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Atopic dermatitis: Current standards of diagnosis and treatment, including the latest methods of management

Review

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Abstract

Atopic dermatitis (AD) is a chronic relapsing disease which causes characteristic eczematous skin lesions. The most common symptoms of atopic dermatitis are persistent pruritus, xerosis, and skin lesions with a typical location and appearance that changes with the patient's age. The prevalence of the disease in the pediatric population is estimated at 10% to 30%, while in adults it ranges from 1% to 3%. The number of people who suffer from AD is rising every year. The pathophysiology of the disease is complex and multifactorial. It involves elements of epidermal barrier dysfunction, alterations in cellular immune response, IgE hypersensitivity, and environmental factors. AD significantly reduces the quality of life of both patients and their families. Patients with AD are at higher risk for neuropsychiatric disorders such as depression, attention-deficit/hyperactivity disorder, and headaches. The decreased quality of life of AD patients and their families is associated with the discomfort of recurrent and chronic inflammatory skin lesions, persistent pruritus, and the inconvenience of long-term therapy. It also affects the psychological development of children, contributes to behavioral disorders (hyperactivity, hypersensitivity) and impacts many areas of family life such as sleep, leisure activities, and relationships between family members. The basic treatment of AD is avoidance of potential harmful factors, proper care in the treatment of exacerbations, topical corticosteroids, and calcineurin inhibitors in proactive therapy. In some patients who meet age criteria, phototherapy and cyclosporine should be considered. In individuals with severe AD who do not respond to topical treatment and who will not benefit from general therapy, dupilumab, a biologic drug, is the treatment of choice. Biologic treatment has an increasingly important place in the effective and modern therapy of AD. Currently, new biologic drugs are being researched, which may bring a therapeutic revolution in AD in the future. Allergen immunotherapy in patients with AD should be carefully evaluated on an individual basis, as proper selection of patients with documented IgE-dependent sensitization is important for the success of this therapy. Close collaboration with the patient and their caregivers, education, and psychological support as appropriate are integral to the treatment.

Keywords

atopic dermatitis • diagnosis of atopic dermatitis • treatment of atopic dermatitis

1. Definition of atopic dermatitis

Atopic dermatitis (AD) is one of the most common childhood skin conditions. It is a chronic, relapsing disease with eczematous skin lesions, pruritus, and accompanying inflammation involving Th2 helper lymphocytes [1]. The typical symptoms are persistent itching and dryness of the skin. The lesions have a typical localization and appearance that change with the patient's age. The skin lesions usually appear on the cheeks and the trunk in infants, and with increasing age they localize mainly on the elbows and popliteal folds. Because of its persistence and recurrence, as well as the intense pruritus that accompanies the disease, AD affects the patient's quality of life and disrupts family functioning [2]. The pathophysiology of AD is complex and multifactorial. It includes elements of epidermal barrier dysfunction, changes in cellular immune response, IgE hypersensitivity, and environmental factors [3].

2. Epidemiology

Most commonly, AD is diagnosed in early childhood. During the first five years of life, symptoms appear in up to 90% of patients, with more than 50% of the symptoms occurring during the child's first year of life. In most cases, we observe resolution of symptoms with age and remission in adults. However, in recent years, there has been a rise in the incidence of AD with so-called late onset. According to data reported by Korean researchers, 26.5% of infants under the age of two were diagnosed with AD, and this percentage dropped with age from 11.6% at age three to 4.6% at age 19 [4]. There has been a considerable upsurge in incidence

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over the past 25 years, and the number of diagnosed cases of AD has more than doubled, as revealed by the International Study of Asthma and Allergies in Childhood (ISAAC) Phase III study [5]. The prevalence of AD according to the ISAAC in Korea, which has been carried out every five years since 1995, showed that the cumulative prevalence of AD in Korean elementary school children has been steadily increasing from 19.7% in 1995 to 35.6% in 2010 [4]. The incidence of the disease in the pediatric population is estimated to be between 10% and 30%, while in adult patients it is estimated to be between 1% and 3%. The number of people suffering from AD is growing every year [6]. Symptoms of AD can worsen due to IgE-mediated hypersensitivity, as well as the epidermal barrier defect, which is associated with exacerbation of the disease with all the factors responsible for aggravation of skin dryness (e.g., air conditioning, central heating, poor airflow, and exposure to detergents); hence AD can have the status of a civilization disease. Many patients have a family history of atopic diseases. AD is often comorbid with other atopic diseases and is associated with the term "allergic march." Studies show that between 35% and 66% of people with AD will develop allergic rhinitis, and between 30% and 60% will suffer from bronchial asthma [7, 8].

3. Etiopathogenesis

The pathogenesis of AD is complex, with many factors being considered: genetic, environmental, non-immunological, and immunological with overlapping epidermal barrier dysfunction [9, 10, 11].

3.1. Genetic factors

Research shows that genetic factors have a major role in the pathogenesis of AD. AD is a polygenically inherited disease, and researchers have identified many chromosomal loci associated with atopy. Genes are responsible for the development of atopy encode cytokines, immunoglobulin chains, cell receptors, and transcription factors [12, 13]. Polymorphism of the filaggrin gene, which accounts for the epidermal barrier defect, is also important in the etiopathogenesis of AD. Loss-of-function mutations in filaggrin are a predisposing risk factor for severe atopic dermatitis due to potential elevation of transepidermal water loss (TEWL), pH changes, and dehydration. Other genetic variations that may alter skin barrier function have also been mapped [14]. It is estimated that approximately 70% of patients with AD have a family history of atopic disease, and familial predisposition appears to worsen the prognosis of these patients. Comorbidity of AD has been demonstrated in 72–86% of monozygotic twins and 21–23% of dizygotic twins [15].

3.2. Environmental factors

There are a number of factors that can complicate the course of AD, by potentially causing eczema and pruritus. We must consider the role of the environment and the effects of chemicals in triggering AD. More specifically, these factors include irritants (including soaps and shampoos as well as clothing), airborne formaldehyde, fragrances, and preservatives in foods. The use of harsh, alkaline detergents in skin care products can adversely affect the pH of the skin, thereby further altering enzyme activity and causing inflammation. Aeroallergens, food allergens, microbes, contact allergens, sweat, and scratching are also common culprits. In younger children with AD, food allergens may be of importance, most typically foods such as egg, milk, or peanuts, whereas in older children and adults, sensitization to environmental allergens such as house dust mites, animal allergens, or pollen is more frequently observed. Environmental pollutants can trigger responses from both the innate and adaptive immune pathways [3, 16].

3.3. Immunological factors

With advances in medicine, immunological factors and their contribution to the pathogenesis of AD are being better understood. They include multiple disorders of Th2 lymphocytes and the cytokines they release (including IL-4, IL-5, IL-13, IL-31); these increase IgE production, exacerbate skin inflammation, and lead to more skin barrier damage in AD [17]. The symptoms of AD have been linked to the production and release of Th2-type cytokines (IL-4, IL-5, IL-13, IL-31), the levels of which are markedly higher in AD patients compared to healthy individuals. Depending on the disease duration and inflammatory phase, both Th2 and Th1 cytokines are involved in the development of symptoms. The response of T lymphocytes and domination of cytokines that they secrete differs considerably during AD flare-up and remission [17, 18]. In the initial phase of skin inflammation, the effect of IL-4 released by inflammatory infiltration cells is important. This cytokine can be produced and released by mast cells, basophils, and eosinophils in the course of acute eczema-like reaction. In the acute stage of AD-related inflammation, there is a pronounced expression of IL-31, observed within itchy inflammatory skin lesions. This increase in IL-31 expression may be caused both by histamine and *Staphylococcus aureus* superantigens. In the chronic phase of skin inflammation, we also note an increase in the expression of IL-5, which prolongs the lifespan of eosinophils and maintains their activity [19]. Skin inflammation in AD patients is promoted by Th17 and Th22 lymphocytes, which release cytokines such as IL-17, IL-19, and IL-22. The percentage of Th17 cells circulating in the peripheral blood of AD patients is related to the severity of the disease. Th17 lymphocytes appear to play an essential role in protection against bacterial pathogens. In addition, they may be of major significance in the pathogenesis of a variety of inflammatory diseases that were previously described as mediated by Th1 lymphocytes [18, 20].

