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Atopic dermatitis - pathogenesis, types, differentiation, prevention, treatment

Barbara Wilczyńska

University Children's Hospital in Lublin, Profesora Antoniego Gębali 6, 20-093 Lublin

b.machulska@interia.pl

https://orcid.org/0009-0001-4939-7550

Monika Grzybek

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

monika.c@vp.pl

https://orcid.org/0009-0003-2246-800X

Anna Kasprzak

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

a.kasprzak93@wp.pl

https://orcid.org/0009-0002-1491-245X

Monika Kułaga

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

monikakulaga93@gmail.com

https://orcid.org/0009-0001-3949-2124

Diana Mazur-Lesińska

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

diana_mazur@wp.pl

https://orcid.org/0009-0000-2489-9100

Barbara Szostak

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

barbara.szostak02@gmail.com

https://orcid.org/0009-0000-8035-7584

Sylwia Wielgosz -Biała

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

sylwia.wielgosz@o2.pl

https://orcid.org/0009-0003-0567-5998

Krzysztof Tyszkiewicz

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

tyszkiewicz.krzysztof@wp.pl

https://orcid.org/0009-0005-0208-2286

Borys Łozowski

University Clinical Hospital No 4 in Lublin, Doktora Kazimierza Jaczewskiego 8, 20-954 Lublin

borys.lozowski@gmail.com

https://orcid.org/0000-0002-1990-040X

Małgorzata Kasprzak

Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, al. Kraśnicka 100, 20-718 Lublin

malgorzata.m.kasprzak@gmail.com

https://orcid.org/0009-0007-3791-1632

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Abstract:

Atopic dermatitis (AD), defined according to the current World Health Organisation (WHO, 1990) nomenclature as *eczema*, is a chronic, recurrent, inflammatory skin disease, usually beginning in early childhood, characterised by severe pruritus, typical localisation, characteristic lesion morphology, and very - often coexisting with other atopic diseases.
Atopic dermatitis is strongly associated with allergic respiratory diseases such as asthma and allergic rhinitis, hence the name "allergic triad".

There has been a significant increase in the incidence over the past 25 years, with the number of diagnosed cases of the condition increasing more than twofold and even more
in some countries. There is a wide variation in prevalence of 1% and 20% between countries, with the most recent data indicating that the disease has reached a certain
in English-speaking countries and affects 20% of the population. The increase in the prevalence of AD, is likely to be influenced by negative environmental changes, such as climate, exposure to second-hand smoke, major industrialisation and the consequent increase in air and food pollution and food pollution, as well as the consumption of highly processed fast food.
This issue requires further research, with particular attention to infancy
and early childhood, when the immune system is maturing. These factors, as well as certain environmental allergens, have a strong influence on the onset of the first symptoms associated with the disease, as well as its course.

The pathophysiology of AD is complex and still not fully understood. Research on AD has shown that the structure and function of the epidermal barrier is disrupted, most likely due to abnormal processes of the innate and adaptive immune response. Both immunological factors - mechanism I and IV of the allergic reaction according to the Gell and Coombs classification - and non-allergic factors play a role in the course of the disease. There is no doubt that it is a polygenically inherited disease, and only the predisposition to atopy, modified during individual life by environmental factors, is inherited.

Diagnosis and clinical picture. The diagnosis of AD is based on the clinical picture.
Therefore, it is extremely important to be able to make a differential diagnosis
including but not limited to: seborrhoeic dermatitis, scabies, allergic contact eczema, ichthyosis, cutaneous lymphomas, psoriasis and immunodeficiency skin lesions. The most common diagnosis is based on criteria established in 1980 by Hanifin and Rajka (Table 1).

