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Management of Atopic Dermatitis in Children: A Pediatrician State of the Art

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Abstract

Atopic dermatitis (AD) is one of the most common skin conditions in children and adolescents. This disease is characterized by acute and chronic lesions. Acute lesions can occur at any age and have a recurring character. Localization of acute lesions is a characteristic for a certain age of the child. Chronic lesions are present after the second year of life and characterized by pruritus and lichenification. Ichthyosis and xerosis are also characteristics of chronic lesions. The authors represent two hypotheses about pathophysiology of atopic dermatitis: “inside-out” hypothesis suggests that pathophysiological process is the result of an inflammatory response, while the “outside-inside” hypothesis suggests that changes of the epidermal barrier are responsible for the process in lesions in atopic dermatitis. There is no gold standard, clinical or laboratory, for the diagnosis of atopic dermatitis. The diagnosis should be based on anamnesis, clinical features and laboratory results. The therapeutic approach includes general and specific measures. General measures including topical moisturizers, bathing and bathing practices and wet-wrap therapy. Specific measures include topical corticosteroids and topical calcineurin inhibitors. Systemic immunosuppressant agents and phototherapy are a second-line treatment and used when the atopic dermatitis is not controlled. These patients must be treated by a dermatologist or pediatricians.

Keywords: atopic dermatitis, children, corticosteroids, emollients, topical moisturizers, skin care, eczema

1. Introduction

Atopic dermatitis (AD) is one of the most common skin conditions in children and adolescents. This disease is characterized by chronic eczematous and itchy lesions with typical

distributions, and relapsing [1, 2]. Atopic dermatitis has a tendency to spontaneous withdrawal, so the incidence of this disease diminished with increasing age. The basic pathophysiological features of this disease are an epidermal barrier dysfunction and an altered immunoallergic profile [3]. Firsthand contact due to their symptoms, these patients have with the primary healthcare team, most often pediatricians and general practitioners. The diagnosis of atopic dermatitis can be defined with standardized clinical criteria and scoring systems [4]. It is important to notice that this disorder can be a major therapeutic challenge for the physician and patient, especially intense and incessant itching. The therapeutic approach includes general and specific measures. General measures include topical moisturizers, bathing and bathing practices and wet-wrap therapy. Children more likely have food-induced exacerbations. If a specific food is suspected to cause an exacerbation of atopic dermatitis, certain dietary interventions can be used. Specific measures include topical corticosteroids and topical calcineurin inhibitors. Systemic immunosuppressant agents and phototherapy are a second-line treatment and used when the atopic dermatitis is not controlled. These patients must be treated by a dermatologist or pediatricians.

2. Pathophysiology of atopic dermatitis

The lack of filaggrin plays an important role in the pathophysiology of atopic dermatitis. The large *polyprotein profilaggrin degraded* to produce monomeric *filaggrin* in the stratum corneum of the skin. Profilaggrin and filaggrin contribute to the structure of the epidermis and the functional barrier (profilaggrin and filaggrin each make different contributions to epidermal structure and barrier function) [5].

Filaggrins with intermediate filaments form solid connections in cornified layers contributing to formation of a water loss barrier, maintaining epidermal hydration and form so-called “natural moisturizing factor” [5, 6]. Beside damaged skin barrier, in the pathophysiology of atopic dermatitis, numerous cells of innate and adaptive immune cells are involved. Keratinocytes in typical lesions release a large amount of several different proinflammatory cytokines, chemokines, and high levels of TSLP (thymic stromal lipoprotein) which promote Th2 immune response [7]. The Th2 immune response releases a large number of cytokines (IL-4, IL-13, IL-25, IL-33), which cause keratinocyte dysfunction and secondary changes in epidermal barrier. The authors state that Th2 immune response contributes to downregulation of filaggrin expression in differentiated keratinocytes [8]. Beside the filaggrin, Th2 cytokines (IL-17, IL-22, IL-25 and IL-31) significantly downregulate the expression of other proteins of stratum corneum like loricrin and involucrin [6, 8, 9].

There is an increased number of inflammatory cells such as T lymphocytes, dendritic cells, macrophages, mast cells and eosinophils in lesions characteristic for atopic dermatitis [7, 10].