Regulatory T lymphocytes (Treg) are responsible for the activation of autoreactive and effector T lymphocytes and are

absolutely essential in the process of peripheral self-antigen tolerance. They are mainly involved in the production of IL-10 and TGF (transforming growth factor). Mutations in FOXP3, a nuclear factor whose expression is found on the surface of natural and adaptive Treg cells, lead to the development of polyendocrinopathy syndrome, an X chromosome–associated enteropathy that is characterized by elevated IgE levels, food allergy, and signs of eczema [19].

Dendritic cells (DCs) specialized in antigen presentation may also be involved in the pathogenesis of AD. These are classified into two main types: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). mDCs are further subdivided into two varieties: Langerhans cells and inflammatory dendritic epidermal cells (IDECs). Langerhans cells participate in the initiation of the immune response and in stimulating the T lymphocyte phenotype towards Th2. They are responsible for the presentation of peptides originating from allergens to antigen-specific T lymphocytes in the skin. Concentration of the receptors for IgE (FcεRI) on their surface induces the secretion of various chemotactic factors (e.g., CCL2, CCL22, CCL17, and IL-16), which in turn may facilitate the presentation of allergens to T lymphocytes. Receptors for IgE and inflammatory epidermal dendritic cells are more prominent in chronic inflammation in AD patients in the foci of inflammatory skin lesions. When stimulated, pDCs are capable of producing antiviral type I interferons. Patients with AD have been reported to exhibit elevated numbers of these cells in the peripheral blood, while they are scarce within skin lesions, which may partially explain the susceptibility of AD patients to skin viral infections [19].

When exposed to various factors such as allergens, microbial activity, scratching, and pruritus, keratinocytes react by releasing cytokines that modulate inflammation, including TSLP (thymic stroma lymphopoietin), IL-33, and IL-25. TSLP is not found in healthy and non-lesional skin of AD patients, but it is significantly expressed in acute and chronic inflammatory skin lesions in the course of AD. In synergy with IL-1 and TNF-α, TSLP stimulates the synthesis of high concentrations of Th2 profile cytokines by human mast cells. Interleukin 33 activates Th2 lymphocytes and innate lymphoid cells (ILC2). In turn, ILC2 in conjunction with IL-33, IL-25 and TSLP appears to explain and differentiate the mechanism of the atopic march [19, 21, 22].

Eosinophils also play a key role in AD. Stimulated cells are found in peripheral blood and in skin lesions. They release numerous proteins with a strong cytotoxic effect, as well as chemical mediators responsible for the development of inflammation within the tissues. Eosinophils are of great importance in neuroimmune interactions, which are enhanced by brain-derived growth factors (they limit the apoptosis of eosinophils and enhance their chemotaxis) [19].

In most cases, the skin of patients with AD is colonized by *Staphylococcus aureus*. In the scalp and neck regions, on the other hand, there is often colonization by Malassezia species. *Staphylococcus aureus* may exacerbate skin inflammation in AD patients by releasing superantigen exotoxins. These stimulate the activation of T lymphocytes and antigen-presenting cells or keratinocytes. In some patients, IgE-mediated sensitization to bacterial antigens also occurs. Patients suffering from AD are more prone to bacterial, fungal, or viral skin colonization if they are deficient in antimicrobial proteins, such as dermicidin, cathelicidin: LL-37, or human β-defensin. The expression of β-defensins is limited by cytokines such as IL-4 and IL-13 [19].

Approximately 80% of adult patients with AD have elevated serum IgE (> 150 kU/l), which is often associated with sensitization to aeroallergens and/or food allergens. No IgE-mediated allergic process can be documented in about 20% of individuals with classic AD symptoms. In children, this condition is called intrinsic or non-allergic atopic dermatitis (IAD). Owing to the profoundly impaired structure and function of the epidermal barrier, IgE-mediated sensitization to environmental allergens progresses over time in up to 80% of cases. Patients with the extrinsic allergic type of AD (extrinsic atopic dermatitis, or EAD) show higher tissue eosinophilia and higher tissue release of post-inflammatory cytokines, as well as increased expression of the receptor for IgE. Allergen-specific IgE is essential in skin inflammation, as it activates mast cells and dendritic cells. Autoimmunity may also be relevant in the pathophysiology of AD. IgE directed against autoantigens can stimulate an immediate-type response and stimulate dendritic cells [19]. Stressful situations have been reported to worsen symptoms in AD. Under stress, there is a dysregulation of cytokine signaling, which may promote the stimulation of the Th2 lymphocyte system as well as reduce immunity to possible skin infections [23].

4. Epidermal barrier defect

Patients with AD are diagnosed with a defective epidermal barrier. It is genetically determined and connected with many abnormalities in the structure and function of the epidermis, not only of dead skin, but also of apparently healthy skin [24]. The primary barrier between the external and the internal environment, the stratum corneum is the main obstacle in the absorption of different substances. It consists of corneocytes and intercellular substance, which is made up of lipids (sterols, ceramides, phosphoglycerols, and fatty acids). In AD-affected skin, the amount of lipids is considerably diminished, both in lesional and nonlesional areas. The production of stratum corneum lipid coat is impaired, mainly due to abnormal enzymatic activity [25]. Skin affected by the epidermal barrier defect is more prone to the penetration of environmental allergens and haptens, which may lead to atopic and contact allergy. The chief symptom linked to a defect in the epidermal barrier is dryness of the skin and, what follows, increased TEWL. It has been shown that TEWL increases fourfold in the area of eczematous lesions, and twofold

on non-lesional skin compared to healthy subjects [26]. TEWL has been found to be elevated in both dry skin without eczema and in clinically normal skin in patients with AD [24]. Xerosis has been linked to an increase in pruritus and consequent scratching, which causes skin irritation and excoriated skin. As a consequence, contact of environmental substances and allergens with the immune system is facilitated, so skin infections can occur. Dry skin also presents as flaky scaling or even lichenification. Disturbances of stratum corneum homeostasis are also associated with mutations in the filaggrin gene in patients with atopic dermatitis. Filaggrin has a vital function in maintaining a normal epidermal barrier. Mutations in the filaggrin gene cause disorders in the arrangement of lipid lamellae, decrease of natural moisturizing factor (NMF), and increase of TEWL [14, 26].

5. Clinical picture of atopic dermatitis

The diagnosis of AD is based on the clinical picture. For years, Hanifin and Rajka's diagnostic criteria have been most common (Table 1) [27]. The presence of three major and three minor criteria is sufficient for the diagnosis of AD. Pruritus is an inherent feature of AD, as is the chronic and relapsing course of the disease. A family history of AD is reported in about 60% of patients.

To evaluate the localization of the lesions, it is necessary to take into account the stage of the disease and the age of the patient. The typical features of atopic dermatitis are papules, which are often clustered and present on an erythematous, sometimes exudative surface. The lesions have different shapes and are not sharply demarcated from the surrounding tissue. In the acute phase, we can observe papules and erythema, edema, sometimes vesicles and oozing. When the entire or nearly the entire skin surface is inflamed, erythroderma may occur, accompanied by lymphadenopathy and a rise in body temperature. Scratching and the formation of excoriated wounds promote skin infection, in which case honey-yellow scabs may appear (infections caused by staphylococci and/or streptococci). In the chronic phase of the disease, skin lesions are drier, scaly, and often lichenified. Lichenification on the face makes the patient look significantly older.

The pattern of skin lesions in AD is different in different age groups. In infants, the skin is dry and rough (the diaper area is often spared), and the lesions may also be oozing. They are located predominantly on the face, cheeks, and forehead. Itchy dry patches are also reported, usually on the outer surfaces of the limbs but also on the abdomen, chest, and back.

In the next stage of the disease, the so-called pediatric phase, which begins at the age of two and lasts until adolescence, the oozing lesions like those in infants are less prevalent. The most frequently occurring lesions are typical of chronic disease with papules and patches with lichenification. They may be localized on hands, feet, in the volar region of wrists and ankles, as well as in elbow and knee joints. The Dennie-Morgan line, which is symmetrical single or double skin folds under the lower eyelid, may also occur. Cracking and oozing in the lower part of the earlobes and eczema behind the ears can present as well. Enlarged peripheral lymph nodes may be found on examination. In addition, cheilitis caused by licking the lips, perioral eczema, and inflammation of the corners of the mouth can also be observed. In a flare-up, due to intensive pruritus, scabs and excoriations are often present. About 70% of children also develop hand eczema with hyperkeratosis and fingertip cracks (pulpitis sicca).