Table 1. Major and minor criteria of atopic dermatitis according to and Rajka (1980, according to Waszczykowska, 2004)

Main symptoms of AD	**Minor symptoms of AD**
• pruritus, • chronic and recurrent course, • characteristic morphology • family history of atopy	- dry skin, - corneal cone - ichthyosis, - cataract - immediate skin reactions, - darkening around the eyes - elevated IgE levels, - white dandruff - early appearance of skin lesions, - neck fold - susceptibility to recurrent skin infections, - itching after sweating - impact of stress and environmental factors on exacerbations - non-specific hand and/or foot eczema, - food intolerance - eczema around the nipples, - wool intolerance, - lip inflammation, - recurrent conjunctivitis, - Dennie-Morgan fold - facial erythema, - accentuation of hair follicles

In order to establish a diagnosis, 3 of the 4 major criteria and, although not obligatory, 3 of the minor criteria must be met. They are of ancillary importance in establishing the diagnosis in the absence of one of the main symptoms. In some countries, the UK Working Party's Criteria are used to simplify diagnosis. The diagnosis of AD is based on the finding of an obligatory criterion (pruritus of skin) and 3 of the 5 major criteria (Table 2).

Table 2. Criteria for the diagnosis of atopic dermatitis in children according to the UK Working party's diagnostic Criteria

Mandatory criterion	**Additional criterion**
pruritus of skin	• involvement of the elbow or popliteal fossa or the neck or the skin around the ankle joints, up to the age of 10 years eczematous lesions on the cheeks • personal history of atopy (asthma, allergic rhinitis) and, in children under 4 years of age, a family history of atopy in first-degree relatives • dryness of the skin during the last year • eczematous lesions on the volar side and, in children under 4 years of age, lesions on the cheeks and on the proximal surfaces of the limbs • starting at 2 years of age (criterion does not apply to children under 4 years of age)

In the youngest children, lesions in the form of erythematous foci, sometimes with exudate and scabs, are localised on the face and head and on the upright surfaces of the limbs and trunk. The anogenital (nappy) area is lesion-free.

In older children, adolescents and adults, the lesions can be in any location, but are most characteristically found in the and popliteal fossae and popliteal fossae. During clinical exacerbations, osteoporotic lesions are present, while during clinical remission, dry skin, lichenification, papular and nodular lesions are observed, accompanied by severe itching and nodular lesions accompanied by severe itching. Colonisation with Staphylococcus *aureus* (*S. aureus*) is often found in patients with atopic dermatitis. A correlation has been observed between the degree of colonisation and severity of lesions in atopic dermatitis, eosinophilia and the concentration of total and specific IgE, but also the degree of epidermal barrier damage, assessed by the degree of transepidermal water loss (TEWL).

Widely available and validated scales to determine disease severity, including SCORAD (Scoring Atopic Dermatitis Index), EASI (Eczema Area and Severity Index), Patient-Oriented Eczema Measure (POEM), are available to assess lesion severity and help monitor treatment. Patient-prepared scales are available in apps. Using SCORAD, the extent and severity of lesions are objectively assessed, and the severity of pruritus and sleep disturbance are also

evaluated. The extent of the lesions is assessed with the rule of nines, while erythema, swelling, oedema, oozing/strup, pruritus, lichenisation and dry skin are considered when determining severity on a four-point scale (0 – none, 3 – most severe). Pruritus and sleep disturbances are assessed with a visual analogue scale (0-10 points), taking the average of the last 3 days and nights. In children under 7 years of age, this scale is assessed by the parents. The maximum score is 130 points. Patients scoring less than 25 points are diagnosed with mild AD, between 25-50 points with moderate AD and above 50 points with severe AD. The scale – EASI – assesses only the extent and severity of the skin lesions. The maximum score is 72 points.

