

## ATOPIC DERMATITIS: CURRENT STATE OF THE PROBLEM IN UKRAINE AND THE WORLD.

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### Summary

**Introduction.** Social and environmental disasters in recent years have induced an increase in morbidity, which poses a threat to the health and life of the population not only in Ukraine but also in the world. Among the most common skin diseases is atopic dermatitis (AD), a chronic recurrent disease characterized by skin inflammation, disruption of the epidermal barrier, and, as a result, a decrease in the skin's ability to retain moisture. Today general practitioners are usually the first to encounter this pathology, and they must assess self level of competence in a particular case and provide the necessary medical care or justify a referral to a dermatologist.

**The aim.** To carry out an analytical review of domestic and foreign literature on the problem of atopic dermatitis (AD), methods of diagnosis and personalized approach to the treatment of this disease and to substantiate further directions of necessary scientific research to improve appropriate medical care.

**Materials and methods.** A search, synthesis and analysis of world and national scientific publications on a personalized approach to the diagnosis and treatment of atopic dermatitis were conducted. A systematic approach, bibliosemantic method and method of structural and logical analysis were applied.

**Results and discussion.** AD occurs with a frequency of up to 20 % among children and up to 10 % among adults in European countries. In Ukraine, as of 2020, the prevalence of AD among the pediatric population ranges from 9.0 to 28.5 %.

The study of the complex pathogenesis of the disease, where genetic factors, immune dysregulation and epidermal barrier disorders play a key role, has allowed scientists to identify endotypes and phenotypes of AD, which has become an important step in the development of personalized therapy for patients with AD. It was biological drugs (blockers of IL-4 and IL-13 and JK-inhibitors) that made a breakthrough in the treatment of severe AD. Another promising direction in the treatment of AD is the use of probiotics, as it is known that in patients with AD there is a decrease in the number of commensal bacterial skin flora and colonization of the skin with *S. aureus*.

**Conclusions.** Thus, the incidence of atopic dermatitis, which is characterized by a complex etiopathogenesis, is increasing every year in the population of Ukraine and the world. The medical and social significance of AD opens up new challenges for the search for new approaches to the management of patients with AD. In recent years, biologic therapies have been actively introduced into medical practice, opening up new opportunities for personalized management of patients with severe forms of AD. As for the treatment of mild and moderate forms of AD, the issue is still relevant, given the problem of corticophobia in society. That is why at this stage, attention to the treatment and prevention approach should be more focused, and treatment methods with high efficacy and low side effect profile should be a priority. The literature review revealed that the problem remains relevant, despite the large number of studies on the etiology, pathogenesis and treatment of AD, which substantiates promising areas for the development and application of methods of modern effective personalized treatment of AD.

**Key words:** atopic dermatitis, personalized medicine, biological therapy, probiotics

## INTRODUCTION

Social and environmental disasters in recent years have induced an increase in morbidity, which poses a threat to the health and life of the population not only in Ukraine but also in the world. Among the common pathologies are skin diseases, which are usually not fatal, but they can accompany fatal diseases or exist in isolation, however, their impact on the quality of life is undoubtedly recognized as significantly destructive. At the current stage of medical development, general practitioners are usually the first to encounter this pathology, and they must assess self level of competence in a particular case and provide the necessary medical care or justify a referral to a dermatologist. It is the lack of proper knowledge and skills of doctors that often causes advanced cases of the disease, which is accompanied by complications and progression of its course. Among the most common skin diseases seen by general practitioners and dermatologists is atopic dermatitis (AD), a chronic recurrent disease characterized by skin inflammation, disruption of the epidermal barrier, and, as a result, a decrease in the skin's ability to retain moisture [1].

Therefore, we set out to conduct an analytical review of Ukrainian and foreign literature on atopic dermatitis and to substantiate further directions for the necessary research to improve appropriate medical care.

## RESULTS AND DISCUSSION

**Semiotics.** The concept of «atopic dermatitis» was first proposed by Wize and Sulzberger in 1935. In 1972, atopic dermatitis was included in the International Classification of Diseases (ICD) – Code L20 Atopic dermatitis.

**Epidemiology.** Atopic dermatitis is one of the most common skin diseases in the world. It occurs with varying frequency in different countries and ethnic groups, for European countries this figure is up to 20 % among children and up to 10 % among adults [1].

