

RECOMMENDED STRATEGIES FOR ATOPIC DERMATITIS MANAGEMENT IN ROMANIA

Prof. George-Sorin Tiplica¹, MD, PhD, Prof. Carmen Maria Salavastru², MD, PhD,
Prof. Jacek C. Szepietowski³, MD, PhD, Prof. Magdalena Czarnecka-Operacz⁴, MD, PhD,
Assist. Prof. Alina Suru², MD, PhD, Assist. Prof. Ionela Manole¹, MD, PhD student

¹ Dermatology II, Colentina Hospital, „Carol Davila” University of Medicine and Pharmacy,
Bucharest, Romania

² Paediatric Dermatology, Colentina Hospital, „Carol Davila” University of Medicine and Pharmacy,
Bucharest, Romania

³ Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Poland

⁴ Department of Dermatology, Poznan University of Medical Sciences, Poznan, Poland

ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disease with a relapsing course that has a significant impact on the quality of life of both patients and their families. The pathogenesis of AD is due to a multitude of factors and can be associated with other allergy-related diseases, including asthma, food allergies or rhinitis. Treatment of AD aims to reduce duration, severity, and frequency of disease exacerbations. Understanding the maintenance of skin barrier integrity by continuing the use of basic therapy can prevent breaks. Patient and family education is important.

Keywords: atopic dermatitis, skin barrier, assessment tools, bathing, calcineurin inhibitors, corticosteroids, emollients, phototherapy, azathioprine, ciclosporin A, methotrexate, mycophenolate mofetil, dupilumab

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease, with a relapsing course, affecting up to 20% of children and 1-3% of the adult population (1) and has a significant impact on the quality of life of both patients and their families. The pathogenesis of AD is due to a multitude of factors including genetic predisposition, immunological factors, environmental triggers, impairment of skin barrier and imbalance of skin and the intestinal microbiome. Clinical findings include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification, with lesions distribution that varies with age: on cheeks during infancy, in flexures in adolescence, while in adulthood it manifests on the face, neck, upper part of the trunk and also in flexures. AD can be associated with other allergy-related diseases, including asthma, food allergies or rhinitis and is commonly correlated

with high serum IgE levels. AD can lead to several complications such as bacterial (*Staphylococcus aureus*) or viral superinfections (eczema herpeticum, eczema molluscatum, eczema vaccinatum) or exfoliative dermatitis, with significant hydro-electrolytic imbalance. The condition is usually managed by the avoidance of environmental causes, together with topical or systemic treatments, when the disease is on a flare.

CLINICAL DIAGNOSTIC

The diagnosis of AD is clinical, based on anamnesis, lesion morphology, and distribution, as well as associated clinical signs (2,3). Various study groups attempted to identify sets of criteria. The best known are the Hanifin and Rajka criteria, but these can be difficult to appreciate. The British Atopic Dermatitis study group has developed a simple, commonly used set of criteria, currently used

also in Romania (Table 1). We also signify the existence of the American Academy of Dermatology criteria, adapted after Hanifin and Rajka, which are less laborious and simpler to use (Table 2).

Clinical manifestations in patients with AD are represented by erythema, edema, xerosis, erosions, excoriations and exudation, crusts and lichenification (4). All of these manifestations may vary depending on the age of the patient and the duration of the disease. In the infantile form, the acute manifestations prevail, while in the adult form the chronic presentations predominate.

Acute lesions are represented by erythematous, edematous, pruritic papules and plaques, imprecisely delimited, accompanied by scratching lesions. Sometimes exudative, vesicular, and crusted lesions may be observed. *Subacute lesions* are represented by erythematous papules and plaques with excoriations and scales. *Chronic lesions* are represented by indurated, keratotic plaques with lichenification and lesions of prurigo nodularis.

