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RECOMMENDED STRATEGIES FOR ATOPIC DERMATITIS MANAGEMENT IN ROMANIA

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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

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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)*

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 TCS7 (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 molluscatum) 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

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REFERENCES

1. Williams HC, editor. Atopic dermatitis: the epidemiology, causes and prevention of atopic eczema. *Cambridge University Press;* 2000 Feb 24.
2. Eichenfield LF, Tom WL, Chamlin SL et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol.* 2014 Feb 1;70(2):338-51.
3. Weidinger S, Novak N. Atopic dermatitis. *The Lancet,* Volume 387, Issue 10023, 1109-1122, March 12, 2016.
4. Wollenberg A, Barbarot S, Bieber T et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: Part I. *J Eur Acad Dermatol Venereol.* 2018 May 1;32(5):657-82.
5. Baron SE, Cohen SN, Archer CB et al. Guidance on the diagnosis and clinical management of atopic eczema. *Clin Exp Dermatol.* 2012 May;37:7-12.

6. Kang K et al. Atopic Dermatitis in Jean L. Bolognia. Dermatology. Second Edition. *Elsevier.* 2008: 181:195
7. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: Development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol.* 2004 Dec 1;140(12):1513-9.
8. Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol.* 2013 Dec;169(6):1326-32.
9. Chia BK, Tey HL. Systematic review on the efficacy, safety, and cost-effectiveness of topical calcineurin inhibitors in atopic dermatitis. *Dermatitis.* 2015 May 1;26(3):122-32.
10. Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: An interpretability study. *Br J Dermatol.* 2015 May; 172(5):1353-7.
11. Boguniewicz M, Alexis AF, Beck LA et al. Expert perspectives on management of moderate-to-severe atopic dermatitis: A multidisciplinary consensus addressing current and emerging therapies. *J Allergy Clin Immunol: In Practice.* 2017 Nov 1;5(6):1519-31.
12. Eichenfield LF, Tom WL, Berger TG et al. Guidelines of care for the management of atopic dermatitis: Section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014 Jul 1;71(1):116-32.
13. Tiplica GS, Kaszuba A, Malinauskienė L et al. Prevention of flares in children with atopic dermatitis with regular use of an emollient containing glycerol and paraffin: A randomized controlled study. *Pediatr Dermatol.* 2017 May; 34(3):282-9.
14. Tiplica GS, Boralevi F, Konno P et al. The regular use of an emollient improves symptoms of atopic dermatitis in children: A randomized controlled study.*J Eur Acad Dermatol Venereol.* 2018 Jul; 32(7):1180-7.
15. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, Gieler U, Lipozencic J, Luger T, Oranje AP, Schäfer T. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol.* 2012 Aug;26(8):1045-60.
16. Niedner R. Therapie mit systemischen Glukokortikoiden. *Der Hautarzt* 2001. 52(11), 1062-1074.
17. Meurer M, Eichenfield LF, Ho V, Potter PC, Werfel T, Hultsch T. Addition of pimecrolimus cream 1% to a topical corticosteroid treatment regimen in paediatric patients with severe atopic dermatitis: A randomized, double-blind trial. *J Dermatolog Treat.* 2010 May 1; 21(3):157-66.
18. Li AW, Yin ES, Antaya RJ. Topical corticosteroid phobia in atopic dermatitis: A systematic review. *JAMA dermatol.* 2017 Oct 1; 153(10):1036-42.
19. Stuetz A, Baumann K, Grassberger M, Wolff K, Meingassner JG. Discovery of topical calcineurin inhibitors and pharmacological profile of pimecrolimus. *Int Arch Allergy Immunol.* 2006;141(3):199-212.
20. Broeders JA, Ali UA, Fischer G. Systematic review and meta-analysis of randomized clinical trials (RCTs) comparing topical calcineurin inhibitors with topical corticosteroids for atopic dermatitis: A 15-year experience. *J Am Acad Dermatol.* 2016 Aug 1;75(2):410-9.