In Ukraine, the incidence of AD is gradually increasing, and as of 2020, the prevalence of AD among the pediatric population ranges from 9.0 to 28.5 %. The prevalence of atopic dermatitis in children in the Kyiv region is 10.1 % (Okhotnikova, 2020 [2]).

Earlier data, presented in 2018, show variability in the prevalence of AD in different regions of Ukraine: among 6-7-year-old children – from 3.8 % in Kyiv to 6.1 % in Kharkiv – and among children aged 13-14 years from 3.9 % (Kyiv) to 5.1 % (Kharkiv) (according to ISAAC results) [3].

According to the results of a study in Vinnytsia region, AD occurs in 11.9 % of children aged 3-6 years, and in 5.9 % of children aged 7-18 years [4].

The problem is exacerbated by the fact that the highest prevalence of AD is observed among children under the age of 2 years, when there is no adequate verbal contact with the patient, so a proper assessment of subjective manifestations is impossible, limited only to external examination of the lesions. By adolescence, the incidence of pathology gradually decreases and is relatively stable among the adult population [1].

It is worth noting that the statistics presented do not fully reflect the state of the problem, as some patients are treated independently with improvised means and do not seek medical care, while others are treated by doctors, often using outdated approaches. Unfortunately, today some doctors still use outdated terms or inaccurately diagnose, for example, «allergic diathesis», «childhood eczema», «exudative-catarrhal diathesis», «allergic dermatitis», etc., which distorts the statistics of AD incidence[2]. Thus, these factors make it impossible to cover all categories of patients with AD for statistical analysis.

Active educational activities among doctors and patients and emphasizing the importance of timely and accurate diagnosis will improve the quality of medical care for patients with AD, as well as more accurately assess the state of the problem in Ukraine.

**Clinical manifestations of atopic dermatitis and diagnosis.** Dry skin and severe itching are characteristic manifestations of atopic dermatitis. The rash is represented by papules and vesicles on an erythematous inflammatory background, crusts, scales and lichenification, and all elements may be present simultaneously. In patients of different ethnic and age groups, the clinical picture differs, for example, in people with highly pigmented skin, the erythema may have a brown color or purple tint, in contrast to the pink or red color of the elements in Caucasians [5].

Another characteristic feature of AD is the typical localization of the rash, and it differs in different age groups of patients: in young children – on the face and extensor surfaces of the limbs, in older children and adults – on the flexor surfaces. At the same time, lichenification is more characteristic of the second category of patients, and eczematous rash prevails in young children [5, 7].

The severity of atopic dermatitis is determined by the SCORAD (Scoring Atopic dermatitis) scale. It consists in assessing the severity of AD in three areas: the prevalence of lesions, the intensity (severity) of lesions and the patient's subjective assessment of his or her condition.

1. Estimation of the prevalence of lesions on the skin surface in percentage according to the rule of nine. In children under 2 years of age: head and neck 8.5 %, trunk 18 %, upper limb 4.5 %, lower limb 6 %. Children over

2 years old and adults: head and neck 4.5 %, trunk 18 %, upper limb 4.5 %, lower limb 9 %, hands 1 %, genitalia 1 %.

The total area of the lesion is S (%). Prevalence rate  $A = S/100$ .

#### 2. Assessment of intensity (severity) of lesions

Erythema (0 to 3 points);

Swelling/intensity of papules (0 to 3 points);

Oozing/crusting (0 to 3 points);

Scratch marks (0 to 3 points);

Lichenification (0 to 3 points).

Intensity score  $B = \text{sum of points}/18$

#### 3. Patient's assessment of their condition

Itching (0 to 10 points)

Insomnia (from 0 to 10 points)

Subjective state index  $C = \text{sum of points}/20$

SCORAD Index =  $A/5 + 7 \times B/2 + C$

Interpretation: up to 20 points – mild (exacerbations 1-2 times a year, prolonged remission), 20-40 points – moderately severe (exacerbations 3-4 times a year, remission < 4 months), more than 40 points – severe (long-term exacerbations, remission < 2 months) [7,8].

#### Etiology and pathogenesis.

AD is a heterogeneous disease with a complex pathogenesis. AD is the first link in the clinical phenomenon of «atopic march», which also includes allergic rhinitis and bronchial asthma, which have common pathophysiological processes [9].

