 times compared to the control group (199.4±13.6 U/l and 67.5±10.1 U/l; $p<0.001$). In the moderately severe course of the disease, the activity of APH is 251.3±15.6 U/l, which is 3.7 times higher than the results in the control group ($p<0.001$). In the severe course of AD, the activity of APH in the blood serum of patients increased by 6 times compared to the control group and averaged 408.8±19.7 U/l ($p<0.001$).

Analysis of the level of α-amylase in the blood shows that in the mild course of AD the activity of this enzyme increased by 4.9 times ($p<0.001$) on average 156.9±20.1 U/l, in the moderate course - by 5.7 times ($p<0,001$) increased to an average of 183.6±10.1 U/l, and in severe form - increased by 8.1 times ($p<0.001$) to 261.0±20.6 U/l (control group - 32.1±5.5 U/l) ($p<0.001$).

Thus, the results show that damage to the hepatobiliary system is observed in children with AD. This leads to a violation of the synthetic and detoxification function of the liver, resulting in the accumulation of intermediate metabolites, histamine-like substances, creating a non-specific granulation of stagnant cells.

DYNAMICS OF CLINICAL AND LABORATORY INDUSTRY IN CHILDREN WITH ATOPIC DERMATITIS UNDER THE EFFECT OF TREATMENT

Based on the tactics of treatment, as well as the goals and objectives of the current study, we divided all children with AD into two groups: Group I (n = 27) included patients receiving basic treatment for AD, depending on the severity of allergic disease according to the SCORAD index. are divided as follows: with mild degree of the disease (9.6±1.1 points) 11, with moderate degree (29.4±2.8 points) 9, with severe degree (61.2±4.1) points) 7 children. Group II (n = 20) included patients receiving "destkiy" anaferon in addition to basic treatment. These patients were also divided into the following groups depending on the severity of the disease: 5 with a mild degree of skin

process (10.4±1.2 points), 9 with a moderate degree (31.3±3.1 points), severe 6 patients with a rate (68.5±4.2 points).

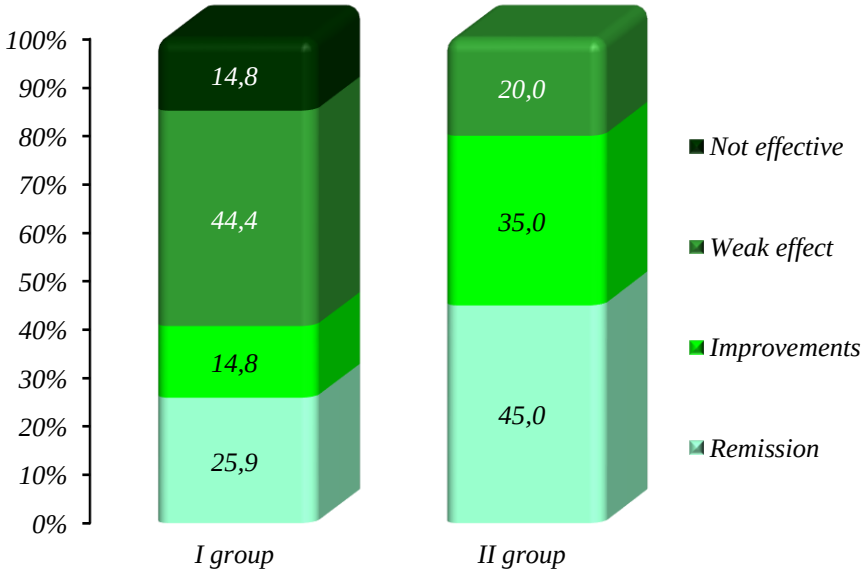
Patients in both groups received both systemic and local basal therapy in accordance with the standards of specialized comprehensive care provided to patients with AD. In addition, all patients in group II received "destkiy" anaferon. All patients used pimecrolimus (1% elidel) cream as a topical anti-inflammatory drug in the treatment complex. Treatment was continued until the symptoms of AD were completely eliminated and lasted an average of 3 weeks [2, 3, 5].

