

Atopic dermatitis: current treatment guidelines. Statement of the experts of the Dermatological Section, Polish Society of Allergology, and the Allergology Section, Polish Society of Dermatology

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Abstract

Atopic dermatitis (AD) is a condition frequently encountered in medical practices across the country. More than 60% of children with AD are at risk to develop allergic rhinitis or asthma (the atopic march). Patients with AD have a unique predisposition to colonization or infection by *Staphylococcus aureus*. Treatments for AD need to rapidly control symptoms of the disease, improve quality of life and prevent exacerbations. Given the chronic and relapsing nature of the disease, therapies need to encourage good compliance and be well tolerated.

Key words: atopic dermatitis, treatment, emollients, cosmeceuticals, topical corticosteroids, topical calcineurin inhibitors, antihistamines.

Introduction

Atopic dermatitis (AD) is a chronic, recurrent, inflammatory cutaneous disease, which may coexist with other IgE-dependent atopic diseases such as bronchial asthma, allergic rhinitis and food allergy [1, 2]. Atopic dermatitis is a result of complex genetic, epigenetic, environmental and immunological interactions with an overlapping epidermal barrier defect [1, 2]. The disease significantly reduces the quality of life of patients and their families, which leads to serious socioeconomic consequences

[3–9]. In early childhood, the incidence of the disease is similar in both sexes, and only around the age of 6 years does the prevalence among girls become higher than in boys (3 : 2) [10, 11]. Atopic dermatitis most often begins in early childhood. It is believed that 60% of all cases begin in the first year of life, and 90% – before the age of 5. The disease tends to regress before 5 years of age in 40–80% of patients and in 60–90% it subsides before 15 years of age [12]. In Poland, the incidence of AD increases in large cities, but decreases in rural areas. The prevalence

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of AD in children ranges from 4.7% to 9.2%, while among adults it is from 0.9% to 1.4% [13].

Treatment. General considerations

The fundamentals of AD treatment are based on a combination of proper skin care, daily use of emollients and anti-inflammatory treatment, while avoiding contact with provocative allergens and irritants [14, 15]. Anti-inflammatory therapy should be properly selected to include topical corticosteroids (TCSs) and/or topical calcineurin inhibitors (TCI) – depending on the disease activity (periods of exacerbation and remission, location of changes etc.).

Contributing factors

One of the most vital elements of taking medical history is identifying potential aggravating factors. Most often, in the case of AD, these are airborne allergens, foods, climatic factors, stress, hormone levels, cigarettes, irritants and microorganisms. Not every patient with AD reacts to all of the above-mentioned factors [14, 16]. Statistically, 20–40% of young children and infants with AD are concurrently diagnosed with a food allergy, most commonly to cow's milk, eggs, fish, peanuts, soya beans and wheat [16]. Food allergy and AD often coexist in the same patient. Skin lesions occurring in AD, associated with food allergy, are more common in patients in the developmental age than in adulthood. They are a manifestation of the body's hypersensitivity to certain foods, the consumption of which leads to atopic and allergic reactions (IgE-mediated, IgE-independent or mixed).

Atopic dermatitis in infants and young children is most often associated with an allergy to cow's milk protein and egg white, whereas older children, adolescents and adults are more commonly allergic to animal and airborne allergens.

Clinical studies have shown that in approximately 50% of the youngest children with AD, exacerbation of skin lesions may occur after ingestion of one or more harmful ingredients. Adolescents and adults with AD also react with exacerbation of lesions after eating certain foods. Unlike in infancy, hypersensitivity reactions to milk protein and egg white ("classical food allergens") are seldom observed in adolescents and adults with AD. In this age group, exacerbation of skin lesions more commonly is a result of an "allergic cross-reaction" caused by simultaneous allergies to pollen and food.

Determination of the etiopathogenic relationship between food hypersensitivity and AD is an indication for the temporary use of an elimination diet in these patients [17]. In contrast, airborne allergens (animal dander, cockroaches, house dust mites, human skin, molds and pollens) are the most common cause of exacerbations in older children and adults [18].