In the course of the disease, **three types** are distinguished according to age:

1. Infancy to 2 years of age – characterised by: pruritus, acute inflammation of the skin, papulopustular and exudative lesions that ooze profusely and are easily reinfected; the lesions are mainly located on the face and perioral parts of the limbs and around the earlobes, while in severe forms the lesions are disseminated and inflammatory on the trunk and in other areas of the body.
2. Childhood period until the age of 12 – this period is characterised by pruritus, dry skin, with erythematous papular lesions of the eczema type, gradually turning into eruptions with lichenisation; the lesions are well-demarcated and foamy. During the heraldic period, there is exfoliation of the fingertips, soles. We distinguish between a limited form, in which lesions are located in the pits of the elbows, below the knees, on the face and on the peripheral parts of the limbs, and a generalised form, in which lesions can be in all areas of the body.
3. Adolescence and adulthood – patients complain of pruritus, inflammatory infiltrates develop with significant lichenisation, chronic lesions are indistinctly demarcated, chronic lesions are vaguely demarcated, predominantly lichenised, may be disseminated, located in all areas of the body, in persons under 30-40 years of age, mainly in the articular flexures.

AD is differentiated with diseases such as:

1. Seborrhoeic dermatitis: the lesions are localised in the scalp (parietal), skin folds and nappy area. The eruptions are erythematous and exfoliative in nature, with seborrhoeic scabs built up,
2. Dermatitis herpetiformis: is an intestinal-skin syndrome in which vesicular papular lesions are accompanied by gluten-dependent enteropathy. The characteristic feature is the multiformity of the lesions, usually located on the elbows, knees, sacrum, buttocks,

scalp and face. The eruptions are accompanied by pruritus. Gluten tolerance varies. Histological and immunopathological evaluation of a skin specimen is the decisive test,

3. Nappy dermatitis: this dermatosis usually starts between 1 and 2 months of age.
   The disease can also affect adults with incontinence. Lesions of an erythematous, oedematous, erosive nature are observed, located in the areas of nappy adherence,
4. Contact and non-specific dermatitis: erythematous and exfoliative lesions, oedematous lesions and vesicles can occur in any location. They are the result of skin exposure to exogenous factors that cause inflammation. There are two types: irritant contact dermatitis and allergic contact dermatitis, which differ in their mechanism of lesion formation. Non-specific dermatitis can occur as a result of intolerance or sensitisation to food allergens. Lesions are uncharacteristic and can occur in any location. As they mature
   and sealing of the gastrointestinal tract, the skin lesions subside,
5. *Psoriasis* - is a disease that can begin in early childhood. The typical lesion is a papule covered with silvery scales. The most common locations for lesions are the scalp, the upright surfaces of the limbs and the sacral region. In children, the droplet form is observed, where the lesions are scattered throughout the skin. In infants, there is often involvement of the nappy area – Jadassohn's psoriasis-like nappy dermatitis,
6. *Erythroderma* – is a generalised inflammatory condition of the skin.
   Often the characteristic features of the dermatoses in question are masked by intense inflammatory symptoms. The information obtained from the history is important, as well as the examination of the oral mucosa and nails. It is important to remember that erythroderma can also be an indicator of paraneoplastic systemic diseases, so in some cases there is a need to extend the diagnosis to immunohistochemistry and histopathological examination of the skin, lymph nodes and other tissues,
7. *Acrodermatitis enteropathica* – the cause of the disease is a lack of zinc absorption capacity. Clinical signs of the disease appear as early as a few days after birth or after cessation of breastfeeding. Typical locations are around the natural orifices of the body and the distal parts of the limbs. These lesions are erythematous, sharply demarcated, covered with erosions and scabs. Vesicles and pustules are observed around the periphery of the lesions. Tongue and oral mucositis, hair loss and atrophy are common additional symptoms. Determination of the serum zinc level, which is very low in people with this disease, is decisive,