Acute lesions in atopic dermatitis have a significantly higher number of Th2 cytokines (IL-4, IL-5, IL-13), while chronic lesions contain IL-4, IL-13, and numerous interferons of Th1 cells [11]. That is so-called biphasic Th cell response.

Environmental factors such as skin irritation, mechanical damage, low skin moisture and colonizing microorganisms also contribute to filaggrin expression changes [10].

Keratinocytes in patients with atopic dermatitis show increased IFN-induced apoptosis [10]. Also, in patients with atopic dermatitis, smaller keratinocytes in lesions are verified.

Inflammatory response leads to variations in epidermal thickness and the size of corneocytes in stratum corneum in region specific flares and atopic dermatitis [9].

The authors represent two hypotheses about pathophysiology of atopic dermatitis: “inside-out” hypothesis suggests that pathophysiological process is the result of an inflammatory response, while the “outside-inside” hypothesis suggests that changes of the epidermal barrier are responsible for the process in lesions in atopic dermatitis [9].

3. Clinical features

The two basic characteristics of atopic dermatitis are [4]:

- specific localization of skin lesions with areas of the clean skin and
- chronic recurring character, with periods when there is no skin lesions at all and with periods of exacerbation of skin symptoms

First, clinical symptoms of atopic dermatitis occur during the first 6 months of life in 45% of children, during the first year of life in 60%, and before the age of 5 years in at least 85% of affected individuals [4]. But it never occurs in the first week of life [12]. The clinical pattern of atopic dermatitis has a characteristic age-dependent distribution and is commonly associated with elevated IgE, peripheral eosinophilia, *Staphylococcus aureus* colonization and comorbidity with other allergic diseases [4, 12].

Atopic dermatitis as a chronic recurrent disease is characterized by acute and chronic lesions. Acute lesions predominantly occur in infants, while chronic lesions are characteristic of the later age [13, 14]. Acute lesions are characterized by erythematous papules or papulovesicles with oozing, as well as plaque and dry skin. Patients with atopic dermatitis commonly have different intensity of itch.

Acute lesions can occur at any age and have a recurring character. Localization of acute lesions is characteristic for a certain age of the child [12].

Chronic lesions are present after the second year of life and characterized by pruritus and lichenification. Ichthyosis and xerosis are also characteristics of chronic lesions [1, 4, 12].

Pruritus is a typical hallmark in all stages, except during the first weeks of life. Itching itself has different intensity and accompanied by excoriations and fibrotic nodules [1, 4].

Atopic dermatitis can cover a wide spectrum in terms of severity, ranging from very mild to very severe phenotypes. For severity assessment of atopic dermatitis, a diagnostic scoring system such as SCORAD or ECZEMA AREA AND SEVERITY INDEX SCORES is often used [1, 4].

3.1. Atopic dermatitis clinical phenotypes

Atopic dermatitis phenotypes in childhood can be divided into two groups: IgE associated and non-IgE associated atopic dermatitis. Group of children with IgE associated atopic dermatitis can be with or without another allergic diseases, especially with allergic respiratory diseases [13, 14]. Clinical phenotypes of atopic dermatitis define according to [2, 12–14].

- A. Age-related clinical pictures with age off onset
- B. Diseases severity
- C. Non-IgE and IgE associated form

Amat et al. in their ORCA cohort study defined three phenotypes of early onset atopic dermatitis: infant with moderate atopic dermatitis severity and low sensitization, infant with a higher atopic dermatitis severity and frequent multiple sensitization and third phenotype children with moderate atopic dermatitis severity and moderate sensitization with parental familial history of asthma [15]. This phenotypic classification was used only for the epidemiological study, while its use was not verified for clinical practice.

3.2. Infantile atopic dermatitis (under 2 years of age)

First symptoms of atopic dermatitis never appear in first 2 weeks of life. First symptoms commonly appear at the age of 3 months [1, 2, 12, 16]. Typical localization of infantile atopic dermatitis is cheeks with characteristic dry skin, erythema and papules with oozing. Lesions can form large plaques with oozing and crusts. Lesions can appear on the forehead, scalp, neck and extensor surface of the extremities, rarely on the trunk. The diaper area is usually spared. Lesions in this phase may be mild, which make it difficult to diagnose. When there are no erythematous lesions in typical places, the skin is dry, rough, and desquamated [1, 2, 16].

A substantial portion of patients can go into complete remission before 2 years of age [16].