In patients, it was found that the intensity of pruritus significantly decreased 2 weeks after the start of treatment in children with AD. In group I, the degree of expression of subjective symptoms during this period was 35.08%, and in group II - 35.58%.

One week after treatment, the clinical symptoms of AD decreased statistically by 43.12% in group I and by 37.22% in group II. Two weeks later, the reduction in these symptoms was 60.13% in group I and 77.16% in group II. Three weeks later, it was found that the average SCORAD index decreased significantly ($p<0.05$) in group I by 67.30% and in group II by 85.94%. One month after the start of treatment, the average SCORAD index decreased by 72.9% in group I and 94.13% in the second group ($p<0.05$).

The results of the study showed that in children receiving anaferon, mild skin hyperemia disappeared in 1-2 days, infiltration was completely eliminated in 2-3 days, rash in 4 days, itching in the skin was reduced in 2 days and completely faded in 5-6 days. In moderate AD, a decrease in skin hyperemia was observed on day 2, and complete disappearance on day 5 [7]. The rash decreased by 2 times in the 3rd day in 65% of patients and completely disappeared in 7-10 days. Itching in the skin decreased in 3 days of treatment in more than 50% of children, and completely disappeared by the end of the 2nd week in 74% of patients. In severe disease, hyperemia of the skin decreased in 5 days and completely disappeared in 7 days, infiltration decreased in 5-6 days, completely disappeared in 7 days, and rashes and itching of the skin in 30% of patients were significantly reduced in 5 days.

In group I children receiving basal therapy, complete remission was observed 25.0±1.4 days after the start of treatment, and in group II receiving anaferon in addition to basic therapy, complete remission was observed. Thus, in addition to baseline treatment, clinical remission was achieved 5.1 days faster in children receiving immunomodulatory therapy with anaferon ($p<0.001$) than in the comparison group. Higher clinical efficacy was observed in group II patients 4 weeks after the start of therapy. The clinical effectiveness of treatment was higher in group II patients 4 weeks after the start of treatment. In group II, the therapeutic efficacy was characterized by clinical remission in 9 children (45.0%), significant improvement in 5 (35.0%) children, and improvement in 6 children (20.0%). Clinical remission after baseline therapy in group I was observed in 7 (25.9%) patients and significant improvement in 4 (14.8%) patients, which was a significantly lower number of patients compared to the same group II indicators. ($p<0.05$). Improvement was noted in 13 (44.4%) patients (graph 3).

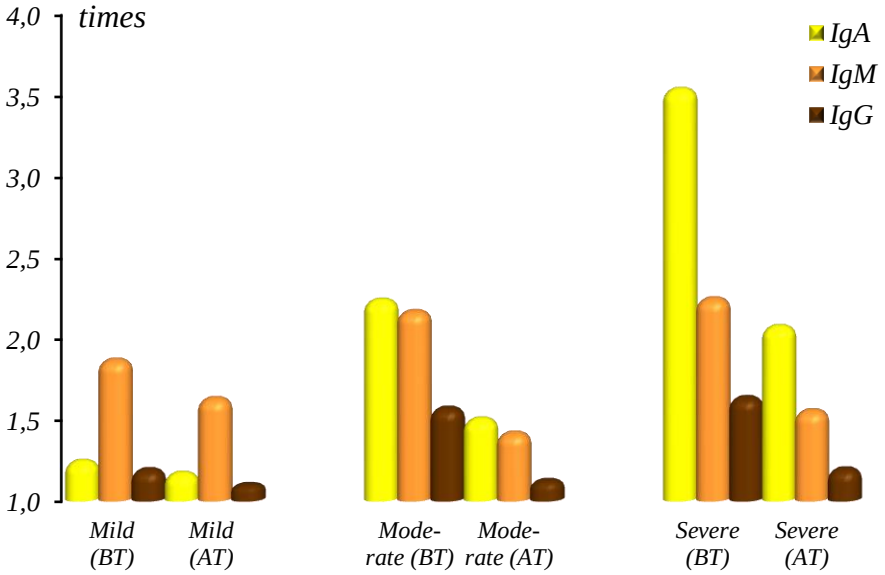


Graph 3. Dynamics of reduction of clinical symptoms as a result of treatment.