TABLE 1. Criteria of the British Atopic Dermatitis Group – adapted after Baron et al. (5)

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|--|
| Major criterion: pruritic skin condition in the last 6 months |
| Minor criteria: for diagnosis are required ≥ 3 |
| 1. onset under the age of 2 |
| 2. history of flexural involvement |
| 3. history of generally dry skin; |
| 4. history of other atopic diseases (or history in first degree relatives if the child is aged < 4 years); |
| 5. visible flexural dermatitis |

TABLE 2. American Academy of Dermatology Criteria – adapted after Eichenfield et al. (2)

| |
|--|
| Essential features – mandatory: |
| 1. Pruritus |
| 2. Eczema (acute, subacute, chronic): |
| – Typical morphology and age-specific patterns** |
| – Chronic or recurrent history |
| *Patterns include: |
| 1. Facial, neck, and extensor involvement in infants and children |
| 2. Current or previous flexural lesions in any age group |
| 3. Sparing of the groin and axillary regions |
| Important features – seen in most cases, adding support to the diagnosis: |
| – Early age of onset |
| – Atopy (personal and/or family history, immunoglobulin E reactivity) |
| – Xerosis |
| Associated features – these clinical associations help to suggest the diagnosis of atopic dermatitis but are nonspecific: |
| – Atypical vascular responses (eg. facial pallor, white dermographism, delayed blanch response) |
| – Keratosis pilaris / pityriasis alba / hyperlinear palms / ichthyosis |
| – Ocular/periorbital changes |
| – Perifollicular accentuation/lichenification/prurigo lesions |
| Exclusionary conditions –it should be noted that a diagnosis of atopic dermatitis depends on excluding: scabies, seborrheic dermatitis, contact dermatitis (irritant or allergic), ichthyoses, cutaneous T-cell lymphoma, psoriasis, photosensitivity dermatosis, immune deficiency diseases, erythroderma of other causes. |

Infantile atopic dermatitis (from birth up to 6 months) is characterized by facial lesions, with erythema affecting the cheeks, but respecting the mid-facial area and progression to papules and exudative plaques with cracking and crusts that can affect the scalp and the extremities. Usually, the diaper area is not affected (6). Respiratory infections, dental eruptions, weaning can lead to extensive lesions and the onset of diversification, where new foods come into contact with the skin, can cause perioral and neck lesions (5).

Childhood atopic dermatitis (2-12 years) may appear de novo or following an infantile AD. It is characterized by subacute and chronic lesions that affect the flexural limb areas, the neck or trunk, with a less exudative aspect and a tendency to lichenification (6). There is predominant damage to the areas more accessible to the grating, such as the skin of the wrists. Skin lesions may also be accompanied by nail changes.

AD of the adolescent and adult shows predominantly flexural damage. Some patients have dermatitis of the face, eyelids, scalp and neck, and others may have chronic hand dermatitis. Severe forms present the risk of progression to exfoliative dermatitis.

ASSESSMENT TOOLS FOR AD

Once the diagnosis of AD has been established, the severity of the disease is assessed based on objective signs and subjective symptoms. The classic score used in AD, which evaluates both objective and symptomatic signs is SCORAD (Scoring of Atopic Dermatitis). AD with SCORAD over 50 is considered severe; values between 25 and 50 define the moderate form of the disease, while the SCORAD values below 25 define the mild form (4). Another validated severity score used for AD is EASI (Eczema Area and Severity Index) (2) which uses objective physician estimates of disease extent and severity with values that may range from 0 to 72.

Patient-reported outcome measure

The POEM (Patient Oriented Eczema Measure) score is a validated 7-item questionnaire used to assess the severity of AD, as experienced by the patient (7,8). In addition to clinical severity scores, quality of life impairment scores such as DLQI (Dermatology Life Quality Index) and cDLQI (Child Dermatology Life Quality Index) are also applied.