First-line therapy: basic treatment

Primary therapy of AD is based on education, prevention and restoration of the disturbed epidermal barrier function by total emollient therapy (Table 1). Emollients should be selected on a case-by-case basis depending on the degree of skin dryness, diurnal and nocturnal activities as well as possible contact allergy. The restoration of lipids in the damaged epidermal barrier of an AD patient can be achieved using the so-called active emollients, a mixture of fats that physiologically occur in the stratum corneum. These compounds, such as ceramides, free fatty acids and cholesterol, are actively transported using specific receptors and ATP to the cytoplasm of the cells in the living layers of the epidermis, where they are metabolized and then, together with endogenous lipids, they form a lipid barrier of the skin. In AD, the best results are achieved with active emollients that consist predominantly of ceramides because they are the most deficient in this disease [19]. Restoration of the epidermal barrier is achieved following each application of emollients, but long-lasting improvement of its function takes 2 to 4 weeks of regular treatment, which is associated with the physiological process of differentiation of the epidermis, with the final product of the stratum corneum rich in lipid membranes.

The crucial part of topical treatment of AD is the use of modern emollients that contain agonists of peroxisome proliferator-activated receptors (PPARs). These are highly unsaturated fatty acids, certain flavonoids, which cause activation of specific nuclear receptors and thus increase the synthesis of endogenous lipids, improving the function of the epidermal barrier; they also have an anti-inflammatory effect similar to corticosteroids by inhibiting nuclear factor- κ B (NF- κ B), Th2 cell response, mast cells and interleukin 4 [20, 21]. An important objective of the treatment is to restore proper hydration levels of the epidermis. Proper hydration of the stratum corneum can be achieved through the use of emollients that, in addition to lipids, also contain urea – the main component of natural moisturizing factor (NMF), whose role is to contain water and glycerol, which is responsible for the transport of water from the dermis to the epidermis.

Treatment of AD with a palmitic acid derivative (PEA) has been seen to yield good results – PEA is physiologically present in the epidermis, and in AD its amount is drastically reduced. Its topical application stimulates the production of endogenous lipids; it has antimicrobial properties and also acts on histamine receptors, preventing the degranulation of mast cells [22]. Lubrication of dry skin reduces pruritus, hydrates skin and promotes the alleviation of inflammation. Regular use of emollients 3–4 times a day reduces the need for TCSs (a steroid-sparing effect) [23, 24]. Atopic skin requires special care [15, 24]. The patient's skin condition is significantly

Table 1. First-line therapy of atopic dermatitis (AD) (based on [15], [24])

Education	Explain/demonstrate how to apply emollients
	Various topical medications should be used with intervals
	In children > 12 months, use shampoos recommended in AD
	When talking to the patient (guardian), make sure the recommendations are understood and followed
	Revision of recommendations at least once a year
Prevention	Avoid allergens and irritants:
	Tobacco smoke
	Infections
	Wool clothing
	Stress
Skin cleansing	Delicate and precise, mechanical cleansing
	Detergents with/without aseptic substances
	Suitable galenic forms
	pH in the range of 6
	Fast bath ≤ 5 min, including 2-min bathing in oil at 27–30°C
	Adding 1/2 cup of sodium hypochlorite to the bath eliminates itching
	Bath salts – facilitate the removal of exfoliated skin, skin scales, particularly beneficial in severe impetiginization
Emollient therapy	Application min. 2–3 times a day!
	Glycerol is better tolerated than urea or sodium chloride
	Propylene glycol can easily cause irritation in young children < 2 years of age and should not be used in these patients
	In children < 2 years of age it is recommended to use emollients without protein allergens and haptens
	Do not use emollients containing peanut extracts which increase the risk of sensitization and allergies!
	Emollients are poorly tolerated in inflammation sites – use the appropriate doses of emollients (250–500 g/week)

improved by short water baths at 36–37°C, after which application of emollients is recommended within 5 min.

Cosmeceuticals

Cosmeceuticals are a separate group of topical preparations which, due to their high content of active ingredients, have therapeutic properties or significantly support skin care. They are used to rebuild and restore the normal function of the epidermal barrier and reduce local inflammation in AD. The most important active compounds used in cosmeceuticals include: vitamins (e.g. vitamins A, C, K, niacin), minerals, unsaturated fatty acids, antioxidants (e.g. rutin), plant extracts (e.g. chestnut, ginkgo biloba, arnica), phytoestrogens, β-carotene, active anti-inflammatory compounds, fruit acids, cytokines and the recently discovered ectoin. Ectoin is capable of limiting the inflammatory processes induced by external factors, such as ultraviolet radiation. It reduces the extent of DNA damage, accelerates cellular repair mechanisms, protects Langerhans cells, increases the fluidity of the lipid layer and protects against water loss from the epidermis.

The most important role of ectoin is the protection of keratinocytes in the epidermis against adverse environ-

mental factors including UV rays, high temperatures and dryness [25, 26].