In adulthood (adolescents and adults), lesions are mainly seen in the flexural folds, on the face and neck, upper arms and back, and on the dorsal surfaces of the hands and feet, including the fingers. In adults, they usually manifest as dry, scaly papules and flakes on an erythematous surface. Because of the long-lasting, chronic nature of these lesions, lichenification frequently occurs. Hand eczema may be a symptom of AD, but a higher frequency of allergic or non-allergic contact eczema is noted in patients with AD due to easier penetration of irritants and contact allergens through the insufficient epidermal barrier. In adults with chronic AD, the so-called dirty neck symptom, that is, a discolored (brown) ring around the neck, may be seen. Nipple eczema occurs in about 12% to 23% of patients as symmetric involvement of the nipple areola, often in the form of papular and vesicular lesions [28].

6. Diagnosis and differentiation

The diagnosis of AD relies on the clinical picture, and for many years the most commonly used criteria have been the Hanifin and Rajka diagnostic guidelines. In the majority of cases, the

Table 1. AD criteria, according to Hanifin and Rajka [27]

Major criteria	Minor criteria
- pruritus - chronic, recurrent dermatitis - typical morphology and localization of the lesions - personal or family history of atopy	- dryness of the skin - fish-scale skin - immediate skin reactivity - elevated IgE levels - early age of onset - susceptibility to recurrent skin infections - nonspecific hand/foot dermatitis - nipple eczema - cheilitis - recurrent conjunctivitis - Dennie-Morgan infraorbital fold - keratoconus - cataracts - darkening around the eyes - pityriasis alba - anterior neck folds - itch when sweating - food intolerance - intolerance to wool - exacerbations after stress - white dermographism - facial erythema - perifollicular accentuation

diagnosis is not very difficult. Differentiation is necessary in patients with less typical course and clinical picture.

In infants, AD should be differentiated from seborrheic dermatitis, irritant contact eczema, psoriasis, ichthyosis, tinea cruris, and sarcoptosis. It is also important to take into account metabolic disorders and primary immunodeficiencies. In older children, adolescents, and adults, AD should be differentiated mainly from contact dermatitis, symptomatic scabies, sarcoptosis, and Duhring's disease. A secondary parasitic, viral, fungal, or bacterial infection causing a flare-up also requires proper diagnosis because it entails causal treatment.

Laboratory diagnostics makes it possible to identify existing disturbances in immunological processes. Approximately 80% of adults with AD have elevated serum immunoglobulin E values (> 150 kU/l). High IgE levels are usually associated with sensitization to aeroallergens, food allergens, allergic rhinoconjunctivitis, and bronchial asthma. In some people (about 20% of patients) with typical symptoms of AD, IgE-mediated allergy cannot be documented. In children, this form of the disease is defined as intrinsic or non-allergic type of AD (IAD). However, due to the defect of the epidermal barrier about 80% of patients will usually develop IgE-mediated sensitization to environmental allergens in the future. Patients with the so-called allergic, extrinsic type of AD (EAD) exhibit higher tissue eosinophilia, increased release of proinflammatory cytokines and expression of FcεRI on the surface of dendritic cells, compared to patients with non-allergic AD. Through activation of mast cells and dendritic cells, allergen-specific IgE plays a crucial role in the progression of skin inflammation. The effect of histamine receptors on lymphocytes, antigen-presenting cells, and keratinocytes may further worsen skin inflammation [19].

7. Skin prick tests and measurement of serum allergen-specific IgE

Skin prick tests (SPT), which are done by puncturing the epidermis with a lancet containing common inhalatory and food allergens, are used to diagnose IgE-dependent allergy. The tests are performed on uninjured skin, usually on the forearm, and less commonly on the upper back. Antihistamines, glucocorticosteroids, and phototherapy should be discontinued before the procedure. Positive SPT reactions are not always clinically significant. They may be the result of tolerance to an allergen, such as food allergens causing symptoms in childhood, but without clinical significance in adulthood. A positive skin reaction for a negative control may be due to its overreactivity (dermographism). A negative reaction for a positive control (histamine) indicates inadequate skin reactivity. Serum concentration of allergen-specific immunoglobulin class E is also used in diagnosis. This test is safe, does not depend on the skin reactivity or treatment (it does not require discontinuation of drugs), is not influenced by skin condition and may be also performed in patients with inflammatory lesions, which would exclude the possibility of skin prick tests [29]. For inhalatory allergy, the sensitivity and specificity of skin prick tests are estimated at 80–90% and 70–95%, respectively. In cases of symptoms suggestive of food allergy, the results of such tests are not conclusive about the absence or presence of allergy to a particular food; the outcomes should be interpreted with caution. Only a minority of patients with positive skin prick tests develop clinical symptoms during oral provocation with food containing the allergen that produces a positive SPT result. The results can be verified by testing allergen-specific IgE or by using molecular diagnostic options [30].

8. Molecular diagnostics

CRD (component-resolved diagnostics), a molecular test based on the detection of antibodies to allergen compounds, is a new tool in allergy diagnostics that is performed in specialist centers. By means of commercial tests, this diagnostic method has become available for a wider group of patients (the Faber, ALEX, ISAC tests). However, the relatively high cost of this method is still a limitation. CRD allows prediction of cross-reactivity in a patient. Cross-reactivity is a common issue, due to the high affinity of proteins that are part of a given allergen (the so-called allergen components) to proteins from other allergen sources, even to distant species. Allergen-specific IgE antibodies that are originally produced against one allergen may cross-react with many other similar allergens. A cross-reaction is very likely to occur when the identity of the protein sequence is 80%, and is rare when the similarity is 50%. One example of cross allergy is the coexistence of allergic rhinitis caused by pollen allergy and food allergy: oral allergy syndrome (OAS), also known as pollen-food syndrome (PFS, pollen food syndrome, or PFAS, pollen food allergy syndrome). The term PFAS better illustrates the cross-reactivity between pollen and food. The syndrome of oral allergic symptoms occurs mainly in adolescents and young adults; however, the frequency of its occurrence in Polish children has not been established [31, 32].

9. Patch tests

Patch testing (PT) should be carried out in every patient with chronic or recurrent eczema, irrespective of the suspected etiology. PT is the gold standard in the diagnosis of eczema and is important in the differential diagnosis. Patients with AD may also have contact allergy. Patch testing is a classical method for the detection of contact allergy, for example, type IV immune reactions in the Gell-Coombs classification to haptens: small molecule chemical compounds of natural or synthetic origin (plants, metals, fragrances, drugs, and textile dyes, etc.). The miniscule haptens penetrate into the dermis as the epidermal barrier is no obstacle for them. In the skin, these substances bind with the body's own proteins, and the products of this interaction are usually tolerated by the immune system. However, tolerance

may be compromised and type IV hypersensitivity may develop. In patch testing, suspected haptens are placed on the subject's skin surface in appropriate concentrations and media. PT is performed without age restrictions: the indications are the same for children as for adults. Routine patch tests include the Polish Basic Series comprising 30 most allergenic substances; however, this number is the minimum and may be expanded to incorporate additional suspected substances [30].

10. Atopy patch tests

Atopy patch tests (APT) have been suggested to investigate the relationship between exposure to proteinaceous airborne allergens (house dust mites, pollen) and the onset or flare-up of atopic eczema. These tests have not been introduced into general allergological practice, and are mainly used in clinical research. The diagnostic relevance of the atopy patch test with aeroallergens in AD is still disputed, but new reports indicate that they may be useful as an adjunctive tool in routine clinical examinations in patients with AD and/or respiratory allergy [33]. APTs with food allergens in the diagnosis of AD are a subject of considerable controversy [30].

11. Medical history as a diagnostic tool in food allergy

When we suspect that food allergens exacerbate the course of AD, it is essential to take a repeated history, in order to identify the food component causing hypersensitivity reactions. The first diagnostic goal is the identification of specific hypersensitivity, regardless of its allergic or non-allergic pathogenesis. A flare-up of AD which occurs each time and in a recurrent manner after the ingestion of a specific food, other possible causes excluded, makes it possible to demonstrate hypersensitivity. The diagnostic value of medical history is usually high for immediate type I reactions in the Gell and Coombs classification, but low for delayed reactions.