8. Scabies – typical locations are the interdigital spaces, proximal phalanges, flexures of the wrist surfaces, palms, soles and genital areas. The classic symptom is pruritus, increasing in the evening. On the skin, papules, vesicles, crusts and scabs are mainly observed,
9. Abortive ichthyosis disease – considered a criterion for lesser AD. Exfoliative lesions appear in the first months of life. Predilection sites are the upright surfaces of the limbs and trunk. Hyperkeratosis also affects the hands and feet. The areas of the articular flexures and skin folds remain free,
10. Comel-Netherton syndrome – an autosomal recessive inherited disorder characterised by: ichthyosis, hair abnormalities, severe atopic diathesis with elevated serum IgE antibodies,
11. Hyper-IgE syndrome – the condition is characterised by a triad of symptoms: recurrent abscesses, pneumonia, elevated IgE levels. The first symptoms are found already in newborns. Most patients have coarse facial features and a wide nose. Tooth eruption disorder or tooth loss may be present. The cutaneous manifestation is chronic inflammation involving mainly the joint flexures and face,
12. Histiocytosis - usually affects children under 2 years of age. The primary lesion is a papule from which a scab develops. Over time, generalised erythematous and exfoliative lesions develop. The most frequent lesions are located on the proximal surfaces of the limbs and seborrhoeic areas. They are often accompanied by pruritus. Petechiae may appear on the skin of the hands and feet,
13. Lymphomas – mainly affects T-cell lymphomas. Erythematous and scaly patches appear on the skin. After a prolonged period of time, the entire body surface is involved and erythroderma develops. The skin is thickened and itching occurs. A characteristic symptom is lymphadenopathy.

Primary prevention in AD concerns children at risk without any symptoms of the disease. Its aim is to prevent the development of the disease. It includes prolonging breastfeeding, not smoking during pregnancy, limiting exposure to airborne allergens, mainly house dust mites, and using emollients from the first day of life. Exclusive breastfeeding until 4-6 months of age is recommended for both children at population risk and those in high-risk groups. Breastfeeding makes it possible to reduce adverse reactions to foreign proteins. Moreover, breast milk covers all nutritional needs, is the natural and most valuable food, and contains many biologically active substances, including those with immunological properties. **Secondary prophylaxis** covers patients with early signs of the disease. Its aim is to prevent

the occurrence or worsening of the disease symptoms. The use of emollients (every 4-6 hours), avoidance of irritants, stress and elimination of allergens responsible for the symptoms are recommended. Occupational counselling is an important part of this prevention.

Tertiary prophylaxis is recommended in patients with full-blown AD in order to reduce the severity of symptoms and their frequency of recurrence and to prevent the development of concomitant diseases. This prophylaxis includes psychological counselling and patient education on how to control disease symptoms and live with the disease. When taking a history, look for potential factors that exacerbate clinical symptoms. The most common are exposure to airborne and contact allergens, foods, various environmental irritants (including cigarette smoke and microorganisms), climatic factors, stress, and endocrine disruption. Not every AD patient reacts to all of the above factors. Hypersensitivity to airborne allergens is more common in older children, adolescents and adults. Prophylactic management includes avoidance of clinically relevant allergens, e.g. pollen (trees, shrubs, grasses, weeds, cereals) during the pollen season, house dust mite allergens, contact allergens in case of positive test results and their association with clinical symptoms. It is important to ventilate and spend less time indoors.

Treatment of AD is a strategy and requires a plan and control. The choice of therapy depends on the severity of the disease, the patient's age and comorbidities. Therapy should be carried out not only during disease exacerbation, but also during remission. The cornerstone of AD treatment is the combination of daily emollient therapy and appropriate skin care with anti-inflammatory treatment and avoidance of contact with provocative allergens and irritants. Anti-inflammatory therapy should be appropriately selected: topical corticosteroids (TGCs) and/or topical calcineurin inhibitors (TCIs) - depending on the activity of the disease (e.g. periods of disease). depending on disease activity (periods of exacerbation and remission, location of lesions), etc. Considering the large number of external as well as internal factors involved in the in the pathogenesis of AD and the association of the disease with atopy genes, there is little chance of developing a drug that will cause complete and permanent resolution of the disease. Currently, the aim of treatment is to improve the patient's quality of life with minimal risk of local as well as general complications.

