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Severe atopic dermatitis in children: therapeutic dilemmas

Atopowe zapalenie skóry o ciężkim przebiegu u dzieci: dylematy terapeutyczne

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Abstract

Atopic dermatitis is the most common skin disorder diagnosed in early childhood. Some children do not experience a relief of symptoms as they get older, and severe atopic dermatitis may develop, with manifestations including widespread skin lesions and unremitting itching. The disease is both physically and emotionally disabling, and significantly compromises the patient's quality of life. Indications to intensify therapy include resistance to topical treatment and multidrug resistance. However, in many cases non-adherence to the treatment regimen, including inadequate skin care techniques, contribute to the development of severe or refractory atopic dermatitis. Persistent eczematous lesions may be a result of exacerbating environmental factors, secondary infection, and hypersensitivity reactions to topical treatments or other allergens. Wet-wrap treatment with topical corticosteroids, narrow-band UVB phototherapy and systemic immunosuppressive drugs, such as cyclosporine A, methotrexate, mycophenolate mofetil and azathioprine, are recommended for the treatment of severe atopic dermatitis in children. However, there are no evidence-based guidelines for using these agents. Systemic corticosteroids should be avoided, but they can be used for a short period of time for the immediate relief of acute flares before introducing other therapies. Patients need a holistic approach including education and modern biopsychosocial techniques. Paediatric studies are currently under way to test the safety and tolerability of dupilumab which was approved by the US Food and Drug Administration in 2017 for the treatment of adults with moderate-to-severe atopic dermatitis.

Keywords: atopic dermatitis, adherence, therapy, immunosuppressive drugs

Streszczenie

Atopowe zapalenie skóry jest najczęstszym schorzeniem skóry rozpoznawanym we wczesnym dzieciństwie. U części dzieci objawy nie łagodnieją w miarę dorastania, lecz rozwija się atopowe zapalenie skóry o ciężkim przebiegu z uogólnionymi zmianami skórnymi, uporczywym świądem; choroba przyczynia się do cierpienia fizycznego i psychicznego, znacząco pogarszając jakość życia. Sygnałem do intensyfikacji terapii powinna być oporność na leczenie zewnętrzne i wielolekowość. Jednak w wielu przypadkach przyczyną ciężkiego i opornego na terapię atopowego zapalenia skóry jest niedostosowanie się do zaleceń terapeutycznych (*non-adherence*), w tym nieprawidłowa pielęgnacja skóry. Uporczywość zmian wypryskowych może być także skutkiem narażenia na środowiskowe czynniki drażniące, wtórnej infekcji, reakcji nadwrażliwości na leki zewnętrzne czy inne alergeny. W ciężkim atopowym zapaleniu skóry u dzieci zaleca się stosowanie mokrych opatrunków z kortykosteroidami miejscowymi, fototerapii światłem wąskopasmowym UVB, ogólnoustrojowych leków immunosupresyjnych, takich jak cyklosporyna A, metotreksat, mykofenolan mofetylu i azatiopryna. Brak jest wytycznych opartych na dowodach naukowych dotyczących leczenia tymi lekami. Należy unikać kortykosteroidów ogólnych, ale można zastosować krótkotrwałą terapię w celu szybkiego opanowania dużych zaostrzeń przed wdrożeniem innych form leczenia. Pacjenci wymagają podejścia holistycznego, obejmującego edukację i stosowanie nowoczesnych technik biopsychospołecznych. W populacji pediatrycznej obecnie prowadzone są badania kliniczne oceniające bezpieczeństwo i tolerancję dupilumabu, leku biologicznego zaaprobowanego w 2017 roku przez amerykańską Agencję ds. Żywności i Leków w leczeniu umiarkowanego i ciężkiego atopowego zapalenia skóry u dorosłych.