Wet-wrap treatment

So-called “wet-wrap treatment” (WWT) can be used in children aged from 6 months to 10 years with severe AD (SCORAD index over 50). The method uses two layers of dressings: moist dressing, saturated with medications (emollients or 0.05% fluticasone propionate or mometasone furoate at a dilution of 1 : 3 for the body or 1 : 9 for the face), which is placed directly on the skin, and the overlying dry dressing. The therapy lasts 3–14 days under close medical supervision, and requires monitoring of morning cortisol levels. A possible side effect may be adrenal suppression [27].

Wet dressing has cooling, anti-inflammatory and antipruritic effects. It forms a mechanical barrier against environmental factors and prevents the child from scratching, potentially also reducing the amount of TCS used. On the other hand, it causes high TCS absorption, increasing the risk of bacterial infection of the hair follicles and skin atrophy. In addition, this form of therapy requires training

to be provided to caregivers or patients, which raises its cost [28].

A consensus published in 2006 emphasizes that WWT is a relatively safe therapy in severe and recurrent cases of AD, well tolerated by children and significantly improving their quality of life [29]. Spectacularly good therapeutic effects can be seen as early as after 1 week of treatment; however, in some cases, a significant worsening of AD can develop within 4 weeks after cessation of treatment, hence research is being conducted on the proactive use of WWT in home care [29]. The results of studies encourage the use of this method, yet further controlled standardized clinical trials are needed before any recommendations can be made [30].

Second-line therapy: mild anti-inflammatory treatment

Topical corticosteroids

Topical corticosteroids have been the basis of AD treatment for over 50 years. They provide an excellent therapeutic effect in combination with emollients. Due to dry skin, TCSs are preferred in the form of ointments, except in the case of exuding skin lesions, where lighter forms must be used (lotion, spray, cream). The use of TCSs reduces skin colonization by *Staphylococcus aureus* [14]. During exacerbations it is recommended to use a TCS of medium potency. Due to the high efficiency obtained in a short time after initiation of treatment and their low price, TCSs are often overused. In children, these medications should be used very carefully, under close dermatological follow-up due to differences in the skin structure compared to adults. In Poland, only hydrocortisone acetate and hydrocortisone butyrate are approved for use in children under 1 year of age, whereas mometasone furoate, fluticasone propionate and methylprednisolone aceponate – characterized by high selectivity and affinity to receptors – are approved for use in children above 2 years of age. Other TCSs are only approved for use in patients aged 12 years or older.

Side effects of corticosteroids

Long-term use of TCSs, particularly those from high potency groups, is associated with common side effects: skin atrophy, permanent telangiectasia, stretch marks, hypertrichosis, depigmentation, perioral dermatitis, acne rosacea, bacterial and/or fungal infections and withdrawal effects (exacerbation of skin lesions after discontinuation of the drug), as well as tachyphylaxis (gradual decrease in efficacy with prolonged treatment). Local application of strong TCSs on large surfaces in children, especially infants, can cause undesirable systemic symptoms: inhibition of the hypothalamic-pituitary-adrenal axis, growth retardation and osteoporosis. Fear of side effects (as well as the increasingly common steroid pho-

bia) is a common cause of poor compliance with doctor's recommendations by patients or, in the case of children, by parents, which results in a lack of treatment efficacy. To avoid potential side effects, it is recommended to use the so-called intermittent therapy, involving the use of TCSs only 2–3 days per week, alternating with emollients. Topical corticosteroids should be used according to the manufacturer's recommendations, once a day, as their more frequent use does not increase treatment efficacy but increases the risk of side effects [14, 18, 24, 31–33].

“Steroid phobia” (“corticophobia”)

More than half of AD patients are afraid to use TCSs, as revealed by studies on steroid phobia among these patients. In addition, it has been shown that patients have little knowledge of the therapeutic potential of TCSs and their adverse effects, and the main source of information about TCSs for patients is doctors and pharmacists. The problem of steroid phobia is not limited to Poland but is widespread in Europe and results in ineffectiveness of local AD therapy. It seems that the effectiveness of AD treatment could be improved by proper education of patients and personal interaction fostering mutual trust between patients and healthcare professionals [34].