21. Reitamo S, Rustin M, Ruzicka T et al. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. *J Allergy Clin Immunol.* 2002 Mar 1;109(3):547-55.
22. Sheng-Li C, Yan J, Wang FS. Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: A meta-analysis of randomized clinical trials. *Pediatric pharmacology.* 2011;8(1).
23. Reitamo S, Wollenberg A, Schöpf E et al. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. *Arch Dermatol.* 2000 Aug 1;136(8):999-1006.
24. Wetzel S, Wollenberg A. Eczema molluscatum in tacrolimus treated atopic dermatitis. *Eur J Dermatol.* 2004 Jan 1;14(1):73-4.
25. Lübbe J, Pournaras CC, Saurat JH. Eczema herpeticum during treatment of atopic dermatitis with 0.1% tacrolimus ointment. *Dermatology.* 2000;201(3):249-51.
26. Legendre L, Barnetche T, Mazereeuw-Hautier J, Meyer N, Murrell D, Paul C. Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: A systematic review and meta-analysis. *J Am Acad Dermatol.* 2015 Jun 1;72(6):992-1002.
27. https://www.ema.europa.eu/en/documents/product-information/protopic-epar-product-information_ro.pdf (Last accessed on 04 July 2019)
28. Patrizi A, Raone B, Ravaioli GM. Management of atopic dermatitis: safety and efficacy of phototherapy. *Clin Cosmet Investig Dermatol.* 2015; 8:511.
29. Sidbury R, Davis DM, Cohen DE et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol.* 2014 Aug 1; 71(2):327-49.
30. Ring J, Alomar A, Bieber T et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part II. *J Eur Acad Dermatol Venereol.* 2012 26(9):1176-93
31. Patrizi A, Raone B, Ravaioli GM. Safety and Efficacy of Phototherapy in the Management of Eczema. InUltraviolet Light in Human Health, Diseases and Environment 2017 (pp. 319-331). *Springer, Cham.*
32. Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: A systematic review. *J Allergy Clin Immunol.* 2014 Feb 1; 133(2):429-38.
33. Schmitt J, Schäkel K, Fölster-Holst R et al. Prednisolone vs. ciclosporin for severe adult eczema. An investigator – initiated double-blind placebo – controlled multicentre trial. *Br J Dermatol.* 2010 Mar;162(3):661-8.
34. Berth-Jones J, Exton LS, Ladoyanni E et al. British Association of Dermatologists guidelines for the safe and effective prescribing of oral ciclosporin in dermatology 2018. *Br J Dermatol.* 2019 Jun;180(6):1312-38.
35. Berth-Jones J, Takwale A, Tan E et al. Azathioprine in severe adult atopic dermatitis: A double-blind, placebo-controlled, crossover trial. *Br J Dermatol.* 2002 Aug;147(2):324-30.
36. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: A double-blind, randomised controlled trial. *The Lancet.* 2006 Mar 11; 367(9513):839-46.
37. Caufield M, Tom WL. Oral azathioprine for recalcitrant pediatric atopic dermatitis: clinical response and thiopurine monitoring. *J Am Acad Dermatol.* 2013 Jan 1; 68(1):29-35.
38. Murphy LA, Atherton D. A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. *Br J Dermatol.* 2002 Aug;147(2):308-15.
39. Meggitt SJ, Anstey AV, Mohd Mustapa MF, Reynolds NJ, Wakelin S. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011. *Br J Dermatol.* 2011 Oct; 165(4):711-34.
40. Orvis AK, Wesson SK, Breza Jr TS, Church AA, Mitchell CL, Watkins SW. Mycophenolate mofetil in dermatology. *J Am Acad Dermatol.* 2009 Feb 1; 60(2):183-99.
41. Murray ML, Cohen JB. Mycophenolate mofetil therapy for moderate to severe atopic dermatitis. *Clin Exp Dermatol.* 2007 Jan;32(1):23-7.
42. Heller M, Shin HT, Orlow SJ, Schaffer JV. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. *Br J Dermatol.* 2007 Jul;157(1):127-32.
43. Warren RB, Weatherhead SC, Smith CH et al. British Association of Dermatologists' guidelines for the safe and effective prescribing of methotrexate for skin disease 2016. *Br J Dermatol.* 2016 Jul; 175(1):23-44.
44. Simpson EL, Bieber T, Guttman-Yassky E et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med.* 2016 Dec 15; 375(24):2335-48.
45. Thaçi D, Simpson EL, Deleuran M, et al. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: A pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). *J Dermatol Sci.* 2019 Mar 12.