All patients with disorders of the hepatobiliary system received antisecretory and antispasmodic terapy, hepatoprotectants and diet therapy were prescribed. In the group of patients receiving complex therapy after treatment with anaferon, was noted that, the activity of APH in mild form was 2.0 times ($p<0.001$), in moderate form 2.2 times ($p<0.001$), in severe form 2.4 times ($p<0.001$).) statistically reliability decrease. As a result of the treatment,It is observed that the activity of α-amylase in the blood decreased slightly compared to previous indicators by 3.1 times ($p<0.001$), moderately by 2.5 times ($p<0.001$), severe by 2.6 times ($p<0.001$).

The use of anaferon has a significant normalizing effect on cellular and humoral parameters of immunity in children with AD. In children with mild AD treated with immunomodulators treated with anaferon, the amount of CD3+ receptor T lymphocytes increased reliability by 14.7% ($p<0.001$) and did not differ from the control level. After appropriate treatment in this group, the number of lymphocytes, leukocytes, CD4+, CD+ 8, CD+ 16 and CD19+ subpopulations did not change statistically significantly and approached the level of indicators in the control group. Although IgE levels decreased by 2.2 times ($p = 0.043$) compared with before treatment results, they were still 4.0 times ($p = 0.006$) higher than the normal values of the control group. The level of IgM is 63% ($p = 0.012$) reliability higher than the control group [2, 4].

In children with moderately severe AD, an increase of 23.0% ($p = 0.011$) of lymphocyte CD3+ subpopulation in the clinical remission phase compared with before treatment values and approaching the level in the control group. The relative index of CD19 subpopulation decreased by 20.5% ($p = 0.035$). Although the number of leukocytes after treatment in this group decreased by 26.0% ($p = 0.028$) compared to before treatment, no statistically significant change in the number of lymphocytes was observed. Against the background of a reliability reduction in the concentration of total IgE in blood samples by 3.6 times ($p = 0.012$), serum IgA (32.7%, $p = 0.017$), IgM (34.5%, $p = 0.035$) and IgG (28.4) %, $p = 0,021$) a reliability decrease in the amount of indicators was observed (graph 4).



Graph 4. Changes in the dynamics of treatment of immunoglobulins in children with AD (control - 1 c.u).

A statistically significant increase in the relative number of T-lymphocytes and (CD4+) helper-inductor population in the severe course of anaferon AD in complex therapy was 30.8% ($p = 0.010$) compared to baseline. Against the background of therapy, the level of cytotoxic lymphocytes (CD8+) did not change significantly ($p = 0.584$), and the number of CD19+ cells decreased reliability significantly by 21.6% compared to baseline ($p = 0.026$). Although the total serum IgE in this group of patients decreased reliability 2.2 times ($p = 0.046$) compared to the initial values 4 weeks after treatment, it is still 17.0 times higher than normal ($p<0.001$). After treatment, the concentration of IgA in the blood serum of patients decreased reliability by 41.4% ($p = 0.003$), and the concentration of IgG and IgM decreased by 26.8% ($p = 0.075$) and 30.7% ($p = 0.028$) before treatment. There was a decrease in the results compared to the control

group, an increase of 19.7% ($p = 0.100$) and 55.5% ($p = 0.004$), respectively.