Topical calcineurin inhibitors

Topical calcineurin inhibitors, tacrolimus and pimecrolimus, inhibit T cell activation and the release of inflammatory cytokines. Pimecrolimus in the form of 1% cream is recommended as first-line therapy in mild AD, and its clinical profile suggests that it may be considered as the treatment of choice for mild to moderate AD, in both children and adults, especially in sensitive areas of the skin [35]. Tacrolimus 0.03% and 0.1% ointment is recommended in moderate to severe atopic eczema. Compared to pimecrolimus, tacrolimus has a faster and more potent action, and clinical improvement after its application is visible already in the first week of treatment. These medications are administered twice daily until resolution of inflammation. They can be safely used for many months on all areas of the skin, including sensitive ones such as the eyelids, face, neck, and intertriginous areas, as well as the genitals in both adults and children. In contrast to TCSs, TCIs do not inhibit the synthesis of collagen, do not cause epidermal thinning or vasodilation, nor do they damage the skin barrier. The most common adverse reactions associated with the use of TCIs are burning and redness of the skin at the site of application, which disappears after a few days [14, 35, 36].

Based on analysis of existing results of the treatment, it is believed that the restrictions on the use of pimecrolimus in infants are unjustified. It is suggested to develop new recommendations and warnings in the labelling of topical calcineurin inhibitors [37].

Proactive (maintenance) therapy

Proactive therapy is based on the use of tacrolimus ointment twice a week for up to 12 months after the disappearance of skin lesions. For patients with relapsing AD, pimecrolimus cream should be applied as maintenance therapy to the previously affected skin following complete resolution of lesions, either once daily for 7 days a week for up to 3 months or less frequently, depending on the advice of the treating physician [37]. Reduction of exacerbations of AD, increased patient compliance, improved quality of life of patients and reduced cost of treatment of AD have been observed among patients using the proactive therapy [38, 39].

Antimicrobial therapy

Each exacerbation of AD can be associated with bacterial infection; staphylococcal infections are the most common. The skin of patients with AD is colonized with this pathogen in 90% of cases. An attempt was made to prove that eradication of *Staphylococcus aureus* significantly reduces the severity of the disease [40]; however, due to increasing drug resistance and the defective antimicrobial peptide profile in AD, sustained decolonization of the skin is practically impossible [41]. Studies indicate the efficacy of octenidine, chlorhexidine, mupirocin, fusidic acid and retapamulin [40, 42, 43]. Due to the above-mentioned antibiotic resistance, chronic use of topical antibiotics is not recommended. The rationale for the use of oral antibiotics is exacerbation of AD with clinical signs of bacterial infection [44–46]; in other cases, treatment with oral antibiotics is not recommended [14, 47]. It is important to note that anti-inflammatory treatment alone (TCIs, TCSs, UV) reduces *Staphylococcus aureus* colonization in AD [14, 42]. Skin infection caused by herpes simplex virus (HSV) is often manifested as Kaposi varicelliform eruption that requires systemic antiviral therapy [48]. Ketoconazole and ciclopiroxolamine are proposed for the treatment of superficial infections caused by *Malassezia sympodialis* [49–51].

Tannins

Tannins have played an important role in dermatology for many years. Because of their astringent, anti-inflammatory, antipruritic, antimicrobial and desiccant properties, they are widely used in the treatment of inflammatory and exudative skin diseases such as AD. Lack of absorption after application, leading to absence of systemic effects, allows tannins to be used with no age limits in infants, children, the elderly, as well as in pregnant women. Tannins can be used regularly and there have been no reported interactions during simultaneous application with other medicinal products [52]. It comes in three forms: lotions, creams and a solution for baths and wraps. In situations where there is minimal exudate, dryness and peeling, the use of tannins in the form of

creams is preferred. The mechanism of action of tannins and emollient cream base make this formulation effective in inflammatory skin diseases with skin dryness, either alone in mild forms of AD, or in combination with local corticosteroids, antifungals and antibiotics in more severe cases complicated with secondary infection [53]. The lotion form of tannins additionally contains zinc oxide and talc, which exhibit hygroscopic properties, making it favorable for use as monotherapy or adjunctive therapy of skin lesions accompanied by exudate and located in the vicinity of intertriginous areas. Synthetic tannins are available in the form of solutions recommended for partial and whole body baths, washing and wraps [54].

Antihistamines

First-generation antihistamines (AH1), among which only hydroxyzine is currently recommended, can inhibit histamine activity in the subcortical centers of the central nervous system (CNS), exerting an antipruritic and sedative effect, which is advantageous in the case of AD patients who experience sleep disorders and difficulties in falling asleep. Antihistaminic activity may accelerate the repair of the damaged epidermal barrier [55, 56]. Gschwandtner *et al.* demonstrated that the addition of histamine to keratinocyte cultures (*in vitro*) resulted in a significant decrease in the expression of keratin 1/10, filaggrin and loricrin [55]. Second-generation antihistamines (AH2) are particularly useful in patients with AD accompanied by conjunctivitis or allergic rhinitis [15]. Higher specificity of binding to histamine H1 receptor, longer half-life and hydrophilic structure of AH2 contribute to improved efficacy and safety of these drugs [57].

