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The Turkish guideline for the diagnosis and management of atopic dermatitis-2018

Türkiye atopik dermatit tanı ve tedavi kılavuzu-2018

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Abstract

Background and Design: Atopic dermatitis (AD) has a complicated etiopathogenesis and difficulties in diagnosis and treatment from time to time. Because of the disease which different approaches can be seen rationalize the need for an algorithm for the diagnosis, classification, etiopathogenesis, diagnostic tests and therapeutic approach. Therefore, authors from Dermatoallergy Working Group of the Turkish Society of Dermatology aimed to create an AD guideline for the diagnosis, treatment and followup.
Materials and Methods: Each section of the guideline has been written by a different author. The prepared sections were evaluated in part by e-mail correspondence and have taken its final form after revision in the last meeting held by the participation of all authors.
Results: The guideline includes the diagnosis, classification, etiopathogenesis, diagnostic tests and therapeutic approach of AD. Lesions show age-related morphology and distribution. There are no *in vivo/in vitro* tests that have high sensitivity and specificity that can be used to identify AD and trigger factors. The first step of treatment consists of moisturizers, topical corticosteroids and calcineurin inhibitors, respectively. Moisturizers are used therapeutically in all forms of AD. Topical corticosteroids are the first agents to be used when moisturizers are inadequate. Topical calcineurin inhibitors should be used in lesions resistant to corticosteroids, for proactive treatment, special areas. Antimicrobial agents and antiseptics should only be added to treatment when clinical signs of infection are present. And in topical treatment-resistant cases, second-line treatment is phototherapy or oral cyclosporine. The biologic agent, dupilumab, is promising in the treatment of severe AD.
Conclusion: AD is a disease that can be challenging for the physician in terms of treatment and follow-up. Depending on evidence-based data (and individual experiences), this guideline will have a leading role in the diagnosis and treatment of AD and help the physician to overcome the challenges in the management.
Keywords: Atopic dermatitis, algorithm, guideline, diagnosis, treatment, Turkey

Öz

Amaç: Atopik dermatit (AD), tanı ve tedavisinde zaman zaman zorluklar yaşanan bir hastalıktır. Farklı yaklaşımların görülebildiği bir hastalık olması, hastalığın tanı, sınıflama, etiyopatogenez, tanısal testler ve tedavi yaklaşımları açısından bir algoritma içerisinde değerlendirilmesi

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gerekliliğini doğurmuştur. Bu amaçla Türk Dermatoloji Derneği Dermatoallerji Çalışma Grubu içerisinde yer alan yazarlar, AD tanı ve tedavisinde kanıta dayalı bir yol gösterici olması açısından bu AD kılavuzunu oluşturmayı hedeflemişlerdir.

Gereç ve Yöntem: Kılavuz, her bölümü ayrı bir yazar tarafından yazılacak biçimde planlanmış; kılavuzun ana hatları belirlendikten sonra yazarlar tarafından hazırlanan bölümler e-posta yazışmaları ile diğer yazarlar tarafından da değerlendirilmiştir ve bir araya gelinerek yapılan toplantıda tartışılmıştır. Son olarak, kılavuz tümüyle gözden geçirilerek hazır hale getirilmiştir.

Bulgular: Kılavuz, tanım, patogenez, klinik bulgular, tanı, ayırıcı tanı, skorlama sistemleri, tanıda deri testleri ve tedavi yaklaşımlarını içermektedir. Günümüzde AD tanısında ve tetikleyici faktörlerin ortaya konulmasında kullanılabilecek sensitivite ve spesifitesi yüksek, uygulanması kolay *in vivo/in vitro* test bulunmamaktadır. Tedavinin ilk basamağını sırasıyla nemlendiriciler, topikal kortikosteroidler TSK ve kalsinörin inhibitörleri oluşturur. Nemlendiriciler AD'nin tüm formlarında tedavide kullanılır. Nemlendiricilerin yetersiz kaldığı durumlarda ilk kullanılacak ajanlar TKS'lerdir. TKS'lere dirençli lezyonlarda, uzun süreli kortikosteroid kullanımında, proaktif tedavide ve belli bölgelerde ise topikal kalsinörin inhibitörleri tercih edilmelidir. Antimikrobiyal ajanlar ve antiseptikler sadece klinik olarak enfeksiyon bulgularının olduğu durumlarda tedaviye eklenmelidir. Topikal tedavinin yanıtsız kaldığı durumlarda ikinci basamak tedavide fototerapi ve oral siklosporin yer alır. Ülkemizde henüz ruhsat almamış olan biyolojik ajan dupilumab şiddetli ve dirençli AD tedavisinde ümit vermektedir.