LABORATORY TESTS

There are no laboratory-specific biomarkers for AD diagnosis (3,4,11). The most typical feature,

TABLE 3. AD scores interpretation in terms of severity (9,10)

| Score | Mild AD | Moderate AD | Severe AD |
|--------|---------|-------------|-----------|
| SCORAD | <25 | 25-50 | >50 |
| EASI | <7 | 7-21 | >21 |

the increase of serum total or specific allergen IgE level, is not present in all AD patients. Although the total IgE level tends to vary with the severity of the disease, it is not a reliable indicator because some severely ill patients may have normal values of IgE; also, the IgE levels can be elevated in several non-atopic conditions (eg parasitic infections, certain forms of cancer or autoimmune diseases). Increases in tissue mast cell levels and peripheral eosinophil counts have been evaluated and have shown inconsistent associations (2). Classically two groups of disease are defined: *intrinsic AD* (non-IgE associated) which affects about 30% of patients; they do not show respiratory allergies, serum total IgE is normal, and allergen-specific IgE are undetectable and *extrinsic AD* (IgE associated) which affects about 70%-80% of patients; they associate personal and/or family history of respiratory allergies with high total serum and allergen-specific IgE levels (6).

THERAPY

Treatment of AD aims to reduce duration, severity and frequency of disease exacerbations (flares). AD is a chronic disease and patient management is sustainable. Patient and family education is important. Understanding the maintenance of skin barrier integrity by continuing the use of basic therapy can prevent breaks (4,5).

GENERAL MEASURES

Topical therapies

Cleansing and bathing

Bathing and softening of the skin can help remove crusts, scales, irritants and allergens, with beneficial effects. However, if the water is left to evaporate from the skin, it will lead to transepidermal water loss (TEWL). Therefore, applying the moisturizer is recommended to be done immediately after bathing, for good hydration.

Soaps containing surfactants aggresses the skin barrier causing lesions, dry and irritated skin. Syndet synthetic detergent soaps are recommended as being better tolerated (12). The shower is recommended to be short, 5 minutes, with the use of washing oil in the last 2 minutes to reduce TEWL.

Moisturizers

Emollients are local moisturizers used to control xerosis and TEWL. Emollients are the basic treatment for mild AD and adjuvant treatment for moderate and severe forms.

Traditional agents contain emollient, occlusive and/or humectant ingredients. Emollient substances (eg glycol- and glyceryl stearate, soy sterols) lubricate and soften the skin, occlusive agents (eg petrolatum, dimethicone, mineral oil) form a layer that delays evaporation of water, while humectants (e.g. glycerol, lactic acid, urea) attract and retain water (12). The cost of good quality emollients may restrict their use; emollients are not reimbursed by health care/insurers in most European countries. These costs can also be raised taking into account the large amounts of emollient used (up to 100 g/week for children and 500 g for adults). Therefore, the reduced application of emollients may be a significant factor in disease exacerbation.

In infants and children, the type of emollient used should be carefully chosen taking into account that urea and propylene glycol can cause irritant reactions and renal toxicity if they are absorbed systemically. Regular use of emollients in children with mild to moderate AD reduces flares and corticosteroid consumption and, therefore, supports their use as a first-line treatment for these patients (13,14).

Emollients “plus” are non-medicated products that contain active ingredients such as saponins, flavonoids and riboflavins from oat extract, or *Aquaphilus dolomiae* or *Vitreoscilla filiformis* bacterial lysates that influence skin microbial of AD patients (4).

Topical antimicrobials and antiseptics

An additional option for AD treatment is the addition of antiseptics to bath water such as sodium hypochlorite that inhibits the number of bacteria. Bath salts can also be used especially for impetiginized or ichthyosiform skin (4).

Dietary interventions

Food allergy is an important key factor in AD flares, most frequently being related to cow's milk, hen's egg, wheat, soy, tree nuts and peanuts (15). Suspicion of a certain food allergy should be evaluated in collaboration with an allergologist and dietary interventions should be recommended only in refractory cases to avoid malnutrition issues.