In children taking anaferon in mild AD, there was a reliability decrease in IFN-γ and IL-4 concentrations by 3.2 times ($p = 0.043$) and was noted that, a reliability decrease of 2.1 times ($p = 0.039$), but these values from the control group, respectively 4.9 times ($p = 0.005$) and 2.0 times ($p = 0.039$) increased and differed ($p<0.001$). Moderately severe reductions in IFN-γ and IL-4 concentrations were reported to be 2.0-times ($p = 0.008$) and 47.3% ($p = 0.006$), respectively, however, these values were 8.8 times ($p<0.001$) and 2.7 times ($p = 0.001$) higher than in the control group.

In severe AD, a significant decrease in serum concentrations of IFN-γ and IL-4 was observed, compared with 46.9% ($p = 0.028$) and 41.1% ($p = 0.026$), respectively, compared with before treatment values, but control 12.3 times ($p<0.001$) and 3.9 times ($p = 0.001$) higher than in the group.

A comparative assessment of non-specific resistance in mild AD showed no significant difference in peripheral blood CİC levels ($p = 0.686$) and NBT-test activity ($p = 0.336$) after treatment. In the moderately severe degree of AD, a significant decrease in the concentration of CİC in the blood was 32.9% ($p = 0.008$). No statistically significant positive dynamics was observed during moderate to severe AD remission,

Parasitic and infectious diseases have a great impact on the development of AD in children. The results of the study showed that 15 out of 23 children with mild AD (65.2%), 36 out of 54 children with moderately severe AD (66.7%) and 19 out of 20 children with severe AD (95.0%) developed giardiasis. was found. All patients with giardiasis received appropriate etiopathogenetic and antiparasitic therapy. One month after the end of treatment, control coprological examinations revealed parasitic infestation in 4 children with mild AD (17.4%), 9 children with moderate AD (16.7%) and 8 children with severe AD (40.0%). confirmed its existence [8].

The research showed that exacerbation of AD was accompanied by colonization of S. aureus on the surface of the damaged skin in 87 (89.7%) children. S. aureus was not detected in the skin of 10 pa-

tients (10.3%). In mild disease, S. aureus growth is observed in children with very weak (bacterial number 10^2), moderately severe - moderate (bacterial number 10^3 - 10^4), and severe - acute (more than 10^4 bacterial number).

When partial remission of the disease was achieved after treatment with pimafucort ointment, a combination drug QKS, the incidence of staphylococcal colonies in the skin was reduced to 28.9% ($p<0.01$). During the period of complete remission of AD, against the background of the use of elidel cream, skin infection with Staphylococcus aureus decreased to 9.3%, and in 90.7% of cases, complete normalization of the skin was observed ($p<0.001$). The mean SCORAD index for the general group of patients with AD during the period of exacerbation was 67.4±5.1. In the partial remission stage of the disease, after treatment with pimafucort ointment, the dynamics of the index tends to decrease and averages 42.6±4.1. During the period of complete remission of the disease - 10 days after the use of elidel cream, the index decreased to a minimum - 25.3±2.9 ($p<0.05$).

Thus, the violation of the skin barrier function, in itself, creates a tendency to join the secondary infection, and, conversely, colonization with pathogenic microbes exacerbates the violation of the skin barrier. Contamination of the skin of patients with AD with Staphylococcus aureus aggravates dermatitis. The study found a very strong contamination of S. aureus in the skin of patients with moderate to severe AD, which is considered a factor that irritates the inflammatory process in the skin and keeps it in a stable state.

RESULTS

1. The following clinical and morphological forms of the disease are more common in children with atopic dermatitis: erythematous-squamous (28.4%), erythematous-squamous with lichenification (31.1%), lichenoid (23.0%). The morphology of skin manifestations during the exacerbation of atopic dermatitis was as follows: popular rash 100%, erythema 96.9%, areas of lichenification 18.6%, excoriations in 50.5% of children [3, 5, 10].

2. In the period of exacerbation of the disease, children with

atopic dermatitis have a deficiency of adult CD3+ lymphocytes (moderately severe 55.6±1.1% and severe 51.1±1.3%) compared to the control group ($p<0.001$) and There was a decrease in the number of CD4+ lymphocytes / helpers (moderately severe 32.1±0.8% and severely 27.6±0.8%), indicating depression of T-cell parameters of the immune system [5, 6].