3.3. Childhood atopic dermatitis (age 2–12 years)

Chronic skin lesions with lichenification and exacerbation of acute lesions are characteristic for atopic dermatitis in this age. Children have lichenified papules and plaques involving the hands, feet, wrists, ankles, periorificial areas on the head, antecubital and popliteal regions. Xerosis becomes dominant at this stage. These patients have a high risk of chronic illness [16].

3.4. Atopic dermatitis in adolescents (age 12–18 years)

In this period of life, the lesions are more fixed to classical areas such as the head, neck, and flexural areas. Lesions in the form of chronic dermatitis can also be seen on the hands [16].

3.5. Stratification based on disease severity

Atopic dermatitis covers a wide spectrum of clinical phenotypes. Most authors classify atopic dermatitis according to the severity of the clinical features into four groups: dry skin only, mild, moderate and severe atopic dermatitis. It is the best to use a valid scoring system, such

as SCORAD (Scoring atopic dermatitis) or Eczema Area and Severity Index Scores, for assessing the severity of atopic dermatitis [16]. The most commonly used scoring system in clinical practice is SCORAD, for which there is an application for Apple, Mac, PC and android system. This scoring system was created and validated by the European Task Force on Atopic Dermatitis (ETFAD) [1, 2, 16].

4. Diagnosis and trigger factors

4.1. Diagnostic criteria

It is not possible to define the gold standard for diagnosis of atopic dermatitis due to its heterogeneity. Diagnosis of atopic dermatitis cannot be set without skin examination [17]. Some diagnostic criteria developed for use in hospital, while others developed for community settings [17]. The ISAAC proposed the full questionnaire-based protocol where a positive response to all three questions is required for the diagnosis of atopic dermatitis. These ISAAC diagnostic criteria are not for daily use, but for epidemiological studies became the gold standard.

The standard diagnostic tool in a community setting is the Hanifin and Rajka criteria [18] (Figure 1). Their criteria are adequate for physicians to make a diagnosis of atopic dermatitis. The diagnosis of atopic dermatitis by Hanifin and Rajka criteria requires the existence at least three major characteristics and at least three minor characteristics [1, 12, 18]. Some other atopic dermatitis diagnostic criteria are more practical for use in a hospital setting such as UK criteria and American Academy of Dermatology (AAD) criteria.

Figure 1. Diagnostic criteria by Hanifin and Rajka [18].

It is very important to use well-defined diagnostic criteria for the diagnosis of atopic dermatitis, especially for those patients who lack the typical phenotype of the disease [4]. Using visible eczema as the only criterion may lead to overdiagnosis of the disease [4].

The following diagnostic algorithm should be applied:

1. Clinical diagnosis based on well-defined diagnostic criteria
2. Patient medical history
3. Positive family history of atopic diseases
4. Blood tests (total IgE, specific IgE)
5. Specific skin test (prick test, prick to prick test, patch test)
6. Exacerbating factors or common triggers in atopic dermatitis
7. Challenge tests

Some facts about the diagnosis of atopic dermatitis should be emphasized:

- the atopy patch test is primarily a way to investigate the mechanisms of eczema
- sensitization can be detected by prick or patch tests or by measuring specific IgE antibodies in the blood
- the decision to make a challenge test should be individualized for each patient
- during the challenge test, children should be supervised for 48 h. In the case of a negative test, it is necessary to examine the child's skin after 24 h [12].

There is no gold standard, clinical or laboratory, for the diagnosis of atopic dermatitis. Diagnosis should be based on anamnesis, clinical features and laboratory results [1, 2, 12, 16].

Although Hanifin and Rajka developed the gold criteria for the clinical diagnosis of atopic dermatitis, in clinical practice, physician also needs to use a valid scoring system to define the severity of clinical features [1].

4.2. Common triggers

Atopic dermatitis exacerbations can be triggered by allergens that are inhaled, ingested or in direct contact with the skin. Most commonly triggers are sweat, contact allergens, aeroallergens and microbial agents.

Sensitization to food allergens (cow's milk and hen's eggs) is associated with infantile atopic dermatitis and related to disease severity [4]. Exposure to aeroallergens (pets, mites, and pollen) has been clearly shown to increase the risk factors for atopic dermatitis and atopic dermatitis severity [1, 4].

Children with atopic dermatitis are at high risk of allergic asthma and allergic rhinitis [4, 12].