Table 3. AD therapy according to disease severity according to the SCORAD scale

Severe AD SCORAD > 50	Hospitalization Cyclosporin A (CycA) Dupilumab Methotrexate (MTX), mycophenolate mofetil (MMF) Azathioprine (AZA) Oral GCS (for a maximum of 7 days)
Moderate AD SCORAD 25-50	Wet dressings Climatotherapy Psychological or psychiatric interventions Phototherapy: UVB 311, UVA1, PUVA(adults) Proactive therapy
Mild AD SCORAD < 25	Antiseptics Topical calcineurin inhibitors (TCIs) Topical glucocorticosteroids (TGCs)
Basic therapy	Emmolient therapy Avoidance of clinically relevant allergens EDUCATION

First line therapy – primary treatment:

The most significant elements of management are adequate patient education, prevention of exacerbations and appropriate skin care. The epidermal barrier defect is an important factor responsible for triggering, exacerbating and maintaining eczematous lesions.

1. It is very important to use preparations that help restore the skin's natural barrier.
   These are moisturising and lubricating preparations (emollients), called active emollients, which contain epidermal components, for example ceramides, unsaturated fatty acids, cholesterol, are actively transported by suitable receptors into the cells of the epidermal layer, where they are metabolised and together with
   together with endogenous lipids, form the lipid layer of the epidermis. Daily skin care based on emollients - modern emollients, so-called emollients plus, are enriched with ingredients of natural origin, such as flavonoids or saponins or bacterial extracts/lysates. Thanks to these, in addition to their standard action, they restore the micro-biological balance, exert some anti-inflammatory, anti-pruritic effects and

support innate immunity. Although they are derived from plant extracts, they do not contain proteins that could lead to transepidermal sensitisation and the development of allergies.

2. Wet dressing therapy (WDT) is a short-term, effective, relatively safe therapeutic option in patients, mainly children from six months to 10 years of age, with severe, treatment-resistant AD (SCORAD >50 points) [69-71]. It should be considered especially in patients in whom standard topical therapy is unsuccessful - patients with acute, oozing skin lesions and erosions, with severe AD. Among other things, this method ensures better absorption and significantly prolonged action of the drugs, reduction in the dose of the preparation used, reduction in pruritus and vasoconstriction, which translates into a reduction in erythematous lesions.

Table 4. Primary therapy in AD

Education	• Use of appropriate doses of emollients (250-500 g/week) • Explain or demonstrate how to apply the therapy. • Maintaining time intervals when different topical drugs are used • Recommendations should be recalled at least once a year!
Prevention	Avoiding allergens and irritants: • cigarette smoke • infections • woollen clothing • stress
Skin cleansing	• gentle and accurate, mechanical • cleaning agents with or without aseptic substances • suitable galenic forms • Physiological pH, within 6 • quick bath ≤ 5 min, including a 2-min oil bath, temperature 27-30°C • adding 1/2 cup of sodium hypochlorite to the bathtub, which eliminates itching • bath salts - facilitate the removal of exfoliated corneocytes, scales, especially beneficial in severe lichenification (impetiginisation)

Emollient therapy	• application at least 2-3 times a day! • glycerol is better tolerated than urea and sodium chloride • propylene glycol is easily irritating to children < 2 years of age and should not be used on them • in children < 2 years of age it is recommended to use emollients free of protein allergens and heptanoids • do not use emollients containing peanut extracts, which increase the risk of sensitisation and allergies! • if using of emollients for inflammation is poorly tolerated - anti-inflammatory drugs (GCS, ICM) should be used first, appropriate doses of emollients should be used (250-500 g/week*)*

Elimination diet. The indication for an elimination diet in patients is to establish an aetiopathogenetic link between food hypersensitivity and AD. The removal of harmful foods from the patient's diet, together with appropriately selected pharmacological treatment, is effective in achieving satisfactory clinical improvement, thus accelerating the treatment process. Individual recommendations for elimination of selected foods from the diet apply only to those patients in whom the adverse effect of food hypersensitivity on the clinical course of the underlying disease has been objectively confirmed.