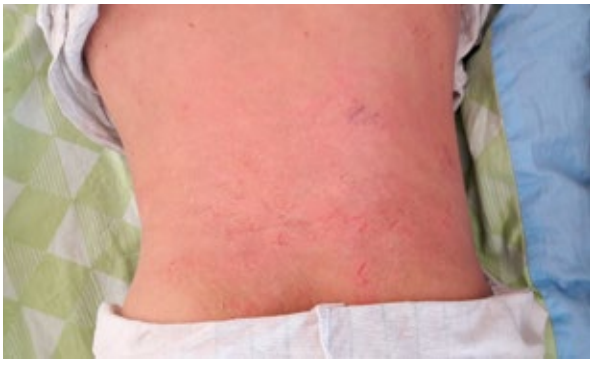
Słowa kluczowe: atopowe zapalenie skóry, *adherence*, terapia, leki immunosupresyjne

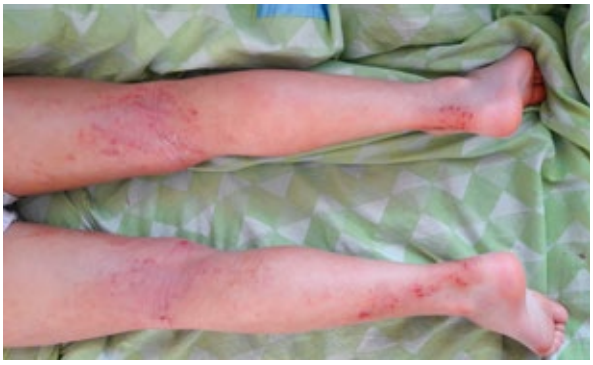
INTRODUCTION

Atopic dermatitis (AD) is the most widespread skin condition affecting young children. The prevalence of the disease during the first decade of life is estimated at 10–20%. The onset of the disorder in infants is most commonly marked with the development of extremely itchy, erythematous-desquamative skin lesions located on the face, arms, lower legs, scalp, and in the diaper area. Skin lesions exacerbate easily under the influence of external conditions (changes in air humidity and weather), some skin care agents or stress. They result from immune disorders and a defect in skin barrier function[1]. AD is a chronic skin condition which continues for many years. Even though about half of affected children show improvement as they grow older, in some patients refractory cutaneous lesions without a tendency for improvement persist and may evolve into severe AD (Figs. 1, 2), and lead to an increased risk of food allergy, asthma and allergic rhinitis[2]. AD can be a serious problem during adolescence and adulthood (with 2–8% of adults affected by the condition). It is estimated that moderate-to-severe AD occurs in up to 25% of all patients with AD, including approximately 2/3 adults and 1/3 children, with the rate rising with age[3]. There is, as yet, no commonly recognised definition of AD severity. Clinical studies are based on a variety of measures which take into account the severity of cutaneous lesions, their location and extensiveness (body surface area, BSA), coexisting symptoms, and the effect of the disease on the quality of life (QoL) (Tab. 1)[4]. In daily clinical practice the severity of AD is rarely assessed using validated tools, which makes it difficult to monitor the results of treatment and disease progression. The goals of therapeutic management are to control the flares of AD and maintain patient improvement in a long-term perspective, with an attempt to limit as far as possible the number of relapses. Basic management includes education, prophylaxis, appropriate skin cleansing regimes and emollient therapy. Medium-potency topical glucocorticoids (GCs) and calcineurin inhibitors are indicated for the treatment of exacerbations and as proactive (maintenance) therapy in cases of AD characterized by recurrent inflammatory lesions. According to guidelines issued by scientific societies, severe AD in children should be treated with wet-wrap therapy, phototherapy and systemic immunosuppressive therapy (Fig. 3)[5–8]. Indications to intensify treatment include resistance to topical therapy and multidrug resistance. Most available guidelines fail to define precisely the period required to evaluate the efficacy of topical treatment. A change of therapy should be considered if no improvement is observed in response to a standard treatment regimen, for example a 14-day course of medium-potency topical GCs. Other factors potentially contributing to the persistence of inflammatory lesions and pruritus should also be taken into account.