3. Moderately severe and severe course of atopic dermatitis differed from the control group ($p<0.001$) in total IgE (78.9±10.1 IU/ ml and 218.4±27.5 IU/ ml, respectively) and CIC. Increase in the amount of (74.7±4.2 c.u. and 81.0±6.1 c.u., respectively), decrease in NBT-test (55.6±2.0 c.u., respectively) . and 49.7±2.9 u.), which leads to a deepening of allergic inflammation in the skin [2, 4].

4. In patients with atopic dermatitis, IL-4 (2,794±0.119 pg / ml in moderately severe course and 3,639±0.191 pg / ml in moderate course) and IFN-γ (33 in moderately severe course) compared with the control group ($p<0.001$). , 50±1.58 pg / ml and 39.15±2.77 pg / ml in severe cases), indicating a violation of cytokine immunoregulation [2, 4, 9].

5. Exacerbation of atopic dermatitis in 89.7% of children was accompanied by colonization of damaged skin with S. aureus: mild to 102 CFU / cm², moderate to severe 103-104 CFU / cm², severe to more than 104 CFU / cm². . S. aureus was found in monoculture in 61.5% of children, and in bacterial associations with S. haemolyticus, S. epidermidis, Enterococcus faecalis, and Candida albicans in 38.5%. In the semi-acute phase of the disease, the frequency of skin colonization with S. aureus decreased to 28.9% against treatment with pimafucort, a topical GCS drug, and to 9.3% against elidel cream during complete remission [3, 5, 7].

6. The use of elidel cream and anaferon, an immunomodulatory drug, in the complex therapy of atopic dermatitis increases the overall effectiveness of treatment, which is reflected in a more significant and sustainable reduction in the severity of the disease, assessed by the SCORAD index. Therapeutic efficacy was characterized by clinical remission in 45.0% of patients, significant improvement in 25.0%, and improvement in 30.0%. Complete clinical remission was observed after 19.9±0.7 days in patients receiving complex therapy,

and only after 25.0±1.4 days in patients receiving basic therapy [1, 2-5].

PRACTICAL RECOMMENDATIONS

1. During the clinical and laboratory examination of children with atopic dermatitis, it is recommended to determine the parameters of the immune and cytokine status of children, non-specific resistance as an indicator of the degree of activity of the allergic inflammatory process and objective assessment of treatment effectiveness.

2. Microbiological examination of the skin to detect the carrier of S. aureus and pathogenic strains before treatment in children with an advanced course of atopic dermatitis may optimize treatment tactics.

3. In case of impaired immunological reactivity, high clinical and anamnestic manifestations of colonization and infection with S. aureus, as well as for the prevention of complications, complex therapy should be carried out using an immunomodulatory drug anaferon in a dose appropriate for the patient's age.

4. In children with atopic dermatitis, the combination of external therapy and systemic anti-inflammatory therapy with elidel cream during the exacerbation of the disease effectively reduces the severity of clinical symptoms of the disease.

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List of abbreviations

AD	– atopic dermatitis
AI	– allergy index
APH	– alkaline phosphatase
ARVI	– acute respiratory viral infections
CIC	– circulating immunocomplexes
ICL	– index of change of leukocytes in the blood
IFN	– interferon
Ig	– immunoglobulin
IL	– interleukin
IRI	– immunoregulatory index
IRLE	– index of the ratio of lymphocytes and eosinophils
IRLE	– index of the ratio of lymphocytes and eosinophils
KFU/sm^2	– colony forming units / cm^2
LI	– lymphocytic index
LII	– leukocyte index of intoxication
NBT	– nitro – blue tetrazolium test
NI	– nuclear index
NK	– natural killers
TEI	– therapeutic effect index
WHO	– World Health Organization

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