The second therapeutic line – topical anti-inflammatory treatment - in the acute setting classical medicine recommends steroid ointments and periodically basic ointments
In the above group of drugs we have:

1. **Topical glucocorticosteroids (TGCs) preparations.** Glucocorticosteroids are an important and recommended group of topical anti-inflammatory drugs for the treatment of AD exacerbations. According to the registration, fluticasone propionate, alclometasone and betamethasone valerate can be used after the first year of life, while mometasone furoate, methylprednisolone aceponate are registered above the second year of life.

   Adequate discontinuation of TGCs is extremely important due to the risk of a rebound effect when the dose is reduced too rapidly. In order to discontinue the drug, it is initially necessary to convert the TGCs to a less potent drug, maintain treatment with the previous formulation with a lower frequency of applications per day or switch to treatment with topical calcineurin inhibitors.
2. **Topical calcineurin inhibitors (TCIs)** Topical calcineurin inhibitors are important anti-inflammatory treatments and have an important place in the treatment of AD. Their

efficacy in the treatment of AD has been confirmed by numerous clinical trials [33-38]. TCIs includes two drugs registered for the treatment of AD: tacrolimus ointment (0.03% and 0.1%) and pimecrolimus cream (1%). In addition to their anti-inflammatory effects, these drugs have the ability to reconstruct the epidermal barrier. They are preferred for use on the skin in the eyelid area, around the mouth, genital area and axilla. Unlike TGCs, topical calcineurin inhibitors do not cause long-term skin damage, and in fact have the ability to reverse local post-erosive damage to some extent. They do not cause inhibition of adrenal function, glaucoma or cataracts.

3. **Phosphodiesterase 4 inhibitors (PDE4-I)** Krisaborol, a non-steroidal anti-inflammatory drug, represents an innovative therapeutic proposal in AD. The mechanism of action of the formulation is different from that of TGCs and TCIs. Krisaborol acts by blocking phosphodiesterase 4, an enzyme that plays a significant role in the development of inflammation, and indirectly the secretion of cytokines such as TNF-alpha, IL-12, IL-23. The drug also improves epidermal barrier function by an indirect mechanism.
4. **Antihistamines.** First-generation antihistamines, through their central action (inhibition of histamine activity in the subcortical centres of the central nervous system), have an antihistamine and sedative effect, which is beneficial in a proportion of AD patients with sleep disorders. Second-generation antihistamines are particularly useful in AD patients with concomitant conjunctivitis or allergic rhinitis.
5. **Tannins** - the mechanism of action of tannins and the emollient base of the cream make it suitable for use in inflammatory skin conditions with dry skin, both in monotherapy of mild forms of AD, and in combined therapy with ICS, antifungals and antibiotics in more severe forms complicated by secondary infection. In addition to tannin, the lotion contains zinc oxide and talc, which have hygroscopic effects. For this reason, this form of the drug is recommended for use in monotherapy or adjunctive therapy of skin lesions accompanied by exudation and located in the area of discharge.
6. **Anti-infective treatment.** Any exacerbation of AD may be accompanied by bacterial superinfection. The main aetiological agent is Staphylococcus aureus. In the majority of patients affected by erythema-exfoliative lesions (approximately 90%), the skin is colonised by this pathogen, so attempts at eradication have significantly reduced the severity of the disease; however, complete eradication is not possible. The use of topical disinfectants such as octonidine, chloroxidine, mupirocin, fusidic acid is justified. If bacterial superinfection occurs, systemic antibiotic therapy is recommended. Herpes virus

infection requires systemic antiviral treatment. Ketoconazole and cyclopiroxolamine are recommended in infection caused by *Malassezia sympodialis* fungus.

Third-line therapy – systemic treatment. For severe atopic dermatitis (AD) and in the absence of improvement after topical treatment, it is recommended to consider the inclusion of systemic drugs: cyclosporine A (CyA), methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF) or corticosteroids.