4.3. Differential diagnosis

Differential diagnosis of atopic dermatitis is shown in **Figure 2**.

Figure 2. Differential diagnosis of atopic dermatitis [1, 4, 19].

5. Management

The management of atopic dermatitis presents a clinical challenge [4, 12, 20].

Some studies emphasize that the breastfeeding at least 4–6 months reduced the incidence of atopic dermatitis in infants, but this effect is most probably transient and last to the 3rd year of life [4]. Some studies on high-risk infants population demonstrate that using different partially and extensively hydrolyzed casein formulas for the first 6 months of life has the capacity to reduce atopic dermatitis by 50% in the first year of life [21].

Management of atopic dermatitis should be adapted to the severity of the clinical manifestation of atopic dermatitis [1]. Therapeutic modalities include basic treatment of the skin, topical and systemic drug application.

5.1. General measures

Basic treatment [1, 22, 23] means to use a skin hydration on a regular base, avoided hot water during showering or bathing, and contact with water should be minimized. Synthetic or wool material clothes should be avoided. Also, detergents and soaps designed for sensitive skin should be used. Further treatment should be adapted to the disease severity. It is very important to educate child's parent/guardian about atopic dermatitis, and treatment challenges.

Topical treatment [1, 22] includes emollients, topical glucocorticosteroids, topical antimicrobial therapy, topical calcineurin inhibitors, wet-wrap therapy. A combination of two different topical agents can be used.

Systemic treatment [22] needs to be considered if topical treatment cannot control the severity of atopic dermatitis. Systemic treatment includes antihistamines, antimicrobial treatment, systemic corticosteroids, Cyclosporin A, Azathioprine, and so on. In a case where the physician has a negative or poor therapeutic response, another specialist (dermatologist, pediatrician, etc.) should be involved in the diagnostic and treatment management to get optimal results.

Also, in some cases, hospitalization in centers with a multidisciplinary team approach might be the best option for the patient.

People with atopic dermatitis should not work in the area with high humidity, places where they need to wash their hands often or use stronger disinfectants/irritants [1, 22].

5.1.1. Hydration, topical moisturizers and emollients

Xerose is a leading clinical sign of atopic dermatitis. Emollient creams represent the basic therapy of atopic dermatitis [23]. The basic mechanism of their effect is to maintain satisfactory skin hydration, preserve the skin barrier and reduce transdermal loss of water. It is recommended that they can be used daily. They can be different in composition: lotions, oils, creams or gels. Studies have shown that one form of emollient has no advantage over others [22, 23]. Oily preparations usually do not contain preservatives, which has advantages in terms of adverse effects. Lotions contain a high concentration of water, which speeds up their evaporation from the skin [22, 23].

The choice of a moisture can be left to the patient, which may be associated with increased *adherence* to recommended *therapy* [22, 24]. Selected moistures should be effective, safe, without additional additives and perfumes. The efficiency of the selected moisture should be reviewed frequently. It can be used 2–4 times a day, which depends on the frequency of bathing/showering. It is recommended to apply immediately after bathing/showering, plus 2–3 a day [23].

5.1.2. Effectiveness and application technique

Original packaging emollients should be carefully stored because of possible contamination with bacteria. The most practical use is the pump-dispenser because there is the smallest risk for contamination [1, 23].

There is no accord in order to use the determined quantity of the applied layer and the surface to be covered with the emollients (the whole body surface or only the affected areas of the skin). The rule of fingertip unit is not generally accepted for them as for corticosteroids.

In principle, in the treatment of atopic dermatitis, a moisturizer or skin care product should be applied to a mild eczematous lesion or dry skin on the facial surface without applying any topical steroids. It is reported that twice a day, external application of a moisturizer significantly inhibits the relapse of inflammation of atopic dermatitis compared with the untreated group [1].

5.1.3. Wet-wrap therapy

Wet-wrap therapy is a method for administering topical corticosteroids in order to increase their absorption [1, 2]. It can be used on the recommendation of a specialist pediatrician or dermatologist. It should be applied for a short period of time (7–14 days), once daily at exclusively restricted area in children with severe atopic dermatitis who did not have an adequate therapeutic response to conventional therapy [22].

In wet-wrap therapy, it is recommended to use low potency and extremely mild corticosteroid preparations [19, 22]. Some authors recommend 5–10% dilution of potency topical corticosteroid preparation.

