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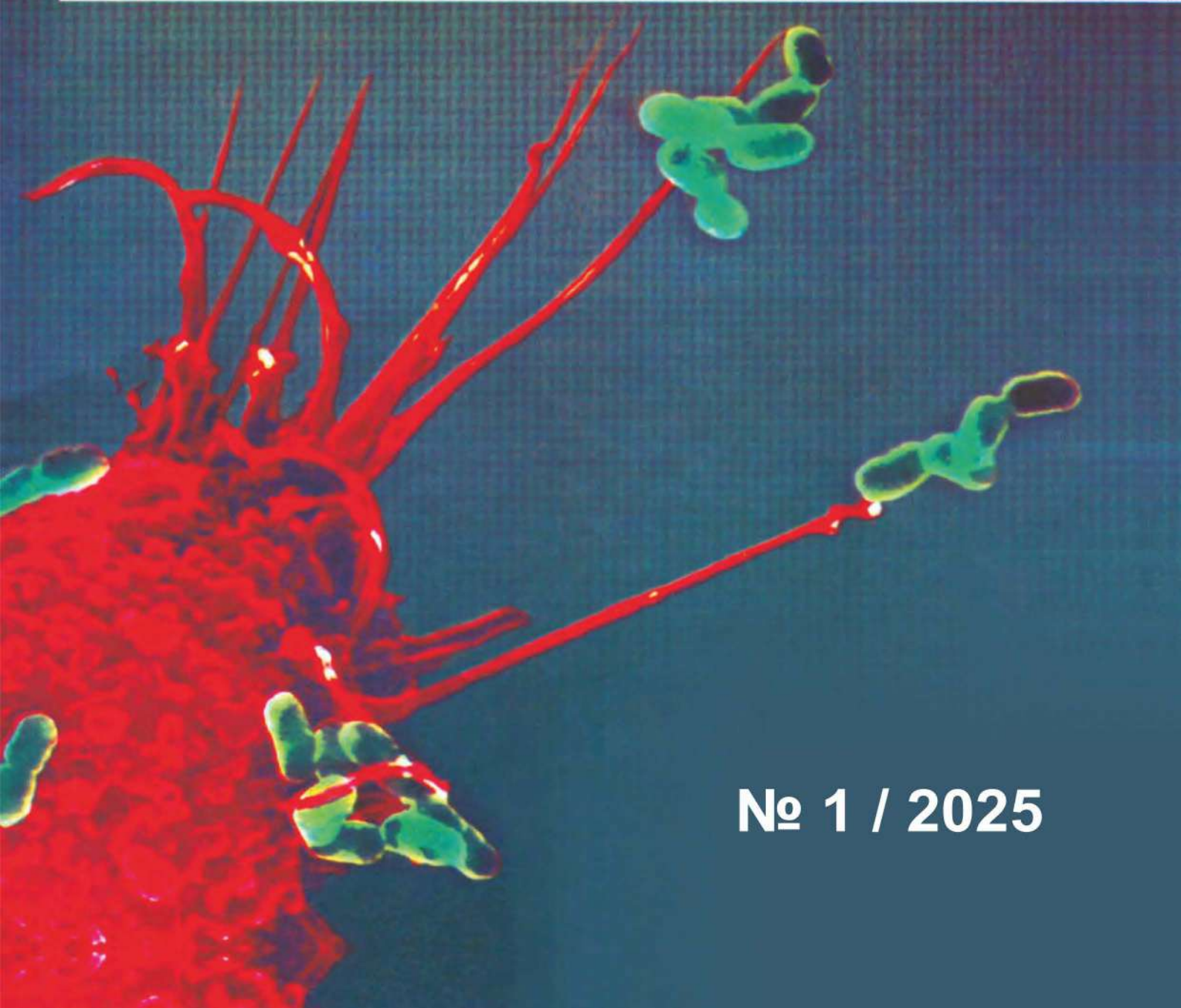
# ИНФЕКЦИЯ, ИММУНИТЕТ и ФАРМАКОЛОГИЯ



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# ASPECTS OF MODERN TREATMENT OF ATOPIC DERMATITIS

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**Keywords:** atopic dermatitis; interleukins; cortisol; Selank; phototherapy.