Topical anti-inflammatory therapies

Topical corticosteroids (TCS)

Topical corticosteroids are the mainstay of treatment in atopic dermatitis, especially in the acute phase when patients require pharmacologic treat-

ment. TCS are classified by potency, from class I – mild (eg hydrocortisone acetate) to class IV – super-potent (eg clobetasol propionate) (16), an aspect that should be considered before choosing the type of TCS in patients with AD, alongside patients age, skin area that should be treated, patient preferences or galenic formulation. In moderate forms of AD, TCS are recommended to be applied once-twice daily, with dose tapering as symptoms improve, to avoid side effects and withdrawal rebound; in mild forms of disease, treatment can be applied twice to thrice weekly, in combination with emollients (15). A more proactive approach, with two weekly applications of TCS on recurrent sites, may control better the flare-ups. Association of TCS and topical calcineurin inhibitors on the same sites do not associate better results as TCS alone (17), but treating sensitive areas of the body such as the face or genital area with topical calcineurin inhibitors and other areas of the body with TCS turned out to be a useful strategy (4,5,12). Potential local side effects of TCS are telangiectasia, atrophy, hypopigmentation, hypertrichosis, rosacea-like perioral dermatitis and striae, while systemic effects may include suppression of the hypothalamic-pituitary-adrenal (HPA) axis, osteoporosis, glaucoma, cataract and growth reduction, particularly in children with AD in whom TCS are used. The use of TCS is frequently associated with patients' anxiety and fear of side effects and this well-recognized corticophobia is the most significant factor that impacts patients' adherence to treatment (18).

Topical calcineurin inhibitors (TCI)

Topical calcineurin inhibitors (tacrolimus ointment 0.03%/0.1% and pimecrolimus cream 1%) are the second class of anti-inflammatory therapy with an indication in the treatment of atopic dermatitis in adults and children above 2 years of age. They act by the induction of a decreased production of pro-inflammatory cytokines through the inhibition of lymphocyte T activation (19). Several trials have compared the efficiency of TCI and TCS for atopic dermatitis, concluding that tacrolimus 0.1% has similar results as a corticosteroid with intermediate potency, while pimecrolimus is less effective than this type of TCS (20-22). TCI are recommended to be applied twice daily for short term; tacrolimus can be used as proactive therapy with two-three applications per week on recurrent sites of disease to reduce recurrences (12,15). TCI are not associated with the risk of skin atrophy, therefore they can be used as steroid-sparing agents, especially for the skin areas that are vulnerable to

adverse events from TCS, such as the eyelids, face, groin and axillae. The most common adverse events associated with the use of TCI are represented by local erythema, pruritus and burning sensations; some patients may experience a transient worsening of the atopic dermatitis (23). Severe bacterial or viral infections (eczema herpeticum, eczema molluscum) in patients treated with TCI have also been reported (23-25). Current data do not report an increased risk of lymphoma in patients treated with TCI (26). During treatment with TCI, skin exposure to sunlight should be minimized and effective sun protection should be recommended (27).

Phototherapy

Phototherapy is considered a second-line treatment in the management of atopic dermatitis, especially in adults, in cases unresponsive to behavioral measures or topical treatments, such as emollients, moisturizers, calcineurin inhibitors and corticosteroids. It includes several forms of light therapy such as natural sunlight, narrowband (NB) or broadband (BB) UVB, UVA, PUVA (topical or systemic psoralen in combination with UVA) or combination of UVA and UVB. The effectiveness of light radiation can be explained through several mechanisms: immunosuppressive effects on the cutaneous inflammatory cells; thickening of the stratum corneum and enhancement of epidermal barrier function or antibacterial activity (28). The most commonly used light therapy is NB-UVB due to its good tolerability and low-risk profile (29). Alternatively, it may be recommended UVA1 with efficiency similar to NB-UVB and more useful in severe phases of atopic dermatitis when used in high dose (30). For better results, it is recommended to associate emollients and topical corticosteroids in the first session of phototherapy to prevent flare ups (29); topical calcineurin inhibitors should be avoided during treatment with UVA, UVB or PUVA (27). Treatment plan implies a number of 2-5 sessions per week, for 2 to 3 months, with initial doses calculated according to the minimal erythematous dose tested before initiation of treatment and with their progressive increase. Phototherapy is usually a well-tolerated therapy and generally associates a low incidence of adverse events. Short term adverse events may include erythema, xerosis, blisters, pruritus, polymorphous light eruptions, hypertrichosis, folliculitis, onycholysis, herpes simplex virus reactivation. As long-term adverse effects are mentioned actinic damage, premalignant cutaneous lesions, cataract formation, non-melanoma skin cancers or melanoma (mainly in association with PUVA therapy) (29,31). Phototherapy should be

avoided in patients with a history of skin cancer, photosensitivity disorders or in patients treated with topical or oral photosensitizing medications.