1. **Cyclosporin A (CycA)** is recommended as first-line treatment in severe forms of chronic AD in adults. In children and adolescents in the most severe clinical situations, treatment with CycA may be considered and should be administered by an experienced dermatologist. CycA administration in cycles of an average of 12 weeks is recommended. Withdrawal of the drug is associated with a risk of skin lesion recurrence. The drug can also be given as a long-term continuous therapy, the duration of treatment should not exceed two years. Patients taking CycA should have their blood pressure and renal function parameters checked regularly. Treatment is associated with a number of possible side effects, including headaches, the occurrence of seizures/paresthesia, gastrointestinal disorders, the development of infections, gingival hyperplasia, excessive hair loss, hyperlipidaemia and electrolyte disturbances. In addition, there is an increased risk of skin tumours and lymphoproliferative growths. Therefore, patients treated with CycA must be monitored regularly by the treating physician.
2. **Methotrexate, AZA and MMF** are not registered for the treatment of AD, but can be used for off-label indications if CycA is ineffective or there are contraindications to its use [10]. Methotrexate (MTX) is the second drug used in the treatment of severe forms of AD after CycA. MTX is currently recommended for the treatment of AD in adults at doses similar to those used for psoriasis, Treatment is usually well tolerated, but the possibility of serious side effects should be kept in mind. Adverse effects have been reported mainly after high doses of MTX. Among the more common adverse effects are: hepatotoxicity, bone marrow suppression, pulmonary fibrosis and renal failure. Methotrexate is teratogenic - women and men should use effective contraception during and for six months after treatment. During MTX treatment, regular check-ups should be performed with a physical examination of the patient and determination of morphology, smear, liver tests, creatinine, urea and urinalysis. Folic acid supplementation and contraception in men and women are required during treatment. Azathioprine (AZA) can be used off-label to treat severe forms of AD in adults

refractory to other treatments, i.e. if CycA is ineffective or contraindicated. Azathioprine can also be used (off-label) in children. The activity of thiopurine methyltransferase (TPMT) should be determined before starting treatment, as patients with congenital deficiency of this enzyme may be at increased risk of myelosuppression. The most commonly observed side effects include bone marrow damage and immune system disorders. In addition, vascular disorders (vasculitis), gastrointestinal disorders (nausea, vomiting) and liver dysfunction may occur. It is therefore necessary to monitor transaminases and blood counts during treatment. Mycophenolate mofetil is a less commonly used drug in the treatment of adults with AD (off-label) at a dose of up to 3 g/day. The drug can be used in the treatment of children and adolescents with AD. Mycophenolate mofetil is teratogenic - men and women must use effective contraception.

3. **Phototherapy** - ultraviolet light has antiproliferative and immunosuppressive effects. UVA and UVB irradiation is particularly recommended.
4. **Biological treatment.** The important involvement of complex immunological mechanisms in the aetiopathogenesis of AD encourages treatment attempts also with the use of biological therapy, especially as it offers the possibility of more specific and less toxic management.

- Omalizumab*, a* humanised monoclonal IgG1 antibody, recognises and masks specific antibody epitopes in the IgE class and thus prevents this immunoglobulin from binding to receptors on mast cells and basophils
- Efalizumab – a recombinant, humanised monoclonal antibody directed against the CD11a subunit of lymphocyte function-associated antigen (LFA-1). LFA-1 plays a significant role in the migration of T lymphocytes into the epidermis
- TNF-g antagonists also have applications in the treatment of AD, which may be related to the fact that TNF-g expression is elevated in the skin, especially in the chronic phase of the condition
- Dupilumab is a novel drug recommended for the treatment of AD. It is an antagonist of the α-subunit of the receptor for IL-4/IL-13 and is the first biologic drug registered worldwide for the treatment of moderate to severe AD that is not controlled by topical treatment or for which such treatment is not indicated. Dupilumab can be used as a second-line treatment in severe AD after initial failure of general therapy. The drug can be applied as monotherapy or in combination with topical corticosteroids (TCS).

Dupilumab has a high safety profile - the most commonly observed side effects are local reactions after subcutaneous administration of the drug and conjunctivitis.