Atopic dermatitis (AD) is one of the most common skin diseases affecting people in developed countries. about 20% of children and 5% of adults. The disease is multifactorial in etiology. Among the genetic factors, the main attention is paid to the mutation of the gene encoding the synthesis of the protein filaggrin, which is involved in the functioning of the skin barrier. In the genesis of immune disorders in AD, the role of cytokines regulating synthesis of IgE, interleukins (IL) - 4, -5, -12, -13, -31. Chronic stress in itchy dermatitis contributes to the development of anxiety-depressive disorders that reduce the quality of life, and stress-mediated increases in cortisol levels can have a significant impact on the disruption of the skin's barrier function.

**Abstract:** Atopic dermatitis (AtD) is one of the most common skin diseases, affecting about 20% of children and 5% of adults in developed countries. The disease is multifactorial in etiology. Among the genetic factors, the main attention is paid to the mutation of the gene encoding the synthesis of the filaggrin protein, which is involved in the functioning of the skin barrier. In the genesis of immune disorders in AD, the role of cytokines regulating the synthesis of IgE - interleukins (IL) -4, -5, -12, -13, -31 is studied. Chronic stress in itchy dermatitis contributes to the development of anxiety and depressive disorders that reduce the quality of life, and stress-mediated increase in cortisol levels can be significant in disrupting the barrier function of the skin. Atopic dermatitis (AtD) (in English literature - atopic eczema) is a polyetiological, inflammatory, immune -mediated skin disease with a hereditary predisposition, accompanied by itching. In developed countries, about 20% of children and about 5% of adults suffer from this disease [1]. In the Russian Federation, the prevalence of AtD in 2018 was 426.3 per 100,000 population, and the incidence was 188.2 cases per 100,000 people [2]. AtD significantly reduces the quality of life (QOL) of patients and is a significant damage to the economy. AtD as a polyetiological The disease cannot be attributed to any one cause. The immune -mediated nature of the disease, which has a genetic predisposition, is undoubted. Among the factors involved in the formation and manifestation of AtD, the role of dysfunction of the barrier function of the skin, IgE -mediated hypersensitivity, allergic reactions to Dermatophagoides mites has been shown pteronyssinus house dust, mold fungi,

Staphylococcus toxins aureus [3]. The implementation of the pathogenic influence of environmental factors is largely determined by the state of the nervous, endocrine and immune systems of the body.

**Genetic factors.** Genome sequencing studieshaveidentified4chromosomalloci associated with the development of AtD: 1) the epidermal differentiation complex EDC ( the epidermal differentiation complex ) on chromosome 1; 2) the genomic region proximal to the LRRC32 locus on chromosome 11; 3) the RAD50/IL13 locus on chromosome 5; 4) the major histocompatibility complex on chromosome 6 [4]. In total, more than 30 candidate genes responsible for immune regulation, in particular T-cell activation, have been described. In recent years, the role of filaggrin gene mutations in disruption of epidermal barrier function has been discovered. Filaggrin is a key protein that ensures the final differentiation of epidermal cells and the formation of the barrier function of the skin. In patients with AtD, according to expert estimates, LOF mutation (loss-of-function) of filaggrin is detected in 25-50% of cases and has a clear connection with the development of atopic bronchial asthma and allergic rhinitis [5]. Recent studies have suggested that the defect in the barrier function of the skin in individuals with LOF mutation allows allergens to penetrate the epidermis and interact with antigen- presenting cells, which leads to the development of AtD or bronchial asthma. However, more than half of the cases of the disease cannot be explained by this anomaly, which prompts further genetic studies.