In pediatric patients, UVB (narrowband- 311 nm) is considered the first treatment line in the pediatric population due to its good safety and efficacy profile compared to PUVA. For DA, there are no long-term studies of the consequences of phototherapy in children (29).

Systemic therapies

Immunomodulatory systemic therapies are used in the care of patients in whom the topical treatment associated or not with phototherapy does not result in disease control or when the quality of life is substantially impaired.

Oral corticosteroids

Due to their known side effects and the risk of rebound flare and increased severity upon their discontinuation, systemic corticosteroids are not generally recommended in patients with moderate-to-severe AD (32). To the same extent, Schimtt et al. have shown that ciclosporin is significantly more efficacious than prednisolone for severe adult eczema; although the latter is frequently used in daily practice, prednisolone is not recommended to induce stable remission of eczema (33). Oral corticosteroids may be recommended in a daily dose of 0.5-1 mg/kg in short-term treatment, with extreme caution in children. Long term treatment may associate as side effects exacerbation of AD, hypertension, glucose intolerance, adrenal suppression, osteoporosis, weight gain and decreased linear growth in children (29,33).

Ciclosporin A (CSA)

Ciclosporin A is considered to be an effective immunosuppressive treatment in patients with moderate to severe AD, in both adults and children aged 2 and older (29). Initially recommended in organ transplantation, CSA has also demonstrated its effectiveness in autoimmune and immune-mediated skin conditions such as psoriasis or AD. CSA acts by suppression of the T helper cell response through inhibition of lymphocyte activation (34). The therapy should start with a dose of 2.5-5 mg/kg/day given orally in divided doses twice daily, with dose tapering of 0.5-1 mg/kg every two weeks after achieving disease control (30). Treatment should not exceed a two-year continuous regimen; short courses of treatment lasting up to six months are advised (34).

The most significant side effects are renal toxicity and hypertension; additionally, there were reported skin infections, headache, gingival hyperplasia, hypertrichosis, increased risk of skin cancer

and lymphoma (29). CSA should be used with caution in combination with NSAIDs, aminoglycosides, quinolones, digoxin, statins, grapefruit juice or grapefruit (34) and should be avoided in combination with UV-therapy.

Azathioprine (AZA)

Azathioprine can be recommended as off label treatment in patients with moderate to severe AD, unresponsive to other topical or systemic therapies (eg. ciclosporin A). AZA demonstrated its efficacy in adults (35,36) and children over the age of 2 years (37,38). The suggested dose of AZA is 1-3 mg/kg/day (30), tapered or discontinued once the lesions' improvement has been achieved. All patients in whom is considered the systemic treatment with AZA should be tested for TMPT (thiopurine S-methyltransferase) activity, to avoid the use of this therapy in those with very low or absent enzyme activity. Side effects are common and can be divided into short-term toxicity (nausea, hypersensitivity), medium-term toxicity (myelotoxicity, susceptibility to infections, hepatotoxicity) and long-term toxicity (carcinogenesis with the risk of developing non-melanoma skin cancer or lymphoma) (39). Several drugs can interact with AZA which should be avoided during therapy: allopurinol and febuxostat, warfarin, ribavirin, live vaccines, other immunosuppressive drugs (cyclophosphamide, methotrexate, ciclosporin) (39). Additionally, AZA should not be combined with UV exposure.

Mycophenolate mofetil (MMF)

MMF is a lymphocyte selective immunosuppressive agent that inhibits de novo purine synthesis (40), with demonstrated efficacy in refractory inflammatory skin conditions. MMF can be recommended as off label treatment in patients with moderate to severe AD that have failed to respond adequately to other treatments. The suggested dose of MMF ranges from 0.5 to 3 g/day in adults (41). Heller et al. – in a retrospective analysis performed in 14 children treated with MMF as systemic monotherapy for severe AD – have shown that MMF can be safe and effective in refractory AD in children (42); still, prospective controlled studies for use of MMF in children and adolescents are needed. Gastrointestinal symptoms (nausea, vomiting, diarrhea and abdominal discomfort) represent the most frequently observed side effects. Also, hematologic (anemia, leucopenia, and thrombocytopenia) and genitourinary symptoms (dysuria, hematuria and urinary tract infection) may be reported (29).