12. Diagnostic elimination and provocation diets

In addition to repeated history taking, food and symptom diary keeping, diagnostic elimination or provocation diets also play an important role. Diagnostic diets can be especially useful in children with AD, but also in people with urticaria who identify food as a trigger for flare-ups. The common term "food" also covers food ingredients with no intrinsic nutritional value (additives used by the food industry, salicylates, essential oils, natural pharmacoactive food components such as histamine or tyramine, or drugs taken orally). The simplest solution is an open provocation test, which has a high negative predictive value. An alternative is a diet consisting in the gradual introduction of suspected foods until the appearance of the expected symptoms. It should be kept in mind that the above-mentioned tests, as well as single or double-blind oral provocation tests, do not serve to diagnose food allergy but to identify the factor that triggers hypersensitivity symptoms. A double-blind, placebo-controlled oral provocation test is optimal for the diagnosis of food hypersensitivity because it is independent of the psychological factors affecting the patient and the researcher. Caution is always required with any provocation trial, as there is a risk of adverse or even serious symptoms (anaphylaxis). Provocation with a suspected food is recommended when it is not possible to clearly identify the food causing symptoms on the basis of the patient's history. The provocation test helps to confirm the cause-effect relationship between the stimulus (consumption of a suspected food) and the reaction: occurrence of hypersensitivity symptoms. These tests are used both for immediate reactions (IgE-dependent food allergies) and delayed reactions to foods in children with AD (e.g., milk, chicken egg, soy, and wheat). It is well known that in patients with AD the same foods may be the source of both IgE-dependent and delayed allergenic reactions. Non-nutritious, non-allergenic food components may also exacerbate the patient's skin condition [30, 34].

13. Allergy to cow's milk protein

One of the most common and complex forms of food allergy in early childhood is cow's milk protein intolerance (CMPI). Cow's milk protein, like other foods, can cause symptoms through both an IgE-dependent and an IgE-independent mechanism. An allergy to cow's milk proteins may aggravate AD. Clinically, CMPI may also manifest with gastrointestinal symptoms such as food protein–induced enteropathy (FPE), food protein–induced enterocolitis syndrome (FPIES), or food protein–induced allergic proctocolitis (FPIAP). In 2013, the UK guidelines for the diagnosis and treatment of IgE-independent cow's milk protein allergy in infants entitled Milk Allergy in Primary Care (MAP) were published. They discuss both forms (IgE-dependent and IgE-independent) and outline practical principles for the management of mild/moderate IgE-independent allergy, the most common clinical form of CMPI. If the clinical history suggests IgE-independent cow's milk protein allergy and the child has not had a severe delayed reaction, trial elimination of the suspected allergen from the diet is recommended, with reintroduction to the diet thereafter. In most infants in this situation, if they are fed modified milk, the treatment should be started with the administration of extensively hydrolyzed formula (eHF); however, in some situations amino acid–based formula (AAF) may be preferable. When a breastfed infant reacts to cow's milk proteins ingested by the mother, it is recommended to first eliminate cow's milk from the mother's diet, and if supplemental feeding is needed, to include a hydrolysate. If the symptoms are markedly relieved after the introduction of an elimination diet, it is necessary to reintroduce the allergen into the diet and reassess the severity of symptoms after provocation to confirm CMPI. Skipping this step leads to unwarranted continuation of an unnecessary diet in many in-

fants, which presents a major nutritional challenge. If the clinical history suggests IgE-mediated CMPI, skin prick tests can be performed or allergen-specific IgE antibodies directed against suspected food allergens can be measured in the blood. However, care must be taken in interpreting these results. Positive results in skin prick tests or the presence of specific IgE only indicate sensitization (i.e., the presence of IgE antibodies) to food allergens, but do not confirm allergy. The final diagnosis of clinically manifest allergy depends on the interpretation of these results against the clinical history. Food allergy has a strong tendency to resolve with age due to maturation of the gastrointestinal tract and development of tolerance to sensitizing food allergens. Individuals sensitized to pollen allergens may cross-react also to food allergens [31, 32, 34, 35, 36].

14. Methods which are not recommended for diagnosis

There are many suggestions of non-recommended methods in diagnosing diseases, including AD, proposed by so-called alternative medicine. They can be divided into those based on rational grounds but amply proven to be of no value, and those that are utterly irrational. The first group includes, for example, the measurement of IgG4/IgG in serum or performing a blastic transformation test. The methods that are irrational but popular among a certain group of patients largely due to their promotion on the Internet include bioresonance, bioenergy therapy, homeopathy, and others. These methods should not be recommended or used [30].

15. Management of atopic dermatitis

AD is a difficult disease to treat, and the discomfort it causes significantly impairs the quality of life for patients and their families. In order to achieve the best possible control of the disease and to improve the patient's comfort, the therapy should be multidirectional and comprehensive. The management also depends on the severity of the disease. Education of the patient and his/her family, prophylaxis, skin care, correct local treatment and, if appropriate, systemic therapy are important elements that we should focus on in order to control the disease. Psychological support of the patient and their family is an essential and integral part of the management.

16. Quality of life in patients with atopic dermatitis

In recent years, researchers have taken more interest in the quality of life of patients, including those with AD. The quality of life of patients with AD has received a lot of attention, with evidence found in numerous publications in the international literature [37, 38]. However, there is much less research on the quality of life of parents of children with AD. Few papers have been published on the subject so far, and this issue requires further investigation. Chronic dermatological diseases, such as AD, although not directly life-threatening, can substantially reduce the quality of life of patients and their families, to a degree comparable to that of sufferers of coronary heart disease, asthma, or diabetes [39, 40, 41, 42, 43]. Patients with AD are at higher risk for neuropsychiatric disorders such as depression, attention-deficit/hyperactivity disorder (ADHD), and headaches [44, 45]. Decreased quality of life in patients with AD is associated with the discomfort of recurrent and chronic inflammatory skin lesions, persistent pruritus, and long-term therapy. The severe deterioration of the quality of life of patients and their families affects the psychological development of children, may lead to their behavioral disorders (hyperactivity, hypersensitivity), and impacts many areas of family life such as sleep, leisure activities, and relationships between family members [46]. Parents often describe children with AD as more irritable, moody, and weepy [47]. AD sufferers have lowered self-esteem, view themselves as less attractive, and find it more difficult than healthy individuals to form social contacts [48]. The 2010 study on the quality of life in a group of children with AD under four years of age, carried out in Gdansk, showed a significant relationship between the severity of inflammatory changes and the intensity of mood disorders, the time it takes to put the child to sleep, problems during family play and activities, and during meals, therapy, and bathing. In the group of patients aged 5 to 16, a correlation was found between inflammatory lesions and increased feelings of embarrassment, shyness, sadness, or concern about the appearance of the skin, peer interactions, playing, going out, doing sports, learning problems, and sleep disturbances. The study also showed a decline in quality of life for families of patients with AD. The disease limited most areas of family life (daily activities, housework, cleaning, meals, rest, and sleep). Because of sleep disorders and the need for long-term treatment, caregivers of children with AD were disheartened and exhausted [49].

17. Itchy skin: A bothersome symptom

Pruritus is an unpleasant sensation that leads to scratching. It is a bothersome symptom of atopic dermatitis that considerably lowers quality of life. Pruritus is regarded as a separate type of surface sensation that is transmitted to the central nervous system through specific neural pathways.

Despite improvement in research methods, the pathomechanism of pruritus in AD is still not fully explained. Researchers take into account stimulation of nerve endings in the skin (cutaneous pruritus), as well as some disorders in the peripheral and central nervous system (neurological pruritus) [50]. Increased secretion of nerve growth factor (NGF) by cells of the basal layer of the epidermis results in hypertrophy of nerve endings and increased number of axons [51]. It has been observed that itch can be induced more easily using provocative factors in patients with AD than in healthy subjects. A lowered pruritic sensory threshold may be associated with a rise in the number of sensory

nerve fibers, neurofilaments, enhanced expression of neuropeptide Y, substance P, and CGRP (calcitonin gene-related peptide) in the affected skin [52]. A number of possible mediators of pruritus are being considered, which include acetylcholine, bradykinin, endothelin 1, endovanilloids, histamine, interleukins 2 and 31, cannabinoids, corticotropin, leukotriene 4, vasoactive intestinal peptide (VIP), opioid peptides, prostaglandins, tryptase, kallikreins, and serotonin.

Pruritus is a subjective symptom; therefore, it is difficult to assess its severity. The tools that are most commonly used for assessment of pruritus are the well-known and approved Visual Analogue Scale (VAS) and Numeric Rating Scale (NRS) [53].