The application technique: a topical corticosteroid is applied to the affected skin, which then covers with a wet layer of tubular bandages, a gauze or a cotton suit, then placed a second dry layer. The recommended duration of a wet-wrap therapy is 12 h, so it is better to apply it overnight [2].

5.1.4. Dietary interventions

Recent studies did not show relation between food allergies and *outbreaks* or exacerbations in atopic dermatitis in children. If parents or a child notice that child's symptoms of atopic dermatitis *aggravated by eating some foods*, a provocation test for that food should be considered. Studies show that this deficient nutrition did not have a positive therapeutic effect on atopic dermatitis in children [24].

What is certainly recommended for infants with atopic dermatitis is exclusive breastfeeding and later transitioning to *solids foods* [1, 24].

5.2. Topical corticosteroids

Topical corticosteroids represent the basic antiinflammatory, immunosuppressive and anti-proliferative therapy in atopic dermatitis. Topical corticosteroids are categorized into *four groups* based on their potency (**Table 1**) [1, 2, 22, 24]. The outbreak of topical corticosteroid therapy should be based on the severity of the clinical picture [1]. For mild atopic dermatitis, we use low potency topical corticosteroid preparations, for severe atopic dermatitis we use high potency topical corticosteroids [22].

<div>Ultra high potency topical corticosteroids</div> <div><ul style="list-style-type: none">•Group I•Clobetasol propionate cream (0.05%)•Diflorasone diacetate ointment (0.05%)</div>	<div>Moderate potency topical corticosteroids</div> <div><ul style="list-style-type: none">•Group IV•Desoximetasone cream (0.05%)•Fluocinonide acetonide ointment (0.025%)•Hydrocortisone valerate ointment (0.2%)•Triamcinolone acetonide cream (0.1%)•Group V•Betamethasone dipropionate lotion (0.02%)•Betamethasone valerate cream (0.1%)•Fluocinonide acetonide cream (0.025%)•Hydrocortisone butyrate cream (0.1%)•Hydrocortisone valerate cream (0.2%)•Triamcinolone acetonide lotion (0.1%)</div>
<div>High potency topical corticosteroids</div> <div><ul style="list-style-type: none">•Group II•Amcinonide ointment (0.1%)•Betamethasone dipropionate ointment (0.05%)•Desoximetasone (cream or ointment) (0.025%)•Fluocinonide (cream, ointment, or gel) (0.05%)•Halcinonide cream (0.1%)•Group III•Betamethasone dipropionate cream (0.05%)•Betamethasone valerate ointment (0.1%)•Diflorasone diacetate cream (0.05%)•Triamcinolone acetonide ointment (0.1%)</div>	<div>Low potency topical corticosteroids</div> <div><ul style="list-style-type: none">•Group VI•Betamethasone valerate lotion (0.05%)•Desonide cream (0.05%)•Fluocinolone acetonide solution (0.01%)•Group VII•Dexamethasone sodium phosphate cream (0.1%)•Hydrocortisone acetate cream (1%)•Methylprednisolone acetate cream (0.25%)</div>

Table 1. Topical corticosteroids potency classification [1, 2].

Also, for areas such as face, neck, axillary and groin, it should be used a mild topical corticosteroid preparations. In these areas, a moderate or potent topical corticosteroid should not be used for more than 3–5 days [24]. Topical corticosteroids can be used once or twice a day. Start the therapy with a single daily application, and if there is no adequate therapeutic response, introduce twice daily application [1, 22, 24]. This simple therapy mode will increase patients adherence to recommended therapy and reduce the fear of side effects of topical corticosteroids by parents and GPs.

The application technique: the topical corticosteroid preparations dosage according to the finger type unit (FTU) rule. One FTU is the amount of a cream which can be applied from the distal skin-crease to the tip of the index finger of an adult and represents approximately 0.5 g. This amount of cream is enough to cover the surface of *two hand* areas (hand area is surface you are *covering with* hand palm down with your fingers closed together) [2, 22]. Topical corticosteroids should be applied half an hour before or after emollient creams.

Keep in mind that children have a proportionally larger body surface compared to body weight, which results in a higher absorption of topical corticosteroids for the same cream amount compared to adults [4, 24].