- Scoring Atopic Dermatitis Index (SCORAD)
- Eczema Area and Severity Index (EASI)
- Investigators' Global Assessment (IGA)
- Patient-Oriented Eczema Measure (POEM)
- Six Area, Six Sign Atopic Dermatitis (SASSAD)
- Three Item Severity (TIS)
- Simple Scoring System (SSS)
- Basic Clinical Scoring System (BCSS)
- Patient-Oriented Scoring of Atopic Dermatitis (PO-SCORAD)
- Self-Administered Eczema Area and Severity Index (SA-EASI)
- Index for Atopic Dermatitis (W-AZS)
- Atopic Dermatitis Antecubital Severity (ADAS)
- Objective Severity Assessment of Atopic Dermatitis (OSAAD)
- Visual Analogue Scale (VAS)

Tab. 1. Methods to assess the severity of AD[4]





Figs. 1, 2. Severe skin inflammation secondary to AD; visible lichenification and excoriations

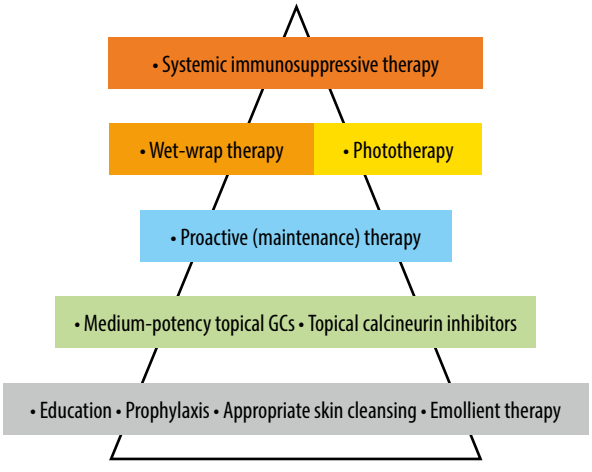


Fig. 3. Algorithm for the management of AD in children

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CAUSES OF THERAPEUTIC FAILURE

A prevalent problem and the main cause of poor therapeutic outcomes in AD is failure to comply with the prescribed treatment regimen (non-adherence). Based on the literature reports the level of adherence during 5-day therapy was 40%, and during 8-week therapy – 32%[9]. The problem of non-adherence was also demonstrated in a study in which 20% of patients with moderate-to-severe AD not responding to treatment with topical GCs showed improvement after the therapy was administered on an inpatient basis[10]. Guidelines drawn up by scientific societies highlight the need to educate patients and their carers[5–8]. A positive effect of educational programmes on long-term reduction in the severity of AD and QoL improvement in children has been shown in a number of studies[11]. Both AD patients and their families may benefit from the support provided by nurses, physicians and psychologists in therapeutic education centres for atopy ("atopy schools"), however, these facilities are available only in larger hospitals. Regardless of the severity of the disease a significant role in all patients is attributed to non-pharmacological management methods including appropriately performed baths, application of emollients, and avoidance of irritants and allergens. The physician's tasks include an evaluation of the severity of pruritus, sleep disorders, daily activities, role of stress and effects of AD on the QoL. A decrease in the QoL in children and caregivers correlates with the severity of disease symptoms[12]. In addition to pharmacological therapy, a necessary component of treatment in severe AD may be psychotherapy. It needs to be stressed that psychological interventions and stress relief techniques have a beneficial effect on the progress of therapy and improve adherence (Tab. 2)[13,14]. An improvement in adherence has been demonstrated in preliminary studies based on a mobile application which sends patients reminders and educational text messages (TMs)[15]. A significant role is also attributed to routine self-evaluation and monitoring of therapeutic effects by patients. A tool used for this purpose in clinical trials is POEM (Patient-Oriented Eczema Measure) recommended by the global initiative HOME (Harmonising Outcome Measures for Eczema)[16].

A decision to change therapy should also be preceded by ruling out potentially coexisting conditions (infections, food allergy) and obtaining assurance that the severe course of the disease is unambiguously attributable to AD. Children with severe AD are at an elevated risk of developing skin infections. For example, they have a greater prevalence of staphylococcal infections and recurrent herpes simplex virus (HSV) infections. Extensive skin lesions referred to as *eczema herpeticum* may be overlooked and inadequately treated.