Chronic pruritus (lasting more than six weeks) usually has a detrimental effect on the patients' mental state, and may cause sleep disorders, depression, or anxiety disorders, thus markedly reducing their quality of life [54, 55]. Sleep disorders affect not only patients with AD but also their family members. Parents of children with AD have been found to have nighttime sleep shortened by an average of 2.6 hours [56].

Pruritus is not only a symptom of dermatological diseases; it can also accompany many internal conditions (liver, hematological, and endocrinological conditions), neurological, infectious (AIDS, parasitic diseases), and psychiatric illnesses [54].

In AD, pruritus is the primary symptom and one of the four main diagnostic criteria, according to Hanifin and Rajka. The severity of pruritus correlates with the severity of the disease process and is part of the assessment of AD severity in the frequently used SCORAD scale [57]. The oSCORAD scale (objective SCORAD) is a modified version, where the assessment of subjective symptoms was excluded. Other tools used to measure the severity of AD include the Eczema Area and Severity Index (EASI), which assesses subjective symptoms and is often used in clinical trials, similarly to the Investigators' Global Assessment (IGA) scale [58].

The prevailing view today is that every patient with AD suffers from pruritus at least during some periods of the disease [59]. A number of factors can aggravate pruritus in AD: sweating, dry skin, physical exertion, emotional stress, some fabrics (such as wool), hot water, and certain foods [60]. According to patient reports, pruritus may be reduced by the use of emollients, topical corticosteroids, antihistamines, cool air or cool bath, and rest, but these antipruritic therapies have had limited long-term effect [60].

18. Non-pharmacological management: Prevention in AD

The increase in the incidence of AD has prompted the search for effective prophylactic methods to prevent the development of the disease. Prophylaxis may involve children at risk without symptoms (primary prophylaxis), as well as those with early or advanced symptoms (secondary prophylaxis). Evidence-based measures for primary prevention include breastfeeding infants up to 3–6 months of age and not smoking during pregnancy. The goal of prophylaxis in people diagnosed with AD is to prevent further progression of the disease, to reduce the frequency of flare-ups, and to decrease the severity of symptoms.

19. Probiotics

One of the prophylactic methods that has been advocated is the use of probiotics. There are many reports in the literature on the role of probiotic bacteria in the primary prevention of AD. It has been suggested that the early gut microflora is involved in the pathogenesis of AD; therefore, it has been argued that modulating it may contribute to the prevention of allergic diseases as well as to their treatment. A review of several papers has shown that the administration of probiotics during pregnancy and in the first weeks or months of a child's life contributes, albeit moderately, to reducing the risk of AD [61]. A recent review included 39 randomized control groups with a total of 2599 participants of both sexes, ranging from one year old to 55 years old, to investigate the use of probiotics such as Lactobacillus and Bifidobacteria taken alone or in combination with other probiotics for four weeks to six months. Analysis of SCORAD-based outcomes by age group revealed no significant difference between probiotic and control among children under two years of age. However, data in the older age groups showed a significant difference in favor of probiotics [62]. Examining the effect of probiotic supplementation over time has yielded controversial results. The choice of probiotic bacteria, the dosage, the period for which the probiotic is administered, and the presence of multiple interfering factors (diet, age, obesity, and environmental exposure) may affect the success of probiotic supplementation therapy. Differences in strain specificity, timing, and length of supplementation, and the influence of additional factors all add to the varying conclusions of meta-analyses. Probiotic use may alter the composition of children's gut flora, modulate immune system reactivity, and likely perform an important role in the prevention of AD. The effects of probiotic administration in the prevention and treatment of allergic diseases are still disputable, and there are no clear definitive recommendations. The use of probiotics requires further research. Well-designed, double-blind randomized trials involving large groups of patients are required to conclusively evaluate the efficacy of probiotics in the prevention of AD [63].

20. Emollients

When it comes to preventive measures, current literature also supports early, daily emollient therapy to decrease the incidence of AD in infants who are at risk [64]. In secondary prevention, appropriate skin care is the most important management strategy. One of the factors responsible for the onset, exacerbation, and persistence of eczematous lesions in AD is a defective epidermal barrier. For this reason, measures to strengthen this barrier prevent inflammatory changes. Proper care during exacerbations,

but also between relapses, contributes to prolonging the remission time and shortening the duration of flare-ups. The natural skin barrier can be restored by emollient preparations, which have moisturizing and lubricating properties. They should be used continuously (if well tolerated), at least twice a day (they are effective for about six hours). Different types of emollient products are available. Some form a protective layer to prevent water loss from the skin, others contain substances that help bind water in the stratum corneum, supply water to the epidermis, or contain natural lipid components. Emollients are usually based on two types of emulsions: oil-in-water and water-in-oil, and easily soluble three-phase emulsions. They are commercially available in the form of ointments, creams, emulsions, shower gels, and bath oils. The most effective products are those containing urea (5–10%), which maintains proper hydration of the stratum corneum, as well as ceramides or other physiological epidermal lipids. A range of different emollient formulations have been described and tested against clinical data in the medical literature. Most have demonstrated beneficial effects, but there is no evidence of a clear advantage in terms of the benefits of a particular emollient in the treatment of AD. For patients, physician or nurse recommendations are the most important consideration when choosing an emollient, so medical professionals should provide evidence-based information about these care products [65].

21. Education: Avoiding aggravating factors and proper skin care

A combination of avoiding potential aggravating factors, daily emollient therapy and proper epidermal care with anti-inflammatory medication applied as needed is the basis of treatment for AD. During the management of a chronic disease such as AD, close collaboration of the patient or their carers/parents with a nurse and a doctor is essential. It is of utmost importance to educate the patient on the nature of the disease, to explain the need for long-term skin care and to discuss the effects of different drug groups.

Regardless of the decision to initiate pharmacological treatment, efforts should be made to minimize factors that worsen disease control. It may be beneficial if a physician or nurse educates the patient about the factors that exacerbate the course of the disease. This includes proper education on how to recognize and eliminate or reduce factors such as irritants (soaps, shampoos, alkaline detergents in skin care products), clothing (such as wool or certain synthetic materials), airborne fragrances or formaldehyde, artificial dyes and preservatives in foods, microorganisms, contact allergens, sweat, and scratching. Attention is called to foods containing large amounts of tyramine (a precursor to histamine), which is found in fish, yellow cheese, and blue cheese, for example. Awareness of these factors may, to some extent, help patients to avoid them and thus prevent flare-ups of the disease.

Instruction on how to apply medications to the skin or how to make wet dressings, for example, is of great value. All educational approaches and techniques are useful: verbal instruction, drawings or photographs, video presentation, "live" demonstration, and individual or group training. The method of choice depends on the needs and educational capabilities of the patient. It is necessary to cleanse the atopic skin gently and thoroughly, in a bath containing emollients with lubricating and moisturizing properties. Baths should contain natural or mineral oils, without detergents. AD sufferers should avoid soaps and detergents with an alkaline reaction and replace them with special bars or syndets. Washing agents should have a low pH (close to 5.5), and should contain as little fragrances, dyes, and preservatives as possible. It is not recommended to use sponges for bathing, as fungi and bacteria contaminating the sponge may colonize the skin. The bath should not be too hot (about 36–37°C), should not exceed a few minutes, and a shower/quick bath is preferred. After the bath, the patient should gently pat the skin dry, without irritating or wiping it, and apply an emollient moisturizer for up to five minutes, when the skin contains the most moisture. Emollients are applied to the entire surface of the damp skin after the bath. Successful emollient therapy requires good collaboration with the patient, hence the importance of education and explaining the need for systematic use of well-tolerated emollients. When atopic lesions flare up, emollient therapy may be poorly tolerated, with burning and increased pruritus, in which case topical anti-inflammatory drugs should be used first. Medicated preparations should be used before emollients [66].

Many patients do not follow the recommended proper skin care, do not use medications as prescribed, do not fill prescriptions, use medications irregularly, or discontinue treatment before they achieve measurable benefits after an apparent improvement. Poor compliance with therapy sometimes results from a conscious decision by the patient or, more often, may be a consequence of cognitive or physical impairment. Complex treatment regimens and misunderstanding of treatment are not without relevance.

22. Food allergens

Food allergens are most often of concern in the youngest children. Cow's milk protein, egg white, soy and wheat are the most common sensitizers. Typically, food allergies become irrelevant in adulthood as tolerance to foods is acquired. The introduction of elimination diets should be considered carefully and without haste, and should be based mainly on the patient's history and observation; additional examinations (skin tests and serum allergen-specific IgE testing) play an auxiliary role [30].