The safety of cetirizine and levocetirizine has been confirmed in two large studies: ETAC and EPAAC, in which AD children aged 1 to 3 years received treatment for 18 months [57, 58]. ETAC (Early Treatment of the Atopic Child) was the first prospective study evaluating the safety and efficacy of cetirizine in the pediatric population. Serious adverse events were rare and more common in the placebo group. It has been shown that the use of cetirizine for a period of 18 months in 1- to 2-year-old children with AD reduced their risk of asthma by half [58]. The EPAAC study involved a group of 510 children with AD between 12 and 24 months of age. No significant adverse effects were observed, except for upper respiratory tract infections, gastrointestinal disorders and exacerbation of allergic diseases. There were no statistically significant differences in the incidence of these adverse events between the groups receiving levocetirizine and placebo [59].

Bilastine and rupatadine are new antihistamines, approved only for the treatment of allergic rhinitis and urticaria. Rupatadine can be used from 6 years of age, and bilastine from 12 years of age (Table 2). Bilastine has a moderate affinity and high selectivity to H1 receptors [60]. After absorption, it is not metabolized and is excret-

Table 2. Approved ages for using certain antihistamines

Antihistamines	Age
Fenistil	2 months
Hydroxyzine	12 months
Cetirizine	2 years
Levocetirizine	2 years
Loratadine	2 years
Desloratadine	1 year
Fexofenadine	12 years
Bilastine	12 years
Rupatadine	6 years

ed with the urine. It has no effect on cardiac arrhythmia even with concomitant administration of ketoconazole. Therapeutic doses of bilastine have no effects on psychomotor functions [60]. Data on antipruritic efficacy of first- and second-generation antihistamines in AD are limited and there is insufficient evidence for the widespread use of these drugs in the treatment of pruritus in AD [24].

Third-line therapy: systemic treatment

In AD patients in whom local therapy fails to improve the skin condition, the following medications can be considered: cyclosporine A, methotrexate, azathioprine, mycophenolate mofetil, systemic corticosteroids and phototherapy [14, 15, 31, 54].

Cyclosporine A (CsA) is recommended as the first-line therapy in severe cases of chronic AD in adults. In children and adolescents, its use should be considered only in severe cases of AD. Recommendations for use in children are based on the results of individual cohorts and individual randomized controlled studies (“off-label” indications) [24, 60, 61]. Cyclosporine A reduces inflammation, the size of lesions, the severity of pruritus, and improves the quality of sleep. The recommended starting dose is 2.5–3.5 mg/kg b.w./day in two divided doses and should not exceed 5 mg/kg b.w./day [61]. After obtaining improvement of skin lesions, it is recommended to reduce the CsA dose by 0.5–1.0 mg/kg b.w./day every 2 weeks [62]. The desired effects of CsA treatment, namely decreased pruritus and inflammation of the skin, can be seen as early as 2–6 weeks after the initiation of the therapy [60, 62]. Withdrawal of the drug is associated with a risk of recurrence of skin lesions within several weeks after discontinuation of treatment; it is estimated, however, that after the treatment the skin condition does not return to the pre-CsA treatment state [61, 62]. The drug can be administered in continuous long-term therapy; however, administration in cycles lasting on average 12 weeks is recommended. It has been shown that CsA at a dose of 2.5–5.0 mg/kg/day given in cycles (cycle

duration of 12–16 weeks) quickly leads to a significant improvement or disappearance of lesions in 80–90% of patients [24]. Despite the unquestionable efficacy of CsA in the treatment of AD, the use of this drug carries the risk of serious side effects. Most side effects that appear during the therapy resolve after discontinuation of the drug. In order to prevent or reduce the risk of their occurrence, strict monitoring of treatment is recommended. Patients receiving this drug should be regularly examined for blood pressure and renal parameters. The risk of nephrotoxicity increases when the dose exceeds 5 mg/kg b.w./day, when there are persistent elevated creatinine values, as well as in the elderly. Permanent kidney damage (tubular disorders, vasculopathy) can occur in patients receiving CsA continuously over a period of more than 2 years [62]. In short-term and intermittent CsA treatment, renal dysfunction is usually transient. In children, the risk of renal toxicity is lower than in adults. Uncommon side effects during treatment with CsA include neurological symptoms such as headaches, convulsions, paresthesia, as well as gastrointestinal disorders, infections, gingival hyperplasia, hirsutism, hyperlipidemia, electrolyte disturbances, increased risk of developing skin cancers and lymphoproliferative disorders. The monitoring of blood CsA concentrations during treatment is not required, since CsA levels are only marginally correlated with its efficacy and toxicity [63]. Despite the lack of clinical evidence, discontinuation of CsA 2 weeks before the scheduled vaccination and re-introduction of the drug 4 to 6 weeks later is recommended [15].