- Cognitive-behavioural therapy (CBT)
- Acceptance and commitment therapy (ACT)
- Parental education programmes
- Biofeedback
- Relaxation techniques including hypnosis and stress-relieving breathing techniques
- Group therapy for children

Tab. 2. Selected biopsychosocial techniques used in AD[13]

INDICATIONS TO INTENSIFY THERAPY

Therapy needs to be intensified only when AD symptoms are poorly or inadequately controlled, even though patients comply with appropriate skin care routines, use antiseptic treatment, and avoid allergens and irritants. More intensive treatment should be considered in patients with extremely itchy skin lesions persisting despite the application of topical corticosteroids, calcineurin inhibitors or crisaborole (a phosphodiesterase 4 inhibitor, currently unavailable in Poland) for at least 3 weeks. Other symptoms suggesting the need to introduce higher-line therapy include frequent skin infections, ocular complications, disturbances of sleep and daily activity, behavioural problems, and reduced QoL. The most common and most challenging problem is usually pruritus, which contributes to sleep disorders, depression and anxiety, and leads to feelings of anger, helplessness, reduced self-esteem, and concentration difficulties. Hydroxyzine and second-generation antihistamines are typically indicated, however, only limited data are available on the antipruritic efficacy of these agents in AD. Also, there is no sufficient evidence supporting the widespread use of antidepressants. Pavlis and Yosipovitch[17] report that cases of persistent nocturnal pruritus without severe eczematous lesions can be treated with mirtazapine at doses of 7.5–15 mg at night (lower than indicated for depression) as the first-line drug. Mirtazapine – an antagonist of noradrenergic, serotonergic and histaminergic H_1 receptors – is a drug approved for the treatment of depression in adult patients. The authors recommend the drug for the relief of pruritus secondary to AD in children over the age of 10. The most common side effects observed during therapy include increased appetite and weight gain. If treatment is unsuccessful, the authors recommend the addition of GABAergic drugs (gabapentin or pregabalin)[17].

WET-WRAP TREATMENT

A very effective therapeutic modality in children aged from 6 months to 10 years affected by more severe eczematous lesions is wet-wrap treatment (WWT). Literature reports suggest using WWT in combination with GCs or with emollients alone, which should be applied to the skin immediately after a bath[18]. In cases requiring acute intervention WWT should start with 3 treatments daily, and when improvement is noted, the frequency should be reduced. Wet wrap dressings should be applied for approximately 2 hours, however, they can also be left on the skin overnight. The removal of wet wraps should be followed by the application of an emollient to the entire body. The main barriers potentially preventing the widespread application

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of the method include discomfort and lack of patient acceptance. A key factor contributing to the success of treatment is education of children's caregivers. In order to simplify the procedure, reduce costs and time expenditures, wet undergarments are suggested instead of bandages. Potential adverse reactions include steroid-induced topical and systemic side effects, allergic reactions, skin maceration, folliculitis, impetigo and herpes. Failure to lubricate the skin properly after WWT removal may result in a more severe skin drying effect.

PHOTOTHERAPY

UV therapy can be administered to children at a minimum age of 8–12 years on account of the need to comply with specific therapeutic recommendations. The recommended method of choice is narrow band-UVB (NB-UVB; 311 nm)[5–8]. PUVA (psoralen + UVA) is not indicated because of an increased risk of neoplastic transformation, especially considering that there is no available evidence to support its superior efficacy in AD[19]. Usually, multiple irradiations are required to achieve improvement, which may be rather inconvenient, particularly in the context of low accessibility of phototherapy centres.