Genetic factors, immune dysregulation and epidermal barrier disorders play a key role in the pathogenesis of AD [10].

Filaggrin is one of the main structural proteins of the skin, which forms the epidermal barrier, thanks to which keratinocytes differentiate and create a barrier that prevents excessive moisture loss and the ingress of allergens and microorganisms. Mutation of the filaggrin gene, which encodes profilaggrin, a precursor of filaggrin (FLG) protein, leads to a dysfunction of the skin barrier by impairing keratinocyte differentiation, reducing the number of ceramides, increasing the number of proteolytic enzymes, impairing the integrity and cohesion of corneocytes, impaired formation of tight junctions and reduced water retention and, as a result, increased transepidermal water loss [10, 11, 14].

In AD, the main link of immune dysregulation is T-cell immunity, the beginning of the immune response is triggered by impaired differentiation of T helper cells with an increase in the number of Th2 (IL-4, IL-5, IL-13,

IL-31, CCL1). IL-4 and IL-13 play an important role in the production of chemokines, skin barrier dysfunction, suppression of antimicrobial peptides (AMP) and allergic inflammation [12].

In the acute phase, the JAK-STAT pathway mediates the signaling of IL-4, IL-5, IL-13, and IL-31. In the chronic phase and in patients of Asian origin with AD, the cytokine profiles of Th17 and Th22 predominate. In the IL-4 type I receptor-mediated pathway, JAK1 and JAK3 are activated, followed by STAT6. On the other hand, in the pathway mediated by IL-4 and IL-13 type II receptors, JAK1 and TYK2 are activated, followed by STAT6 and STAT3 activation [13].

The broken epidermal barrier and environmental triggers stimulate keratinocytes to release IL-1 $\beta$ , IL-25, IL-33, MDC/CCL22 (macrophage-derived chemokine), TARC/CCL17 (thymus-associated regulatory chemokine) and TSLP (thymic stromal lymphopoietin), which activate dendritic cells and Langerhans cells. Activated dendritic cells stimulate Th2 cells to produce IL-4, IL-5, IL-13, IL-31, and IL-33, which leads to barrier dysfunction, decreased AMP production, impaired keratinocyte differentiation, and itching symptoms [13,14].

The skin microbiome in atopic dermatitis has a reduced diversity associated with an increase in *Staphylococcus* and *Corynebacterium* and a decrease in normal flora. *S. aureus* colonizes the skin in AD and plays a key role in the development and exacerbation of AD. *S. aureus* can induce T-cell-independent B-cell expansion, activate proinflammatory cytokines such as TSLP, IL-4, IL-12, and IL-22; and stimulate mast cell degranulation, leading to increased Th2 and skin inflammation [12,15].

#### Endotypes and phenotypes of atopic dermatitis and personalized medicine

With the active development of personalized medicine, more and more attention is being paid to atopic dermatitis endotypes.

An endotype is defined as the molecular mechanisms underlying the visible signs – the phenotype. They are identified based on the definition of biomarkers.

According to the definition of the US Food and Drug Administration (FDA), a biomarker is «a defined characteristic that is measured as an indicator of normal or abnormal biological processes or response to external influences, including therapeutic interventions» [16].

Biomarkers can be divided into two categories.

The first category includes: screening biomarkers (used to identify individuals at risk of developing a disease), diagnostic biomarkers (to identify patients with active disease), prognostic biomarkers (to determine recurrence or progression of disease in patients with a particular disease), and predictive biomarkers (patient

populations that are most likely to benefit from a given therapy).

The second category includes biomarkers of disease severity (to monitor the effects of treatment) and pharmacodynamic biomarkers (to identify possible side effects) [17].

Biomarkers are determined from genomic, transcriptomic, and proteomic data (such as cytokines and chemokines), as well as from morphological information (e.g., immunohistochemistry). They can be measured in biological fluids such as blood, saliva, and urine or in tissue samples (skin biopsy) [16,18].

Since AD is a heterogeneous disease, defined not only by clinical characteristics but also by the fact that different pathophysiological processes are observed in different subgroups of patients, it can be assumed that recently developed biologic drugs targeting specific components of the immune system may not be effective in all patients with AD. Thus, the identification of disease endotypes has become an important step in the development of personalized therapy for patients with AD. Prognostic biomarkers can be further used to identify and select a specific endotype that will respond to targeted treatment [16].