There are two different approaches to choose a topical corticosteroids, one recommending to start therapy with low potency TCS then use moderate potency TCS (“set up approach”), while others recommend reverse access from moderate to low potency topical corticosteroids (“set down approach”). These recommendations are primarily related to mild and moderate atopic dermatitis [1, 2, 24].

There are two forms of TCS therapy for atopic dermatitis: proactive and reactive therapy [1]. Proactive therapy is defined as using of topical corticosteroids in the acute phase, with

intermittent use of topical corticosteroids and a moisturizer during the remission period. Reactive therapy means the using of topical corticosteroids only in case of exacerbation of symptoms, and using only the moisture in the remission phase [1].

5.2.1. Potency and adverse effects

Potency and adverse effects are described in **Tables 1** and **2**.

5.2.2. Effectiveness and application technique

A fingertip unit (FTU) is the *amount* of topical steroid that is *squeezed* out from a standard tube along an adult's *fingertip*. It should be enough to treat an area of skin double the size of the flat of your hand with your fingers together. The recommended dosage will depend on what part of the body is being treated [2, 22, 24].

For adults, the recommended FTUs to be applied in one single dose are, for example, 1 FTU for hands, elbows and knees, 2.5 FTUs for the face and neck, 3 FTUs for the scalp, or 4 FTUs for a hand and arm together, or the buttocks [25].

The following dosages are recommended for a child aged 3–6 months: entire face and neck 1 FTU, an entire arm and hand 1 FTU, an entire leg and foot 1.5 FTUs, the entire front of chest and tummy (abdomen) 1 FTU, and the entire back including buttocks 1.5 FTUs [25].

For a child aged 1–2 years, entire face and neck 1.5 FTUs, an entire arm and hand 1.5 FTUs, an entire leg and foot 2 FTUs, the entire front of chest and abdomen 2 FTUs, the entire back including buttocks 3 FTUs [25].

For a child aged 3–5 years, entire face and neck 1.5 FTUs, an entire arm and hand 2 FTUs, an entire leg and foot 3 FTUs, the entire front of chest and abdomen 3 FTUs, the entire back including buttocks 3.5 FTUs [25].

-
- Acne-like rash, including folliculitis and rosacea
 - Eyelid and perioral dermatitides
 - Epidermal-dermal atrophy, dermal vulnerability (most likely to occur on the geriatric or sunlight damaged skin, intertriginous zone, or facial surface)
 - Delay in wound healing
 - Gluteal granuloma
 - Purpura
 - Telangiectasia and erythema
 - Skin striae
 - Depigmentation
 - Hypertrichosis
 - Hidden or exacerbated dermatophyte infection
 - Secondary infection or exacerbation of existing infection
 - Contact dermatitis
 - May be caused by an ingredient of the preservative or other base material.
 - May be caused by a corticosteroid molecule. In this case, the skin may crossreact with a corticosteroid molecule of similar structure.
 - Others
-

Table 2. Topical corticosteroids adverse effects [1].

For older children aged 6–10 years, entire face and neck 2 FTUs, an entire arm and hand 2.5 FTUs, an entire leg and foot 4.5 FTUs, the entire front of chest and abdomen 3.5 FTUs, and the entire back including buttocks 5 FTUs [25].

5.3. Topical calcineurin inhibitors

Topical calcineurin inhibitors are non-steroidal immunomodulatory agents. The use of topical calcineurin inhibitors preparations *should be under supervision by specialist dermatologists or pediatricians* and for short time of period.

There are three preparations available [1, 22, 24]:

- (1) 0.03% tacrolimus ointment,
- (2) 0.1% tacrolimus ointment and
- (3) 1% pimecrolimus cream.

Tacrolimus ointment 0.03% is approved for use in children over 2 years, while at a higher concentration (0.1%), it can be used only in children over 16 years of age [24]. Evidence from clinical trials supports the safe use of topical tacrolimus 0.03% in infants and younger children [22]. These drugs presents the second line of therapy, and only in case of acute exacerbation that do not respond to TCS.

Their use is recommended for the acute phase of moderate or severe atopic dermatitis in sensitive areas of the skin (e.g., the face, the folds) and in areas where steroid-induced atrophy is present [1, 24]. Numerous studies show that different combinations of TCI and TCS given together have sometimes a better effect than individual treatment [22, 24]. Some combinations did not show an expected effect than single administration. The combination of preparations should be personalized for each individual patient [24]. The TCS recommended to use first, and in inadequate response to therapy switched to low potent TCS with TCI.