**Pathogenesis.** Among the molecular changes underlying the dysfunction of the skin barrier, disturbances in the synthesis of filaggrin , serine protease inhibitors (LEKTI) and chymotrypsin-like factor of the stratum corneum - SCCE, which are involved in the processes of keratinization and ensuring the protective properties of the skin, have been described [6, 7]. Among the factors that reduce the barrier role of the epidermis, increased peptidase activity, deficiency of protease inhibitors, as well as disturbance of the lipid composition of the skin and a number of others are studied [8]. The result of this is an increase in transdermal water loss, dry skin and an increase in pH.

**Immune response in AtD.** For many years, AtD was considered to be an exclusively Th2-dependent disease, but sufficient evidence has accumulated in favor of the participation of Th1 cells in this process [9]. In the acute phase of the skin process, the main effector cells are Th2 lymphocytes, and with the chronicity of the process, the predominance of Th1 immune reactions is noted. Cytokines that regulate the synthesis of IgE, interleukins (IL) -4, -5, -12, -13, -31, as well as granulocyte -macrophage colony-stimulating factor [11], participate in the genesis of immune disorders in AtD. Cytokines necessary for switching the immune response to IgE synthesis, with the participation of the JAK/STAT signaling system, stimulate the expression of intercellular adhesion molecules (ICAM-1), responsible for the migration of eosinophils and mononuclear cells to the foci of skin inflammation. In recent years, the hyperproduction of IL-31 by Th2 cells has been associated with the occurrence of skin itching, and the administration of monoclonal antibodies to the IL-31 receptor significantly reduces it [12]. In patients with AtD, keratinocytes acquire the ability to synthesize thymus-stromal lymphopoietin

(TSLP), which signals T lymphocytes to differentiate predominantly towards the formation of Th2 cells [10]. Thus, immune processes involving Th2 cells are triggered and the production of antigen-specific IgE, the hyperproduction of which determines the development of clinical manifestations of AtD. The levels of IL in the blood of patients with AtD change depending on the phase of the pathological process and the prevalence of skin manifestations: during an exacerbation of AtD in patients with a widespread form of the disease, the level of serum IL-1, IL-8 increases, an increase in the content of IL-4 and IL-8 in the blood is noted in a limited variant [11], and the level of IL-17 increases when the exacerbation subsides [13].

**Hormonal mechanisms in AtD.** There is growing evidence of close links between neuroendocrine disorders, immune disorders and clinical manifestations of allergic dermatoses. It has been noted that in patients with AD, exacerbations of the disease often occur against the background of psychoemotional overstrain [1]. In the implementation of the body's response to stress, the reaction of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system is of great importance. It has been shown that one of the available biomarkers of stress can be the level of cortisol in saliva [7], which reliably correlates with the SCORAD index, reflecting the severity of AtD, which indicates a state of chronic stress in patients with AtD. Under the influence of stress, there is a decrease in the production of dehydroepiandrosterone, activation of the immune response from Th1 cells with a subsequent switch to the Th2 type of response, during which the production of proinflammatory cytokines increases, and an increase in the severity of the skin inflammatory process [3]. It has been established that in patients with AtD, the activity of the HPA axis correlates with the severity of dermatitis [9]. However, it is noteworthy that severe AtD is associated with a decrease in basal cortisol secretion [10]. In patients with AtD, lower values of serum cortisol were noted compared to healthy individuals when stimulated with ACTH [11], which indicates the depletion of the functional reserves of the adrenal cortex under conditions of chronic stress created by atopic inflammation of the skin and its clinical manifestations (itching, peeling, oozing ). Regarding the pituitary regulatory activity in AtD, determined by the level of ACTH in the blood, there are few and contradictory data. Thus, in the study of Z. Tehranchinia et al. (2017), no reliable differences in the level of ACTH were found between patients with AtD and healthy individuals [2]. In the work of M. Rupprecht et al. (1995) studied daily cortisol secretion [6], as well as the response to stimulation with corticotropin -releasing hormone (CRH) in patients with AtD and healthy volunteers. The authors did not reveal reliable differences in daily cortisol secretion between the groups. At the same time, the response to stimulation in patients was significantly lower than in the control group, both in terms of cortisol and ACTH. Chronic stress leads to a decrease in the ability of the endocrine system to adequately respond to acute stress situations, which results in a switch of the immune system from a cellular response to a humoral one [4].