Methotrexate (MTX), azathioprine (AZA) and mycophenolate mofetil (MMF) can be used off-label in adult patients with AD, when CsA is ineffective or there are contraindications to its use. There are not enough randomized, double-blind, placebo-controlled, prospective clinical studies evaluating the treatment with AZA, MTX or MMF in children and adolescents with AD [15].

Methotrexate is indicated for the treatment of severe AD that is resistant to other treatments. It has been emphasized that it is the second most common drug used in the treatment of severe AD after CsA. There are a number of literature reports on the safety and efficacy of MTX in AD. These reports mainly involve adult patients [64]. There are also isolated reports on the efficacy and safety of MTX in children [65]. Currently, MTX is recommended for the treatment of AD in adults at doses similar as in the treatment of psoriasis, i.e. 10–20 mg/week. It can be used in a single dose once a week, but it is more often applied in three doses of 2.5–7.5 mg every 12 h once a week [66]. Other authors recommend the use of MTX at doses of 7.5–25 mg/week for adults and 0.2–0.7 mg/kg/week in children [63]. The treatment is usually well tolerated, but there is potential for serious adverse reactions. It is believed that the incidence and severity of adverse events are dose related. Adverse reactions reported were mostly due to high doses of MTX used as chemother-

apy. More common side effects include hepatotoxicity, bone marrow suppression, pulmonary fibrosis and renal failure. In addition, reduced resistance to infection, leukopenia, anorexia, dizziness, headache, abdominal pain, ulcerative stomatitis, inflammation and ulceration of the bowel are frequently observed [67].

Azathioprine has been used off-label in the treatment of skin conditions including severe AD resistant to other treatments. The exact mechanism of action of AZA in AD is not yet fully understood. *In vitro* studies suggest that AZA has a suppressive and toxic effect on Langerhans cells [68]. It is noted that AZA is very effective in the treatment of AD, but due to its mechanism of action, the therapeutic effect of the drug may be delayed [69]. In some patients the full therapeutic effect is achieved after 12 weeks or even later. It is recommended to use AZA at doses of 1–3 mg/kg b.w./day. Before starting the treatment, the activity of thiopurine methyltransferase (TPMT), an enzyme involved in the metabolism of 6-mercaptopurine, should be assessed, because people with an inherited deficiency of this enzyme have an increased risk of myelosuppression. TPMT gene mutations may affect the efficacy and safety of treatment with AZA. Determination of TPMT levels allows for adjustment of individual doses and reduces the risk of bone marrow damage [70–73].

Due to the fact that AD is common in children, the question arises whether AZA is useful in treating this disease in children. Some authors have used the drug in severe cases of AD in children and reported its efficacy. No toxic effects on the bone marrow have been observed [74, 75]. It has also been shown that AZA not only improves the clinical picture but also lowers total serum IgE levels in children and adolescents with AD [76].

Azathioprine has a number of side effects. The most common ones include bone marrow failure and immune system disorders. Vascular disorders (vasculitis), gastrointestinal disorders (nausea, vomiting), and liver disorders have also been reported. Therefore, it is necessary to monitor transaminases and blood cell counts during treatment. According to the summary of Product Characteristics, blood cell counts should be monitored once a week during the first 8 weeks of therapy. At later stages of treatment, the frequency of blood cell count tests should be reduced to once per month, then once every 3 months. In the case of decreased levels of leukocyte or platelet counts, or if there are other side effects, the dose should be reduced. When using AZA, patients should not be vaccinated with vaccines containing live microorganisms. Reaction to vaccines containing killed microorganisms can also be weakened. Due to the teratogenic effects of AZA, it should not be used during pregnancy and breastfeeding [69].

Systemic corticosteroids (CS) are approved for the treatment of AD, mainly in adult patients for up to

1 week, in carefully selected cases of disease exacerbation [15].