The application technique: an intermittent application 2–3 times a week according to the recommendation of a specialist dermatologist or pediatrician is recommended.

Side effects: the most common side effect of TCI is a transient burning that passes after several days of use [1, 22, 24]. These preparations cannot be used on the skin with signs of infection and uneroded surface.

5.4. Antimicrobial treatments

Regular administration of systemic or topical antibiotics is not recommended in patients with atopic dermatitis [2, 22, 24]. In patients with atopic dermatitis, affected skin is usually colonized with *Staphylococcus aureus* [1, 2]. Previous studies show that there is no benefit from using topical antibiotics, antiseptics, antibacterial soaps or antibacterial bath additives [22, 24]. Also, the use of these agents can cause contact dermatitis or skin colonization with multiresistant strains of bacteria. In children aged 6 months to 17 years with moderate/severe atopic dermatitis and secondary *S. aureus* infection, the use of diluted bleach baths twice weekly with

administration of intranasal mupirocin twice daily (5 days per month) is more affected. This treatment should be repeated for 3 months [1, 2, 22, 24].

In children with frequent skin infections with *S. aureus*, a nasopharyngeal *culture test for whole family* should be done due to frequent intranasal colonization with this bacterium. It should be noted that the regular use of moisturizer and TCS significantly reduces skin colonization with *S. aureus* [22–24].

Eczema herpeticum is a potentially life-threatening infection in children with atopic dermatitis. Herpes infection should always be considered in patients with painful erosions and vesicles. In these patients, systemic antiviral therapy and supportive therapies are required [1, 2].

5.5. Systemic anti-inflammatory therapy

Oral and injectable *systemic* corticosteroids are not recommended for long-term treatment in children with atopic dermatitis because of the possible side effects [1, 2, 22]. But their use as short-term therapy is effective to interrupt acute exacerbation in children with severe atopic dermatitis [22, 24]. Duration of these intermittent therapies should be between 3 days and 3 weeks.

Beclomethasone dipropionate and Flunisolide should be limited for treatment of severe atopic dermatitis in children with atopic dermatitis refractory to standard therapies [19, 20, 26].

Immunosuppressants, such as Cyclosporine A (6–8 weeks), Methotrexate, and Azathioprine, could be used in children older than 16 years with severe atopic dermatitis refractory to standard therapies [1, 20, 24]. Only Cyclosporine A is licensed for use in clinical practice for the treatment of atopic dermatitis. Prescriptions and using of systemic immunosuppressive therapy should be supervised by a specialist pediatrician [1, 20, 22]. Recommendations for the use of these drugs are short durations of therapy and severe atopic dermatitis refractory to standard therapies. Systemic side effects always should be kept in mind.

5.6. Phototherapy

Phototherapy is a second-line therapy for severe atopic dermatitis, and administration should be supervised by a dermatologist [2, 24].

It represents the use of ultraviolet light (UVA or UVB). In atopic dermatitis, UVB narrowband and long-wave UVA are used. The phototherapy is usually applied in elderly children with chronic atopic dermatitis or severe atopic dermatitis or intractable severe atopic dermatitis.

5.7. Antihistamines

The use of antihistamines can be considered in older children with acute flares where there is significant sleep disturbance [24]. Recent studies show that administration of fexofenadine hydrochloride has effects in the treatment of itch and nocturnal pruritus. Application should be limited to 1 week [22, 24].

The use of oral antihistamines is not recommended in the treatment of atopic dermatitis [2]. It is recommended to use a more potent TCS in children with itch or nocturnal pruritus in a short period of time [1, 2, 22].

5.8. Reasons for treatment failure

There are many reasons for treatment failure, most commonly are presented below [1, 27–30].

5.8.1. *Incorrect diagnosis*

Many skin conditions can present with eczema and make confusion in diagnosis, such as psoriasis, skin infection and impetigo, fungal skin infections, seborrheic dermatitis, drug reactions, skin T cell lymphoma, and keratosis pilaris.

5.8.2. *Inconvenience of patients*

Some patients believe that skin lesions are results of the infectious due to poor hygiene and feel uncomfortable to show such lesions to the doctor. In some countries and regions, there is a stigma for people with skin lesions. These patients often do not have adequate therapeutic treatment.