Thus, at the Congress of the European Academy of Dermatology and Venereology in 2022, a study was presented in which the authors compared blood samples and skin biopsy samples of patients with pediatric-onset AD persisting into adulthood (POAD) and adult-onset atopic dermatitis (AOAD). These groups of patients were also compared with a control group of healthy individuals. The results showed that both study groups, compared to the control group, had skin immune and barrier dysregulation with common Th2/Th22 hyperactivation. However, the study demonstrated more severe inflammation in the affected skin with more prominent expression of Th2/Th17/Th22 markers (CCL17/22, S100A8/9, IL-36A, PI3/Elafin, DEFB4) in patients with POAD compared to patients with AOAD (p-value < .05). On the contrary, a higher regulation of Th1-(IFN- $\gamma$ , IL-2, IL-15, CCL5) and Th1 imbalance were observed in the second group. The epidermal barrier was also more compromised in patients with POAD, with greater epidermal hyperplasia and lower expression of markers related to terminal differentiation, lipids, and cell adhesion [19].

Another scientific article by Japanese scientists highlighted the data on AD subtypes according to another classification, which distinguishes two types: extrinsic (with elevated IgE levels) and intrinsic (with normal IgE levels).

Extrinsic AD is the main subtype, in which there is a disruption of the epidermal barrier (high frequency of filaggrin protein mutations), while intrinsic AD accounts

for about 20 % of cases and is characterized by a preserved skin barrier (more common in women). Extrinsic AD occurs in protein allergy and food allergy, and intrinsic AD demonstrates metal allergy, possibly related to suprabasin protein (SBSN) deficiency [20].

European-American and Asian subtypes of AD have also been proposed. Patients of Asian descent with AD are characterized by a unique mixed endotype of immune dysregulation and barrier features. A study comparing affected and unaffected skin of patients of European-American and Asian (Japanese and Korean) subtypes showed marked epidermal hyperplasia and severe parakeratosis in Asians, but relatively preserved barrier proteins, such as FLG and loricrin. The level of IL-19, which was induced by IL-4, IL-13, and IL-17 and enhances the effect of IL-17 on keratinocytes, was significantly higher in AD lesions in patients of Asian descent compared to patients of the European-American subtype [21].

Thus, the results of studies of immunological features in patients with AD of different ethnic, age, and gender groups allow for a personalized approach to their treatment, which significantly increases the effectiveness of therapy and improves the quality of life of patients.

#### **Modern approaches to the treatment of AD**

The first line of therapy for patients with AD is the regular use of emollient cream, mild to moderate topical corticosteroids (TCS) and calcineurin inhibitors [7].

However, in patients with moderate to severe AD, this often does not produce the expected clinical effect and the patient receives only temporary improvement.

In the United States, the method of intensive topical therapy, which includes wet wrap therapy, is widely used for persistent forms of AD.

For wet wrap therapy, mild to moderate TCS are applied to the affected areas, and they can be diluted with emollient cream or petroleum jelly. Then the treated areas are wrapped in a wet bandage, fixed with a layer of dry bandage, and pajamas are worn on top. This method is also used with the application of only emollient under the bandage. The wrapping should be kept on for at least four hours and should be started twice a day, and the wet layer should not be allowed to dry out [22].

If wet wraps are ineffective, phototherapy can be used additionally, namely narrow-band ultraviolet B (NB-UVB), medium-dose ultraviolet A1 (UVA1) or psoralen and ultraviolet A (PUVA therapy). However, NB-UVB and UVA1 are preferred due to their higher safety profile [23, 17].

The decision to initiate systemic therapy should include an assessment of disease severity and quality of life, frequency of exacerbations, general health status,



adherence to topical therapy, psychological needs, and personal attitude to systemic therapy [24].

Biologic therapy is the method of choice among systemic drugs for AD.

Interleukin (IL)-13 is a key factor in the pathogenesis of inflammation in AD, which leads to dysfunction of the skin barrier, impaired immune regulation and chronic inflammation. IL-13 is overexpressed on the skin in patients with AD, and its correlation depends on the phase of AD exacerbation [12, 13].