SYSTEMIC GCs AND IMMUNOSUPPRESSIVE THERAPY

Another recommended therapeutic line in AD is systemic immune suppressive therapy with cyclosporine A (CsA), methotrexate (MTX), azathioprine (AZA), mofetil mycophenolate (MMF), and systemic GCs[5–8]. Glucocorticoids have been used in the treatment of AD since the 1950s and remain the only systemic drugs approved in this indication for paediatric use by the US Food and Drug Administration (FDA). GCs may help to bring particularly severe flare-ups of AD under control, however, they should be used on a short-term basis, and GC treatment should be considered only where subsequent non-steroidal therapy is planned. Available guidelines for the treatment of AD advise against chronic and repeated use of systemic GCs on account of side effects and the rebound phenomenon. Consequently, despite the fact that no immunosuppressive agents are approved for the treatment of AD in children, the drugs are used fairly frequently as off-label use. However, most available reports are of isolated cases or series of patients, and retrospective studies. It is nevertheless assumed that despite differences in pathophysiology between adults and children the available therapies demonstrate similar efficacy[20]. The most commonly prescribed drug is CsA (approved for the therapy of severe AD in adults)[21]. Short-term therapy is usually sufficient in the treatment of children. The recommended initial dose is 5 mg/kg/day, and therapy should be continued for not longer than 6 months. The treatment can be repeated if a relapse occurs. Long-term therapy with lower doses of CsA is also considered safe in the paediatric population[22]. Adverse reactions include mainly gastrointestinal disorders and headaches. The risk of nephrotoxicity and arterial hypertension in children is lower than in adults. Infections during treatment are uncommon and require temporary discontinuation of CsA. Alternatively, severe AD in children may be treated with MTX. An observational study comparing CsA and MTX (3-month therapy) has shown both agents to have a similar safety and efficacy profile[23]. It is necessary to compare the two drugs in a randomised controlled study. To this end, the TREatment of severe Atopic eczema Trial (TREAT) has been scheduled in a group of 102 children aged 2–16 years[24]. The recommended dose of MTX in children is 0.2–0.7 mg/kg/week or depending on age: ≤5 years old – 7.5 mg/week, 6–10 years old – 10 mg/week, ≥11 years old – 15 mg/week. MTX-related adverse reactions are dose-dependent, and most commonly include nausea, oral ulcers, and a transient increase in liver enzyme levels. There have also been promising reports on successful outcomes in the treatment of severe paediatric AD with AZA or MMF. However, the therapeutic effect produced by these drugs is delayed for up to 12 weeks or more after the initiation of treatment, unlike CsA and MTX which are characterised by a rapid onset of action (2–6 weeks within the introduction of CsA therapy, slightly longer during MTX-based treatment). A comparison of MMF and AZA has shown MMF to be associated with fewer side effects[25]. MMF-based treatment of AD in children should start with the dose of 10–40 mg/kg/day, and the dose should be increased by 500 mg every 2–4 weeks. The therapeutic dose is 20–50 mg/kg/day or 600–1200 mg/m^2/day. Common adverse reactions include nausea, vomiting and gastric disorders. Prior to the initiation of AZA treatment in children, thiopurine methyltransferase (TPMT) activity should be assessed, and the dose of AZA should be adjusted to the established TPMT level: 2.5 mg/kg/day when TPMT is 15.1–26.4 U/mL, and 1 mg/kg/day when TPMT 6.3–15.1 U/mL. Patients with congenital TPMT deficiency may be affected by increased myelosuppression, and the drug should not be used if enzyme activity is lower than 6.3 U/mL. The most frequently observed side effects associated with AZA treatment include lymphopaenia, neutropaenia and elevated liver enzyme levels. In view of the lack of sufficient data there are no standardised guidelines for monitoring the safety of immunosuppressive drugs in children. Since therapy involves the potential risk of adverse reactions, prescribing drugs on an off-label basis in paediatric patients requires special caution and laboratory tests performed at an appropriate frequency. After achieving clinical response the dose of the drug should be reduced to the lowest effective dose or – if possible – the drug should be discontinued[26]. The discontinuation of immunosuppressive agents is recommended at least 2 weeks before the scheduled vaccination, and therapy should be initiated at least 4–6 weeks after vaccine administration.

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OTHER THERAPIES

The literature reports also describe a multitude of alternative therapies which can be used in more refractory cases of paediatric AD, including interferon-γ, intravenous immunoglobulins and various biologic drugs[21]. In 2017, the first biologic drug – dupilumab (a human monoclonal antibody inhibiting the function of both interleukin-4 and interleukin-13 receptors) was approved for the treatment of moderate-to-severe AD in adult patients. The safety profile of dupilumab has been found to be superior to conventional immunosuppressive drugs such as CsA or MTX[27–30]. The drug is currently being investigated in clinical trials evaluating its efficacy and safety in children aged ≥6 to <18 years (NCT02407756, NCT02612454) and ≥12 to <18 years (NCT03054428).

CONCLUSIONS

Severe AD in children remains a great therapeutic challenge, as the optimal therapeutic management has not been established. Patients require a holistic approach comprising education and modern biopsychosocial techniques. Further clinical studies of systemic drugs are needed in the paediatric population.

Conflict of interest

The authors do not declare any financial or personal links with other persons or organisations that might adversely affect the content of the publication or claim any right to the publication.

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