5.8.3. *Poor understanding*

Patients sometimes do not clearly understand the instructions given by physician about the therapy and the goals of the therapy. Sometimes child's parents believe that traditional medicines are better than recommended therapy. Also, they expect a quick therapeutic effect. They have no understanding that the disease is a chronic character.

5.8.4. *Psycho-social factors*

Chronic itch and sleep deprivation can lead to anxiety and depression in patients with atopic dermatitis.

5.8.5. *Lack of education*

Inadequate drug administration is most likely a reason for treatment failure. Patients sometimes are not informed enough about the correct application of creams and ointments. Patients sometimes are unable to abide by a prescribed therapeutic regimen due to their daily duties. The higher the number of daily applications, the less the chance that the patient will take them. Also, instructions given to child's parents must be appropriate to their intellectual abilities.

5.8.6. *Fear of adverse drug effects and steroid phobia*

Topical corticosteroid phobia is especially affecting parents of pediatric patients with atopic dermatitis [27]. Establishing the trust-based doctor-patient/parents relationship can help overcome parents' fears about therapy [28, 30]. This fear is commonly caused by misinformation or misadvice given by friends, relatives, other parents and the media. A corticosteroid phobia can lead to poor patient therapy compliance.

5.8.7. *Hypersensitivity reactions to treatment*

Moisturizers can contain different chemicals which may cause irritation or hypersensitivity reactions. Urea containing emollients may cause stinging. Pimecrolimus cream may

cause erythema. Chemical stabilizers of sun topical corticosteroids can cause delayed hypersensitivity responses [20].

5.8.8. *Economic*

The cost of therapy may be more expensive than the patient expects. Also, long-term therapy increases the cost of treatment. This can affect the patient's adherence to therapy.

5.8.9. *Lack of bonding and communication with a doctor*

The physician should empathize with the patient and parents, be aware of patient's fears, anxieties and beliefs. Communication with the patient should be in language which patient and parents can understand. During the examination, the doctor should be patient, talk to a patient without haste and listen to the patient without interruption. Also, the doctor during the repeated visits should create a trust-based relationship with the patient.

More frequent visits to the doctor increase adherence to treatment. Studies show that shorter periods between physicians control increase the patient's compliance with the recommended therapy. Available consultation with well-educated nurse can also improve treatment adherence.

6. Conclusion

Atopic dermatitis (AD) is one of the most common skin conditions in children and adolescents. This disease is characterized by chronic eczematous and itchy lesions with typical distributions, and relapsing. The clinical pattern of atopic dermatitis has a characteristic age-dependent distribution and is commonly associated with elevated IgE, peripheral eosinophilia, *Staphylococcus aureus* colonization and comorbidity with other allergic diseases. There is no gold standard, clinical or laboratory, for the diagnosis of atopic dermatitis. Diagnosis should be based on anamnesis, clinical features and laboratory results.

Xerose is a leading clinical sign of atopic dermatitis; therefore, emollient creams represent the basic therapy of atopic dermatitis. The basic mechanism of their effect is to maintain satisfactory skin hydration, preserve the skin barrier and reduce transdermal loss of water.

Topical corticosteroids represent the basic anti-inflammatory, immunosuppressive and antiproliferative therapy in atopic dermatitis. The outbreak of topical corticosteroid therapy should be based on the severity of the clinical picture. For mild atopic dermatitis, we use low potency topical corticosteroid preparations; for severe atopic dermatitis, we use high potency topical corticosteroids. There are two different approaches to choose a topical corticosteroids, one recommends to start therapy with low potency TCS than using moderate potency TCS ("set up approach"). While others recommend reverse access from moderate to low potency topical corticosteroids ("set down approach"). These recommendations are primarily related to mild and moderate atopic dermatitis.

The expectations of patients and parental expectations in children with atopic dermatitis should always be determined, and the specific concerns of the parents should be sought and addressed.

Abbreviations

AAD	American Academy of Dermatology
ETFAD	the European Task Force on Atopic Dermatitis
FTU	finger type unit
IFN	interferon
IgE	immunoglobulin E
IL	interleukins
ISAAC	International Study of Asthma and Allergies in Childhood
SCORAD	Scoring atopic dermatitis
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
TSLP	thymic stromal lipoprotein
UVA	ultraviolet light A
UVB	ultraviolet light B

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