23. Inhalatory allergens

Inhalant allergens, such as dust mites, may contribute to skin deterioration in some patients. Although there are still few studies

on the efficacy of aeroallergen elimination measures and many authors question their effectiveness, allergen avoidance is recommended by the EAACI (European Academy of Allergy and Clinical Immunology) and WHO (World Health Organization) guidelines [67]. While elimination or avoidance of sensitizing allergens is not always possible, it should be pursued. Education by a trained nurse and/or physician about possible ways to avoid allergens is important. It also seems beneficial to provide written information to the patient on how to reduce exposure to sensitizing inhalant allergens.

24. Other factors that may contribute to skin deterioration in AD

Other complicating factors in atopic skin may include stress, hormonal changes (for instance, menstruation), and infection. The skin of AD patients is sensitive to various nonspecific stimuli and is prone to irritation. These stimuli include not only chemical agents (such as detergents), but also exposure to dry air, cold, abrasion, and other mechanical trauma. Cleaning should be done with suitable protective gloves, while the surfaces exposed to damage (hands, for instance) should be protected with greasy creams. For people with AD, occupational exposure to factors that may lead to symptoms is a major concern. This is important in career counseling. Professions involving exposure to wet conditions, irritants, and allergenic substances, including animals, should be discouraged for people with atopic diseases.

Proper patient education improves the course of AD and facilitates disease control. How the nurse and physician educate the patient about disease management will largely affect the success of treatment and the quality of life of the patient with AD.

25. Topical treatment in AD

25.1. Wet dressings

One therapy method is the use of wet-wrap treatment (WWT). Wet dressings are an effective, simple, and safe method of treating AD. The approach consists in applying two layers of dressings (bandages) to the patient's skin immediately after an evening bath. The inner layer is damp: soaked in an emollient and/or a therapeutic substance. The outer layer is dry and stops water from evaporating too quickly from the moist dressing. Special clothing (T-shirts, leggings, or stockings) may be used if the treatment covers a large area of skin. The dressings are applied for about 3 to 24 hours and used for 7 to 14 days (in severe cases, wet dressings are recommended for four weeks). This therapy is well tolerated by children and improves their quality of life and sleep. Wet dressings have a cooling effect, alleviate pruritus, prevent scratching and the formation of excoriations, increase epidermal hydration and skin absorption of drugs, and slow down TEWL. Moreover, they boost the secretion of lamellar bodies that form the lipid barrier, have anti-inflammatory effects, and accelerate the healing of inflammatory lesions [68, 69, 70].

25.2. Topical corticosteroids

Topical corticosteroids (TCSs) have been the first-line treatment of AD flare-ups for more than half a century. These immunosuppressive, anti-inflammatory, and antiproliferative drugs are still the most commonly used preparations in the treatment of AD. By activating or inhibiting the expression of specific genes, TCSs influence the synthesis of specific protein products: cytokines, kinins, and enzymes. Different TCSs have different potencies. Ointments have higher absorption and potency than creams. The therapeutic effect also depends on the method of application and the type of media and additives used in the preparation. Given the dry environment of atopic epidermis, ointment forms of TCS are preferable. Unfortunately, due to high efficacy and low cost of treatment, these drugs are often overused, despite the fact that long-term topical glucocorticosteroid therapy carries a risk of side effects. The therapy should be used judiciously, with the weakest form of the drug that allows controlling the course of the disease. Strong TCS should be avoided on sensitive and absorptive areas (face, neck, folds, and scrotum). Especially great caution in treatment should be exercised in children, in whom the risk of side effects is higher. The epidermis is thin in children, the stratum corneum, stratum granulosum, and stratum spinosum are underdeveloped, and the number of collagen and elastic fibers in the dermis is much lower than in adults. In addition, children's skin has numerous dilated blood vessels. A high body surface area to body weight ratio is typical in children, which is associated with a larger surface area for skin absorption of TCS. Because of the risk of developing glaucoma, great care should be taken when applying TCS to the skin near the eyes. In contrast, because of the increased risk of developing stretch marks in adolescents, the use of TCS on the thighs, abdomen, and breasts is cautioned. Local adverse effects of topical corticosteroid therapy include skin thinning, stretch marks, perioral inflammation, and post-steroid acne. Systemic side effects, such as hyperglycemia, cataracts, increased blood pressure, adrenal insufficiency, or hypothalamic-pituitary-adrenal axis inhibition, are rare.

One way to reduce the total dose of TCS is alternating therapy, which has a clinical effect similar to that of continuous therapy. It entails alternating the use of TCS with a base, meaning an indifferent preparation with emollient properties. TCS treatment is applied every other day interchangeably with a neutral baseline cream (or in a regimen, for example, TCS alternating with a baseline cream for three days or TCS twice a week and the baseline cream on other days). When topical TCS is applied, a fraction of the drug remains in the intercellular spaces and this is what is largely responsible for the side effects. When applied to the skin in an alternating regimen, the baseline cream binds the amount

of TCS stored in the intercellular spaces between keratinocytes and transports it into the cell, which guarantees the effectiveness of the therapy while limiting the use of the active ingredient and diminishing side effects.

The registered products in Poland for the youngest children, below one year of age, are hydrocortisone acetate and butyrate. In children over two years of age, these are fluticasone propionate, mometasone furoate, and methylprednisolone acetate. However, other topical corticosteroids can be used only from the age of 12. The safe duration of treatment with medium potency TCS is believed to be 12 weeks in adults and 4 weeks in children [71, 72].

25.3. Topical calcineurin inhibitors

Apart from TCS, topical calcineurin inhibitors (tacrolimus and pimecrolimus) are another group of drugs used in the treatment of AD flare-ups, both in adults and in children over two years old. They inhibit the activation of T lymphocytes and the release of inflammatory cytokines. Tacrolimus, when compared to pimecrolimus, has a faster and more potent effect. These drugs can be safely used over many months as part of so-called proactive therapy on all regions of the skin, including areas as sensitive as the eyelids, face, neck, excoriated skin and genitalia in both adults and children. Unlike topical corticosteroids, they do not inhibit collagen synthesis or trigger epidermal abrasion. Along with the current reactive therapy, which is focused on active treatment of disease exacerbations, a new treatment concept based on topical calcineurin inhibitors, proactive therapy, has been proposed. This approach consists of long-term, low-dose application of calcineurin inhibitors to so-called apparently healthy skin, in areas previously affected by eczematous lesions in the course of AD, after remission of these skin lesions has been induced. Proactive therapy with calcineurin inhibitors has been demonstrated to prevent AD flare-ups, shorten their duration, and reduce their severity, thus improving the quality of life of patients with AD. The clinical efficacy of proactive therapy is confirmed by randomized clinical trials, including pediatric age cohorts. A side effect that has been noted is a burning sensation at the site of application, which disappears after some time. Even a long-term 12-month treatment with tacrolimus in children aged from 2 to 15 years has been proven to be effective, safe, and well tolerated [73, 74, 75, 76].

25.4. Topical phosphodiesterase inhibitors

Since 2016, a new group of anti-inflammatory drugs, phosphodiesterase-4 inhibitors, one example of which is crizaborol, has been approved for use in the United States. Crizaborol is recommended for the treatment of mild to moderate AD in adults and adolescents and children over 2 years of age. It inhibits the secretion of some cytokines such as tumor necrosis factor alpha (TNF-α), interleukins (IL-2, IL-4, IL-5), and interferon gamma (IFN-γ) and improves skin barrier function [77].

25.5. Topical antibiotics

In over 90% of cases, the skin of patients with AD is colonized by *Staphylococcus aureus*, which may be responsible for more severe aggravation of the disease. In view of the growing antibiotic resistance, it is recommended to limit the long-term use of topical antibiotics. Proper topical anti-inflammatory treatment (TCS, calcineurin inhibitors) and phototherapy reduce *Staphylococcus aureus* skin colonization [78].