To date, the only blocker of IL-4 and IL-13 is a human recombinant antibody (IgG4) – dupilumab, which is used to treat allergic diseases. The study, which included 138 patients, aimed to investigate the effect of 16-week treatment with dupilumab on clinical response and serum biomarkers in adult patients with moderate-to-severe AD. As a result, a significant improvement in the course of the disease and a decrease in serum biomarkers associated with severity in patients with AD was obtained [25].

However, it is worth noting that despite a fairly high safety profile, the use of dupilumab often causes side effects in the form of conjunctivitis (up to 37 %), facial redness, arthritis and inflammation at the injection site. These effects are usually well managed with appropriate therapy without the need to interrupt dupilumab [26,27].

Tralokinumab is a human monoclonal antibody that specifically binds to IL-13 and prevents the latter from interacting with the receptor, thus inhibiting its activity. The phase III ECZTRA 3 study showed that tralokinumab can be an effective and relatively safe treatment option for patients with moderate to severe AD, which is not controlled by topical treatments alone [28].

Th2-cell immunity, skin barrier dysfunction, and pruritus are known to form a vicious circle of AD. The Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway is one of the main signaling pathways in AD. In particular, TSLP, IL-4, IL-13, and IL-22 play an important role in the Th2 cell-mediated immune response. In addition, the pan-JAK inhibitor has been experimentally shown to inhibit STAT3 activation and improve skin barrier function. Thus, a new generation of drugs – JAK inhibitors are promising in the treatment of severe AD [12, 29].

Currently, there are oral Janus kinase inhibitors (abrocitinib, upacitinib, baricitinib) and topical drugs (ruxolitinib, tofacitinib, ifidancitinib, delgocitinib).

Abrocitinib is currently available in Ukraine.

The oral selective JAK1 inhibitor abrocitinib has demonstrated efficacy and safety in a phase 3 monotherapy study in patients aged  $\geq 12$  years with moderate to severe AD. In the study, more patients in the 200 mg (61.0 %) and 100 mg abrocitinib (44.5 %) groups compared to the

placebo group (10.4 %) achieved EASI-75 ( $P < 0.001$ ) at week 12. Adverse events were reported in 65.8 %, 62.7 % and 53.8 % of patients in the 200 mg, 100 mg and placebo groups, respectively [29].

A study conducted in 2022 evaluated the efficacy of abrocitinib compared to placebo in moderate to severe atopic dermatitis. It evaluated the efficacy and safety of abrocitinib compared to dupilumab. The results showed that abrocitinib at a dose of 200 mg daily was more effective than dupilumab in adults with moderate to severe atopic dermatitis on background topical therapy in inducing early reduction of pruritus and signs of atopic dermatitis. Both treatments were well tolerated for 26 weeks [30].

Another modern and promising direction in the treatment of AD is the use of probiotics. As it is known that patients with AD have a decrease in the amount of commensal bacterial flora of the skin (*Staphylococcus epidermidis* and *Staphylococcus hominis*) and colonization of the skin with *Staphylococcus aureus* [15]. In addition to the imbalance of the skin microbiota, intestinal dysbiosis plays an important role in the development of skin diseases. After all, the gut microbiota is an important component of the immune system regulation, as it is aimed at maintaining the body's homeostasis [31].

In 2021, a multicenter, randomized, double-blind, placebo-controlled study was conducted comparing the effect of probiotics (*Lactobacillus rhamnosus* and *Lactobacillus casei*) and placebo among groups of patients under 2 years of age with AD and cow's milk protein allergy, showed that after 3 months of treatment, both groups showed a decrease in the SCORAD index, with the probiotic group having a significantly higher percentage of children with clinical improvement than the placebo group [32].

## CONCLUSIONS

The incidence of atopic dermatitis, which is characterized by a complex etiopathogenesis, is increasing every year in the population of Ukraine and the world. The chronic course of the disease, dry skin, severe itching, and sleep disturbances significantly impair the quality of life of patients and their families. These factors are a burden on the medical system and an economic burden on the state.

The medical and social significance of AD opens up new challenges for finding new approaches to the management of patients with AD. Extensive study of the pathogenesis of the disease expands the understanding of AD and creates prospects for the development of new treatments. In recent years, biologic therapies have been actively introduced into medical practice, opening up new opportunities for personalized management of patients with severe AD.