- Tralokinumab is a human IgG4 monoclonal antibody that binds specifically to interleukin 13 (IL-13), a type 2 cytokine, and inhibits its interaction with IL-13 receptors. It neutralizes the biological activity of IL-13 by blocking its interaction with the IL-13Rα1/IL-4Rα receptor complex. IL-13 activity is a major cause of type 2 inflammatory disease in humans, such as atopic dermatitis
- Upadacitinib is a reversible, selective inhibitor of Janus kinase JAK 1. Selective blocking of only this one kinase may result in a higher safety profile

In addition, the treatment of AD includes :

5. **Microbiological therapy** – the cause of many skin diseases is a disruption of the intestinal bacterial flora, so that the exit of toxins to the outside world is impaired. Because of this, while the intestinal lymphatic system is damaged, toxins are absorbed from the intestine. Thus, the body, unable to get rid of toxins through the intestine, tries to bring them out through the skin. Given these conditions, it should be believed that microbiological therapy can be helpful in the treatment of endogenous skin disorders. Microbiological therapy is based on restoring the symbiotic balance, optimising the pH of the gut, destroying possible pathological microorganisms, sufficient fluid supply, a balanced, complete diet and on the administration of symbiotic microorganisms and autovaccines.
6. **Psychotherapy** – the long-standing course of AD with persistent pruritus and the presence of skin lesions, which are a significant cosmetic defect and sometimes restrict basic life functions, are the cause of disorders in the psychological sphere - neuroses and psychoses; therefore, during treatment, it is important for patients to cooperate with a psychologist and sometimes a psychiatrist.
7. **Balneotherapy** – thermal water balneotherapy may be considered for the treatment of mild to moderate AD. The results of the cohort study indicate that balneotherapy with thermal water in combination with or without phototherapy can be effective in the treatment of mild moderate AD.
8. **SIT** – specific allergen immunotherapy is the only causal treatment for AD patients. The indication for SIT in AD patients is an inadequate response to previous treatments in a patient who has been confirmed to be sensitised to immunoglobulin E (IgE)-dependent airborne allergens. SIT in AD in this group of patients has high clinical

efficacy, especially in patients sensitised to a single group of allergens. It is a safe method and side effects occur mainly during the induction phase of therapy. The most common are erythema and swelling of the skin at the site of vaccine administration. General reactions are less frequent and take the form of focal reactions distant from the site of allergen administration or general symptoms. Exacerbation of rhinitis or asthma, skin pruritus and urticaria are observed.

9. **Probiotics** have been and continue to be investigated for their potential use in the treatment of AD. The rationale for the use of probiotics is that the bacteria they contain induce a Th1-type immune response, resulting in inhibition of IgE antibody production. Some reports show limited benefit from the use of probiotics in the prevention and treatment of AD. Studies in this area have produced conflicting results and need to be confirmed.

Summary:

In the treatment of AD, experience and close cooperation with the
with the patient and/or their parents, education, avoidance of exacerbating factors, restoration of impaired skin barrier function, reduction of pruritus and elimination of inflammatory lesions and skin infection. Patients require frequent dermatological consultations and, in the case of generalised erythrodermic lesions, hospitalisation.

Author's contribution

Conceptualization: Barbara Wilczyńska

Methodology: Monika Grzybek

Software: Krzysztof Tyszkiewicz and Sylwia Wielgosz

Check: Monika Kułaga, Anna Kasprzak and Borys Łozowski

Formal analysis: Barbara Szostak and Barbara Wilczyńska

Investigation: Monika Grzybek and Diana Mazur-Lesińska

Resources: Małgorzata Kasprzak and Anna Kasprzak

Data curation: Borys Łozowski

Writing - rough preparation: Monika Grzybek and Sylwia Wielgosz

Writing - review and editing: Diana Mazur-Lesińska and Monika Kułaga

Visualization: Barbara Wilczyńska

Supervision: Krzysztof Tyszkiewicz

Project administration: Monika Grzybek

Receiving funding: Barbara Wilczyńska and Małgorzata Kasprzak

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