**Modern approaches to the treatment of AtD.** Clinical guidelines provide for drug and non-drug therapy, diet therapy, and pain relief [3]. Among conservative methods, the use of moisturizing

and softening agents (emollients) is mandatory, which should be used frequently (at least 3-4 times a day). Topical glucocorticosteroids (GCS) in minimally effective doses for 3-4 weeks are provided as external therapy. For the treatment of moderate to severe cases of AtD in case of resistance to other external agents, local use of calcineurin inhibitors (tacrolimus and pimecrolimus) is recommended. In a systematic review by J. Cury Martins et al. (2015) provided evidence of the advantage of this drug in the form of 0.1% ointment over low-dose GCS [5], 1% pimecrolimus ointment and 0.03% tacrolimus ointment. Moreover, tacrolimus in the form of 0.03% ointment was more effective than GCS and pimecrolimus. Both dosage forms of tacrolimus were well tolerated, there were no cases of malignancy or skin atrophy. For the treatment of patients with moderate to severe AtD, a targeted drug, dupilumab, is used as systemic therapy. It is a human recombinant monoclonal antibody that binds to the $\alpha$-subunit of the IL-4 receptor, blocking the function of IL-4 and IL-13, cytokines that play an important role in the genesis of the atopic inflammatory process [6]. Studies are being conducted to evaluate the effectiveness of new biological drugs - specific blockers of proinflammatory cytokines involved in the pathogenesis of AtD - crisaborole, lebrikizumab, tralokinumab, tezepelumab, etc. [8]. Among the physiotherapeutic methods of treatment in cases of moderate and severe disease, the most evidence-based methods are phototherapy methods based on the use of ultraviolet (UV) radiation [4]. UV phototherapy has a variety of therapeutic effects on pathological processes in the skin: anti-inflammatory, immunosuppressive, antiproliferative [8]. In addition, UV rays affect the lipid components of cell membranes due to their effect on lipid peroxidation, affect the functional state and number of Langerhans cells [9]. There are reports of a decrease in the expression of substance P receptors and modulation of NK-1 receptors under the influence of UV rays, which is accompanied by a decrease in the severity of atopic skin inflammation [13].

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## РЕЗЮМЕ
## АСПЕКТЫ СОВРЕМЕННОГО ЛЕЧЕНИЯ АТОПИЧЕСКОГО ДЕРМАТИТА

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**Ключевые слова:** атопический дерматит; интерлейкины; кортизол; Селанк; фототерапия.

В генезе иммунных нарушений при БА изучена роль цитокинов, регулирующих синтез IgE, интерлейкина (IL) -4, -5, -12, -13, -31. Хронический стресс при зудящем дерматите способствует развитию тревожно-депрессивных расстройств, которые снижают качество жизни, а вызванное стрессом повышение уровня кортизола может оказать значительное влияние на нарушение барьерной функции кожи.

## REZUME
## ATOPIK DERMATITNING ZAMONAVIY DAVOLASH ASPEKTLARI

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**Kalit so‘zlar:** atopik dermatit; interleykinlar; kortizol; Selank; fototerapiya.

AtD da immunitet buzilishining genezisida IgE, interleykin (IL) -4, -5, -12, -13, -31 sintezini tartibga soluvchi sitokinlarning roli o‘rganildi). Qichiydigan dermatitning surunkali stressi hayot sifatini pasaytiradigan Anksiyete-depressiv kasalliklarning rivojlanishiga yordam beradi va stressdan kelib chiqadi kortizol darajasi terining to‘siq funktsiyasining buzilishiga sezilarli ta’sir ko‘rsatishi mumkin.