In everyday practice (unlike the published results of clinical trials), the most common causes of discontinuation of treatment with CS include: side effects, lack of effectiveness of treatment, patient non-compliance and treatment discontinuation after clinical improvement. In a 10-year observational study involving Dutch AD patients, treatment with oral glucocorticosteroids, MMF, and CsA was associated with the lowest frequency of side effects (5%, 22% and 24%, respectively). More side effects, mainly gastrointestinal, were seen after treatment with AZA (38%) and MTX (41%). Furthermore, lack of effectiveness of therapy was the cause in 15% for CsA and AZA, 20% for CS, 44% for MMF and 65% for MTX [77].

Probiotics have been studied as a potential treatment of AD. The rationale for the application of probiotics is that bacteria induce Th1 rather than Th2 immune responses, which may reduce the production of IgE antibodies. Some authors reported limited benefits of probiotics in the prevention and treatment of AD. These studies need to be confirmed [78].

Phototherapy

All types of phototherapy are effective in AD: natural light, narrow-band UVB (NB-UVB, 311 nm), broad-band UVB (BB-UVB, 290–320 nm), UVA (320–400 nm), UVA with psoralens (5-methoxypsoralen, 8-methoxypsoralen – photosensitizing compounds taken orally 1 or 2 h prior to irradiation) used orally or topically (PUVA), UVA and UVB (UVAB), and UVA1 (340–400 nm). There is no evidence for the superiority of one method over another due to the scarcity of comparative studies. All we know is that natural sunlight is the least effective compared to artificial light sources. The most commonly used method is UVB phototherapy [63].

Therapeutic protocols differ depending on the region of the world and local recommendations. In the case of broad-spectrum UVB, a skin phototype-based radiation dosage protocol can be used. The starting doses for each phototype are: I: 20 mJ/cm²; II: 25 mJ/cm²; III: 30 mJ/cm²; IV: 40 mJ/cm²; V: 50 mJ/cm²; VI: 60 mJ/cm². At each subsequent irradiation, the doses should be increased by a specific value depending on the phototype: I: 5 mJ/cm²; II: 10 mJ/cm²; III: 15 mJ/cm²; IV: 20 mJ/cm²; V: 25 mJ/cm²; VI: 30 mJ/cm². The subsequent doses should be administered 3–5 times per week [63].

Depending on the minimal erythema dose (MED), the starting dose of BB-UVB should be equal to 50% of MED, in the next 10 treatments the starting dose should be increased by 25%, in treatments 11–20, the dose should be further increased by 10%, and in the subsequent treatments the dose is at the discretion of the attending physician. If the patient misses a treatment session, the following rules apply: 1. when 1 week is missed, the

last dose can be repeated; 2. when 2 weeks are missed, the dose should be reduced by 50%; 3. when 3 weeks are missed, the dose should be reduced by 75%; 4. when 4 weeks are missed, phototherapy should start from the beginning.

Skin phototype-based dosing regimens can also be used in the case of narrow-range UVB. The starting doses for each phototype are: I: 130 mJ/cm²; II: 220 mJ/cm²; III: 260 mJ/cm²; IV: 330 mJ/cm²; V: 350 mJ/cm²; VI: 400 mJ/cm². With each subsequent treatment, the dose should be increased by a value depending on the phototype: I: 15 mJ/cm² (maximum dose 2000 mJ/cm²); II: 25 mJ/cm² (maximum dose 2000 mJ/cm²); III: 40 mJ/cm² (maximum dose 3000 mJ/cm²); IV: 45 mJ/cm² (maximum dose 3000 mJ/cm²); V: 60 mJ/cm² (maximum dose 5000 mJ/cm²); VI: 65 mJ/cm² (maximum dose 5000 mJ/cm²). The subsequent doses should be administered 3–5 times a week [63].

In contrast, the MED-based dosage is as follows: starting dose as in BB-UVB: 50% of MED, in the first 20 treatments, the dose should be increased by 10%, the following treatments – at the discretion of the physician. If the patient misses a treatment session, the following rules apply: 1. when 1 week is missed, the last dose can be repeated; 2. when 2 weeks are missed, the dose should be reduced by 25%; 3. when 3 weeks are missed, the dose should be reduced by 50%; 4. when 4 weeks are missed, phototherapy should start from the beginning.