Despite the efficacy and availability of standard AD therapy, it is not always possible to achieve the

expected treatment outcome due to the problem of widespread corticophobia in society, so the issue of treatment of mild and moderate forms of AD is still relevant. That is why, at this stage, attention to the treatment and prevention approach should be more focused, and treatment methods with high efficacy and low side effect profile should be a priority. The literature review revealed that the problem of atopic dermatitis remains relevant, despite the large number of studies on the etiology, pathogenesis and treatment of AD, which substantiates promising areas for the development and application of methods of modern effective personalized treatment of AD.

## FUNDING AND CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest. The article is self-funded.

## COMPLIANCE WITH ETHICAL REQUIREMENTS

The article complies with ethical norms: the study was conducted in accordance with the principles of bioethics set out in the Helsinki Declaration «Ethical Principles for Medical Research Involving Human Subjects» and the «Universal Declaration of Bioethics and Human Rights (UNESCO)».

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## Резюме

### АТОПІЧНИЙ ДЕРМАТИТ: СУЧАСНИЙ СТАН ПРОБЛЕМИ В УКРАЇНІ І СВІТІ

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**Вступ.** Соціальні та екологічні катаклізми останніх років спричинили зростання захворюваності, що становить загрозу здоров'ю та життю населення не тільки в Україні, а й у світі. Серед найпоширеніших захворювань шкіри є atopічний дерматит (АД) – хронічне рецидивуюче захворювання, що характеризується запаленням шкіри, порушенням епідермального бар'єру і, як наслідок, зниженням здатності шкіри утримувати вологу. Сьогодні лікарі загальної практики зазвичай першими стикаються з цією патологією, і саме вони повинні оцінити власний рівень компетентності в конкретному випадку та надати необхідну медичну допомогу або обґрунтувати направлення до дерматолога.

**Мета.** Здійснити аналітичний огляд вітчизняної та іноземної літератури з питань проблеми atopічного дерматиту (АД), методів діагностики та персоналізованого підходу до лікування даного захворювання та обґрунтувати подальші напрямки необхідних наукових досліджень щодо покращення належної медичної допомоги.

**Матеріали та методи.** Аналітичне вивчення вітчизняної та іноземної літератури

**Результати та обговорення.** АД зустрічається з частотою до 20 % серед дитячого населення та до 10 % серед дорослого у європейських країнах. В Україні станом на 2020 рік розповсюдженість АД серед дитячого населення коливається від 9,0 до 28,5 %.

Вивчення складного патогенезу захворювання, де ключову роль відіграють генетичні фактори, імунні дисрегуляції та порушення епідермального бар'єру дозволило вченим виділити ендотипи та фенотипи АД, що стало важливим етапом в розвитку персоналізованої терапії пацієнтів з АД. Саме біологічні препарати (блокатори ІЛ-4 та ІЛ-13 та інгібітори Янус-кінази) зробили прорив у лікуванні важких форм АД. Іншим перспективним напрямком в лікуванні АД – є застосування пробіотиків, адже відомо, що у хворих на АД спостерігається зменшення кількості коменсальної бактеріальної флори шкіри та колонізація шкірних покривів *S. aureus*.

**Висновки.** Таким чином, в популяції населення України та світу захворюваність на atopічний дерматит, який відзначається складним етіопатогенезом, зростає щороку. Медико-соціальна значущість АД відкриває нові виклики для пошуку новітніх підходів до ведення пацієнтів з АД. Протягом останніх років активно впроваджуються в лікарську практику препарати біологічної терапії, які відкривають нові можливості персоналізованого ведення пацієнтів з важкими формами АД. Щодо лікування легких та середніх форм АД питання є досі актуальним, зважаючи на проблему кортикофобії в суспільстві. Саме тому на цьому етапі увага до лікувально-профілактичного підходу має бути більш сфокусована, методи лікування з високою ефективністю і низьким профілем побічних дій мають бути пріоритетом. Огляд літератури дозволив виявити, що проблема лишається актуальною, незважаючи на велику кількість досліджень щодо етіології, патогенезу та лікування АД, що обґрунтовує перспективні напрямки розробки та застосування методів сучасного ефективного персоналізованого лікування АД.

**Ключові слова:** atopічний дерматит, персоналізована медицина, біологічна терапія, пробіотики