Methotrexate (MTX)

MTX is an immunosuppressant drug with demonstrated efficacy in autoimmune and inflam-

matory skin diseases. MTX can be recommended as off label systemic treatment in refractory cases of AD, in adults and children. The recommended dose is of 5 to 15 mg, administered once a week in adults and 0.2-0.4 mg/kg weekly in children, with folic acid supplementation to reduce the likelihood of hematologic and gastrointestinal toxicity (5 mg weekly to 5 mg daily) (43). The most frequently reported side effects are gastrointestinal symptoms: nausea, vomiting, abdominal discomfort; in long term treatments, severe adverse events can occur: hepatotoxicity (drug-induced hepatitis, hepatic fibrosis), bone marrow suppression (anemia, leucopenia, and thrombocytopenia), pulmonary toxicity (interstitial lung disease), renal toxicity, carcinogenic risk (lymphoma) (43). Patients treated with MTX should be monitored periodically by performing full blood count, liver function tests, renal function tests and serum aminoterminal peptide of procollagen III (used to assess hepatic fibrosis in patients on long term MTX).

Interferon-gamma (IFN-G)

IFN-G, a cytokine with a principal role in the innate and adaptive immune system cascade, has no prescription protocol in Romania; it was used in other European countries, with moderate results in patients with AD. However, its prescription is limited by the high rate of adverse events and high costs (30).

Biologics

Dupilumab, the first biological agent approved for the treatment of moderate-to-severe AD, is a fully human monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signaling. The studies conducted confirmed the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD inadequately controlled by topical medications or for whom their use was inappropriate, with significant improvement of patient-reported itch, symptoms of anxiety or depression and quality of life (44). The recommended dose for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week administered as a subcutaneous injection. The incidence of reported side

effects is quite low, most frequently being mentioned the injection-site reactions, conjunctivitis, nasopharyngitis, infections (herpetic and non-herpetic) or headaches (44,45).

PATIENT MANAGEMENT

TABLE 4. Recommendations for children atopic dermatitis, adapted after (1)

| Form of disease | Recommendations |
|--|---|
| Mild SCORAD < 25 or transient eczema | Reactive therapy with class II corticosteroids or according to local cofactors: topical calcineurin inhibitors, antiseptics, silver-coated textiles |
| Moderate SCORAD 25-50 or recurrent eczema | Proactive therapy with calcineurin inhibitors or class II or III corticosteroids, wet wrap therapy, phototherapy (UVB 311 nm), psychotherapy, climate therapy |
| Severe SCORAD > 50 or persistent eczema | Hospitalization; systemic immunosuppressive therapy: cyclosporine, methotrexate, azathioprine, mycophenolate mofetil |
| Baseline Basic therapy | Educational programs, emollients, bath oil, avoiding allergens |

TABLE 5. Recommendations for adult atopic dermatitis, adapted after (1)

| Form of disease | Recommendations |
|--|---|
| Mild SCORAD < 25 or transient eczema | Reactive therapy with class II corticosteroids or according to local cofactors: topical calcineurin inhibitors, antiseptics, silver-coated textiles |
| Moderate SCORAD 25-50 or recurrent eczema | Proactive therapy with calcineurin inhibitors or class II or III corticosteroids, wet wrap therapy, phototherapy (UVB 311 nm / UVA1), psychotherapy, climate therapy |
| Severe SCORAD > 50 or persistent eczema | Hospitalization; systemic immunosuppressive therapy: cyclosporine, a short course of oral glucocorticoid treatment, dupilumab, methotrexate, azathioprine, mycophenolate mofetil, PUVA, alitretinoin, dupilumab |
| Baseline Basic therapy | Educational programs, emollients, bath oil, avoiding allergens |

Acknowledgement

All authors have contributed equally to the article.

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