25.6. Phototherapy

Another therapeutic alternative is phototherapy, which has immunosuppressive properties. In patients with more severe skin lesions or who have no improvement after topical treatment, phototherapy with UVA1 (340-400 nm), UVB-BB (290-320 nm), and UVB-NB (311-313 nm) may be used. Phototherapy is advised in patients with recurrent and chronic moderate to severe AD (SCORAD>25) associated with acute pruritus and lichenification. Phototherapy is not indicated in AD flare-up phase (except UVA1). It is also not recommended in patients who experience worsening of skin lesions after sun exposure. Due to its safety and efficacy profile, narrow-beam UVB-NB therapy is most commonly used. Treatment, under the supervision of a dermatologist, is applied two to three times a week. Adverse effects include burning sensation, pruritus, dry skin, and eruptions. It is also necessary to protect the eyes during phototherapy. Other complications include increased photoaging of the skin and a higher risk of skin cancer. Phototherapy in combination with proper skin care and suitable topical anti-inflammatory TCS treatment reduces the number and intensity of recurrences. Topical calcineurin inhibitors should be used with caution during phototherapy [79, 80].

26. Systemic treatment

26.1. Immunomodulatory and cytostatic therapy

Immunomodulatory and cytostatic treatment is reserved for patients with acute AD. The drugs in this category that have been registered for AD treatment include cyclosporine A (CsA). CsA is recommended as first-line treatment for patients with severe, chronic AD (SCORAD > 50) who require systemic therapy, initially at a dose of 4-5 mg/kg/day in two split doses, with a dose reduction after improvement of 0.5-1.0 mg/kg/day every two weeks to a minimum therapeutic maintenance dose of 2.5-3 mg/kg/day. The drug can be administered long-term in continuous therapy, up to a maximum of two years, in cycles of an average of 12-16 weeks or in intermittent therapy (so-called weekend therapy) twice a week at adjusted doses. The decision about this treatment should account for possible side effects, possibly even permanent kidney damage [80].

Azathioprine, methotrexate, and mycophenolate mofetil are other off-label treatments used in adult patients with severe AD that is refractory to other therapies [81]. These therapies, however, carry a high risk of undesirable effects. Methotrexate treatment is usually well tolerated, but the potential for serious side effects must be kept in mind, and monitoring of liver function and blood counts is necessary. Azathioprine is very effective in the management of AD, but the full therapeutic effect comes late, only after 12 weeks. Azathioprine, too, requires monitoring of liver function and blood count. Mycophenolate mofetil also has a proven efficacy in the treatment of AD, which is comparable to cyclosporine. Like methotrexate, it is a teratogenic drug so it should not be used during pregnancy. Cyclosporine is a category C drug according to the US Food and Drug Administration [80].

The use of systemic corticosteroids (methylprednisolone and prednisone) should be restricted to short-term (up to one week) treatment of exacerbations in severe AD [80].

26.2. Antihistamines

Histamine is also one of the mediators that is important in AD, as it causes pruritus, and in combination with other mediators, it is also responsible for the development of inflammation. Antihistamines are frequently prescribed to patients with AD, in any phase of the disease. However, the quite widespread expectation among patients that they can markedly improve pruritus may cause disappointment. If we consider the complex etiopathogenesis of AD, the antipruritic efficacy of antihistamines is moderate at best. The pathogenesis of pruritus is complex and still not fully understood, therefore available antipruritic therapies often do not permit effective control of this unpleasant sensation. In skin diseases, antihistamines show high efficacy only in urticaria and mastocytosis, whereas in AD the results are rather poor. In practice, both first-generation drugs, which have a stronger sedative effect (they are recommended in the evening for the treatment of nocturnal pruritus) and newer second-generation drugs are used. Generation I and II drugs can be combined if necessary. Nevertheless, they are only a supplement of the basic treatment [30].

26.3. Antipruritic drugs that act on the nervous system

It is a growing trend that drugs affecting the nervous system are used for the treatment of pruritus. These include antiepileptic drugs modulating GABAergic transmission (gabapentin and pregabalin), antidepressants (amitriptyline, paroxetine, and mirtazapine), μ-opioid receptor antagonists (naloxone and naltrexone), and κ-opioid receptor agonists (nalbufine). Novel drugs with antipruritic action are still being sought. Research is underway to engineer antipruritic drugs that interact with pathways mediated by substance P (tradipitant and sarlopitant), lysophosphatidic acid, histamine H4 receptors, and interleukin 31 (nemolizumab) [59, 82, 83, 84, 85].

AD is now regarded as a predominantly T-lymphocyte-mediated disease, as demonstrated by the clinical efficacy of broad-spectrum drugs targeting T-lymphocytes, such as cyclosporine, or efalizumab and alefacept (although the latter two are no longer available for safety reasons). CsA, oral corticosteroids, and phototherapy are all relatively common treatments for moderate to severe AD. However, cyclosporine, and even more so systemic corticosteroids, are not suitable for long-term use because of their numerous side effects. Phototherapy is very time consuming and not feasible for most patients. An effective and safe therapy is still in high demand [85].

26.4. Biologic treatment: Dupilumab

Medical advances are driving increasingly effective selective therapies for AD. After many years of research, the first biologic drug, dupilumab, was registered. It is the only biologic drug to have passed Phase III trials in AD. In 2017, the U.S. Food and Drug Administration and the European Medicines Agency approved it for the treatment of adult patients with moderate to severe forms of AD eligible for general therapy. Dupilumab is licensed for the treatment of moderate to severe AD in adults and children over 12 who are candidates for general treatment and for children over six with acute AD. Dupilumab is recommended in adults at an initial dose of 600 mg in two injections of 300 mg, followed by 300 mg every two weeks, administered subcutaneously. Dupilumab therapy should be combined with regular use of emollients and, if indicated, concomitant use of TCS or topical calcineurin inhibitors [80, 86].

Dupilumab is an undoubted breakthrough in the treatment of AD. It is a fully human monoclonal antibody of IgG4 class, directed against the receptor for interleukin 4 (IL-4Rα). The presence of the receptor for IL-4 is found on numerous cells associated with Th2 lymphocyte activation. These include B lymphocytes, eosinophils, basophils, monocytes, dendritic cells, and keratinocytes. It is also present on endothelial cells, bronchial epithelial cells, fibroblasts, and airway smooth muscle cells. IL-4Rα receptor blockade inhibits the expression of key pro-inflammatory cytokines involved in the pathogenesis of AD, for instance, IL-4 and IL-13. It also blocks IL-4 and IL-13 signaling through the type II receptor (IL-4Rα/IL-13Rα) [87].

Patients benefit considerably from the treatment. Dupilumab has been shown to not only reduce pruritus but also improve sleep disturbances, mental health, and quality of life after only two weeks of treatment. The findings of research on dupilumab suggest its good tolerability, high safety, and lack of dose-dependent toxicity. The side-effect profile of dupilumab has been found to be favorable when compared to other available general treatments, and superior to conventional immunosuppressive drugs such as cyclosporine or methotrexate [80, 87]. AD patients

who were treated with dupilumab did not exhibit systemic side effects in clinical trials. The most commonly reported adverse reaction was a local reaction after subcutaneous administration of the drug. Conjunctivitis was frequently noted and should be controlled by an ophthalmologist. Studies published to date have revealed that up to 70% of AD patients receiving dupilumab treatment achieved marked improvement [88]. Research published to date on the use of dupilumab in children and adolescents with severe AD has demonstrated positive effects of off-label treatment with this drug [89]. Dupilumab is currently registered in the U.S. for children and adolescents with AD from 6 to 17 years of age. Clinical trials are ongoing in children aged 6 months to 6 years with AD.

26.5. Other biologics in AD: Hope for the future

Biologic therapies have an increasingly prominent place in the effective and modern treatment of AD. Also new data from clinical trials with monoclonal antibodies against IL-4, IL-13 (lebrikizumab, tralokinumab), anti-IL-22 (fezakinumab), and IL-31 (nemolizumab) are promising. Researchers are also focusing attention on TSLP-blocking drugs (tezepelumab) and JAK inhibitors (upadacitinib, tofacitinib) in the hope that they will prove instrumental in the treatment of patients with AD. However, further studies are needed before this revolution in the treatment of AD patients becomes a reality [84, 90, 91].