Maintenance therapy by NB-UVB: when regression of more than 95% is obtained: 1 treatment per week for 4 weeks – same as the last dose, followed by reduction in the dose by 25% every 2 weeks – for 4 weeks, then once a month a dose equal to 50% of the highest dose [63]. PUVA photochemotherapy must also be conducted according to phototype: starting dose in phototype I: 0.5 J/cm²; II: 1.0 J/cm²; III: 1.5 J/cm²; IV: 2.0 J/cm²; V: 2.0 J/cm²; VI: 3.0 J/cm². In each subsequent treatment, the dose should be increased by 0.5 J/cm² in skin phototypes I and II (maximum dose 8 J/cm²), 1.0 J/cm² in phototypes III and IV (maximum dose 12 J/cm²), and 1.5 J/cm² in phototypes V and VI (maximum dose 20 J/cm²) [63].

Phototherapy can be used either alone or in combination with emollients or TCS. Calcineurin inhibitors should be used with caution during phototherapy because of the manufacturer's warnings. It is believed that side effects of phototherapy are uncommon. Their frequency is different depending on the method. Side effects include redness and tenderness after irradiation, itching, burns and solar skin damage. Less common adverse events include skin cancers, melanoma (mainly with PUVA), lentigo, photosensitivity reactions (mainly polymorphic light eruptions), folliculitis, photo-onycholysis, reactivation of HSV, excessive facial hair, cataract (also with PUVA). Patients who use psoralens complain of nausea, vomiting and headaches [63, 79, 80].

In the case of phototherapy and photochemotherapy for children, NB-UVB is recommended as the treatment of choice for patients who have not responded to topical therapy [15, 24]. Cases of skin cancers have been reported in patients who received PUVA treatment as children; for this reason, this is not a first-choice method in the treatment of AD [63].

Specific immunotherapy

Specific allergen immunotherapy (AIT) is the only method of causal treatment of AD. Allergen immunotherapy is indicated in patients with AD in cases of inadequate response to previous treatment with documented IgE-mediated allergy to airborne allergens [15, 81–83]. Based on literature and our own experience we can conclude that AIT in AD has a high clinical efficacy in the treatment of patients with symptoms of allergy to perennial and seasonal aeroallergens, particularly those who are allergic to one group of allergens [15, 84]. To date, the clinical effects of using AIT have been best documented for patients allergic to house dust mites and pollen [84, 85]. There are no contraindications for desensitization of AD patients with other coexisting AD like allergic rhinitis or mild asthma [15, 83]. The effectiveness of AIT depends on the correct classification of patients, proper selection of the composition of the vaccine and its proper handling. The composition of vaccines should be based on the results of a thorough medical history, physical examination, and detailed allergological diagnosis based, among others, on skin prick tests and assessments of specific IgE in serum. The correct composition of the vaccines and the order of their administration in AD patients with polyvalent allergy determines the success of AIT. When planning AIT in patients with AD, allergic diagnosis should not be limited to skin prick tests but should be supplemented with assessment of the level of specific IgE to the respective allergens [84, 85]. Side effects tend to occur mainly during the induction phase of AIT and are usually mild and transient. Most often they appear in the form of erythema and swelling of the skin at the site of vaccination. General reactions are less common and occur as focal reactions distant from the site of administration of the allergen, or as general symptoms. Exacerbation of rhinitis or asthma has been reported, as well as pruritus and urticaria. Less frequently reported non-specific symptoms included increased temperature, headache, dizziness, weakness, and muscle fatigue. In individual cases, hypotension, laryngeal edema and even anaphylactic shock can occur. Usually, side effects of AIT are mild and transient and relate primarily to skin symptoms. However, when using AIT, one must always be prepared for pharmacological and anesthesiological interventions [85]. Allergen immunotherapy should be carried out systematically for at least 4–5 years, by a specialist

doctor, in a safe environment, with due consideration of the possibility of adverse reactions [84, 85].

Alternative treatments

There is insufficient evidence of the efficacy of oral or local use of unsaturated fatty acids, as well as starch and brine baths. There is also insufficient evidence to support the use of Chinese herbs in the treatment of AD. There is no evidence of the effectiveness of AD treatment using methods such as acupuncture, homeopathy, and aromatherapy [15]. It seems that supplementation with vitamins D or E may be useful in the treatment of AD, but this requires further controlled studies before any specific recommendations can be made [15].

Conclusions

The treatment of AD should be based on experience and close cooperation with the patient and/or parents, education, avoidance of aggravating factors of the disease, restoration of disturbed functions of the skin barrier, reduction of itching and elimination of skin inflammation and infection. Patients require frequent dermatological consultations, and in the case of generalized erythrodermic changes hospitalization may be necessary.

Conflict of interest

The authors declare no conflict of interest.

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