26.6. Allergen immunotherapy

Allergen-specific immunotherapy (ITA) is a method of treating allergy by gradually inducing clinical and immunological tolerance to an allergen through the administration of increasing doses of the allergen in the form of an allergen vaccine. Allergen-specific immunotherapy is recommended in patients with a confirmed immunoglobulin E-dependent disease mechanism caused by an allergen or allergens whose extracts are available as vaccines [92]. Allergen immunotherapy is the only treatment that modifies the course of IgE-dependent allergic diseases, principally by inducing long-term tolerance to a specific allergen. Allergen-specific immunotherapy induces IgE-dependent immune tolerance to allergens contained in the vaccine and has immunomodulatory effects which consequently translate into clinical efficacy of this treatment option. ITA leads to a shift in the phenotype of Th lymphocytes from the predominant Th2 in allergic individuals towards Th1, which is predominant in a normally responding immune system. An increase in IL-10 production by T lymphocytes, monocytes, macrophages, and B cells is observed. There is also an increase in the synthesis of TGF-β, which inhibits mast cell function, and together with IL-10, enhances regulatory T cell activity. IL-10 reduces the secretion of proinflammatory cytokines by Th2 cells. Immunoglobulin class switching from IgE towards IgG1, IgG4 and IgA also becomes activated. The efficacy of immunotherapy can be seen in the alleviation or even resolution of disease symptoms and in the reduction of the patient's medication doses [93].

The validity of allergen-specific immunotherapy in AD has long been debated. This treatment approach has a well-documented effect in patients with allergic rhinitis and bronchial asthma. Patients with AD may benefit from ITA, for example by preventing the allergic march. The decision to implement this treatment is always prudently weighed on an individual basis, and the correct selection of patients with documented IgE-dependent sensitization is key to the success of this therapy [92].

Since the first attempts to use ITA, the injectable method of immunotherapy (SCIT, or subcutaneous immunotherapy) prevailed for many years. In the following years, other routes of allergen administration (such as oral sublingual, intranasal, and intranasal) were investigated. At the moment, sublingual immunotherapy (SLIT) is widely used alongside SCIT. Because of the home treatment option and limited injections, SLIT may be an alternative to subcutaneous immunotherapy, especially in children. The added advantage is the safety of the therapy. Sublingual immunotherapy for AD has shown encouraging results. Studies on the use of SLIT in food allergy have demonstrated modest efficacy with minimal local reactions, yet studies on the dose and duration of therapy are lacking [94].

According to the new 2019 guidelines of the Polish Society of Allergology, absolute contraindications to SCIT and SLIT include:

- lack of patient cooperation and informed consent,
- severe, uncontrolled asthma,
- malignant neoplasms,
- active, uncontrolled autoimmune diseases,
- untreated HIV/AIDS
- age below two

Relative contraindications include:

- use of beta blockers or angiotensin converting enzyme inhibitors,
- psychiatric disorders (in each case an individual approach is recommended with the assessment of the possibility of cooperation and obtaining informed consent of the patient),
- congenital or acquired immunosuppressive conditions
- age between two and five
- cardiovascular diseases (cardiological consultation is advised before starting the treatment)
- treated HIV infection
- well-controlled autoimmune diseases (consultation before starting ITA is recommended)
- partially controlled asthma [92].

The 2017 U.S. recommendations [95] also recognize severe systemic allergic reactions during immunotherapy in the past, regardless of the route of vaccine administration, severe local reactions after SLIT, eosinophilic esophagitis, and all diseases that may worsen the anaphylactic reaction and impair the treat-

ment (severe lung disease, severe cardiovascular disease, etc.) as contraindications to ITA. There are also situations in which the sublingual vaccine should be temporarily discontinued. It should not be administered immediately after the placement of orthodontic appliances or immediately after dental procedures, loss of deciduous teeth, any inflammatory lesions, or damage to the oral mucosa [96].

Data from meta-analyses are inconclusive as to whether allergen immunotherapy plays an important role in the treatment of AD, although several authors have reported optimistic results [97, 98]. Recent guidelines from the American Academy of Dermatology say that available data do not clearly support the use of ITA in AD. The European Academy of Dermatology suggests that clinicians may consider allergen immunotherapy in selected patients presenting with sensitization to aeroallergens, mainly house dust mites, with severe AD and clinical exacerbation after exposure to the allergen that causes the reaction. Nevertheless, the role of ITA in AD, especially in children, is still under discussion [99, 100, 101, 102].

27. Personalized therapy

Therapeutic failures in the treatment of AD are due to the multifactorial origin of the disease. Owing to the complex pathogenesis of AD, there is a greater need to customize treatment. It has been suggested that different subtypes of AD (phenotypes, endotypes, genotypes, and immunotypes) can be distinguished based on various characteristics, e.g., patient age, disease onset, symptom severity, flare-up triggers, response to therapy, biomarkers, and genetic and immunological variants. As in the approach to bronchial asthma or chronic rhinitis, phenotyping can personalize therapy, and help optimize treatment according to pathogenesis. Phenotyping can lead to the development of therapies for patients who will benefit from approaches based on targeted immune mechanisms [103].

Abbreviations

AAF - amino acid-based formula, **AD -** atopic dermatitis, **ADHD** - attention-deficit/hyperactivity disorder, **AIDS** - acquired immunodeficiency syndrome, **APT** - atopy path test, **AR** - allergic rhinitis, **asIgE** - allergen-specific IgE antibodies, **CGRP** - *calcitonin gene-related peptide,* **CMPA** – cow's milk protein allergy, **CRD** - component-resolved diagnostics, **CsA** - cyclosporine A, **DCs** - dentritic cells, **EAACI** - European Academy of Allergy and Clinical Immunology, **EAD** - extrinsic atopic dermatitis, **EASI** - Eczema Area and Severity Index, **eHF** - extensively hydrolysed formula, **FcεRI** - IgE receptor, **FOXP3** - forkhead box P3, **FPE** - food protein-induced enteropathy, **FPIAP** - food protein-induced allergic proctocolitis, **FPIES** - food protein-induced enterocolitis syndrom, **GCs** - glucocorticosteroids, **HIV** - *human* immunodeficiency virus, **IAD** - intrinsic atopic dermatitis, **IDECs** - inflammatory dendritic epidermal cells, **IFN-γ -** interferon gamma, **IGA** - Investigators' Global Assessment, **IgA -** immunoglobulin A**, IgE -** immunoglobulin E**, IgG1 -** immunoglobulin G subclass 1**, IgG4 -** immunoglobulin G subclass 4**, ILC2 -** innate lymphoid cells 2**, IL-1 -** interleukin 1**, IL-4 -** interleukin 4**, IL-4Rα -** interleukin 4 receptor**, IL-5 -** interleukin 5**, IL-13 -** interleukin 13**, IL-13Rα -** interleukin 13 receptor**, IL-16, -17, -19, -22, -25, -31, -33 -** interleukins**, ISAAC** - International Study of Asthma and Allergies in Childchood, **ITA** - allergen-specific immunotherapy, **JAK** - Janus activated kinases, **JAK/STAT** - signal transducer and activator of transcription, **MAP** - Milk Allergy in Primary Care, **mDCs** - myeloid dendritic cells, **TCS** - topical corticosteroids, **NGF** - nerve growth factor, **NMF** - natural moisturizing factor, **NRS** - Numeric Rating Scale, **OAS** - oral allergy syndrom, **oSCORAD** - objective SCORAD, **pDCs** plasmacytoid dendritic cells, **PFAS** - pollen food allergy syndrom (PFS- pollen food syndrome), **PT** - patch test, **SCIT** - subcutaneous immunotherapy, **SCORAD** - Severity Scoring of Atopic Dermatatis, **SLIT** - sublingual immunotherapy, **SPT -** skin prick test, **TEWL** - transepidermal water loss, **TGF** - transforming growth factor, **TNF-α** - tumor necrosis factor α, **Treg** regulatory T cells, **TSLP** - thymic stroma lymphoprotein, **VAS** - Visual Analogue Scale, **VIP** - vasoactive intestinal peptide, **WHO** - World Health Organization, **WWT -** wet-wrap treatment.

Authors' Contribution

R.F.: writing – review and editing, visualization, research concept and design, data analysis and interpretation, carrying out the experiments, drafting the article or revising it critically for important intellectual content, literature review, supervising the project, final proofreading and approval of the version for publication; **A.K.:** writing – original draft preparation, visualization, literature review, carrying out the experiments, analysis and interpretation of data, literature review, final proof-reading and approval of the version for publication; **A.F.:** analysis and interpretation of data, designing the figures, drafting the article or revising it critically for important intellectual content, literature review, final proofreading and approval of the version for publication; **D.Z.:** supervising the project, revising the article critically for important intellectual content, literature review, final proofreading and approval of the version for publication.

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Conflict of Interest

The authors have no potential conflicts of interest to declare.

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