Sonuç: AD hekimler için tanı, tedavi ve izlem açısından güçlükler yaratabilen bir hastalıktır. Olabildiğince kanıta dayalı verilerden yola çıkarak hazırlanan bu kılavuz, AD'li olgularda tanı ve tedavi yaklaşımlarının yönlendirilmesinde yol gösterici olacak ve hekimlerin bu süreçlerde yaşadıkları zorlukların aşılmasına katkı sağlayacaktır.

Anahtar Kelimeler: Atopik dermatit, algoritma, kılavuz, tanı, tedavi, Türkiye

Introduction

Atopic dermatitis [AD (atopic eczema)] is a chronic, recurrent, itchy and inflammatory skin disease seen frequently particularly in children[1-3]. The disease shows increases especially in developed countries[4,5]. Its life-long prevalence is increasing across the world. The difficulties experienced from time to time in its diagnosis and treatment have resulted in the need for assessing the disease within an algorithm with respect to diagnosis and treatment approaches. To this end, the authors in the Turkish Dermatology Association Dermatoallergy Workgroup aimed at preparing an AD guideline of our country to serve as an evidence-based guide for the diagnosis and treatment of AD. This guideline was planned in a way that each section of it was to be written by a separate author after the topics were distributed to the authors by a chairperson elected from the AD preparation group within the Dermatoallergy Workgroup. All Medline data, current AD diagnosis and treatment guidelines, meta-analytic studies and expert views that were published between 1980 and 2018 have been reviewed and a set of consensus proposals for the diagnosis and treatment of AD were set out for dermatology specialists in Turkey also utilizing the experiences in Turkey. After determining the outlines of the guideline, the sections prepared by the authors within a certain period of time were also evaluated by other authors through e-mail correspondence. In the meetings held with the authors, all data were discussed in detail, and checked in the light of current literature information, and parts that need modifications were identified. After the changes were made by the authors, the sections that were rearranged were sent by e-mail correspondence to two persons who were elected from the group during a meeting to be reviewed once more. The sections were reviewed again thoroughly in terms of content and language and rearranged by these persons and sent to the group chairperson. After having been evaluated as a whole by the group chairperson, the guideline was finalized.

Definition

AD is a chronic, itchy and inflammatory dermatosis seen in people with atopic disposition and affecting 20-25% of children and 2-3% of adults[1,2]. Atopic disposition is defined as a history of personal or family type I allergy, bronchial asthma, allergic rhinitis and conjunctivitis and/or AD, and/or a tendency to excess production of immunoglobulin E (IgE) antibodies[2,3]. AD mostly begins at infancy between the 3rd and 6th months. While most of the patients have recovery in adolescence, no recovery is seen in a patient group of 10-30%. In a smaller patient group, the first signs appear in adulthood[6].

Pathogenesis

The two basic and interwoven mechanisms responsible for the pathogenesis of AD are disorders of skin structure and function and skin inflammation.

1. Disorders of skin structure and function

Many disorders have been reported in AD that are related to stratum corneum including changes in lipid content such as decreased hydration of stratum corneum and increased water loss[7,8], and decreased chain length, impaired lamellar organization[8-10], decreased filaggrin[11], increased skin pH[8], impaired serine protease activity[12], and abnormal increase in *Staphylococcus aureus* colonization together with decreased skin microbiome diversity[10,13].

2. Skin inflammation

It is the second basic mechanism in the pathogenesis and is characterized by infiltration of inflammatory cells and particularly CD4+ cells. Even in a skin without any lesions, an increase in the number of T-helper (Th) 2 and Th22 cells and to a less degree of Th17 cells and a proinflammatory cytokine environment are observed together with signs of subclinical inflammation[14]. Essentially cytokines associated with Th2 cells such as interleukin (IL)-4, IL-5 and IL-13 and chemokines such as thymus and activation regulating chemokine (TARC) and eotaxin are responsible for the mechanism in a skin with lesions[15]. Chemokines such as TARC/C-C chemokine ligand (CCL) 17 and macrophage derive chemokine/CCL22 that are called Th2 chemokines are the most important chemokines. These are chemotactic for Th2 cells that express chemokine receptor C-C motif chemokine receptor 4[16,17]. In the cellular infiltrate of chronic lesions, alongside Th2, interferon (IFN) and IL-12 producing Th1 cells and to a less degree than in acute lesions Th22 and Th17 are present[18,19]. Th17 and Th22 perform restructuring and fibrosis of the tissue together with cytokines and chemokines secreted from keratinocytes and fibrablasts such as thymic stromal lymphopoietin[18-21]. Besides dermal dendritic cells, epidermal Langerhans cells carrying trimeric high-affinity IgE receptor and inflammatory dendritic cells play a role in antigen presentation in AD. Cells are able to receive antigens with the mediation of IgE bound this receptor and they cause classical rapidly developing (type 1) allergic reactions and stimulate T-cell-mediated delayed-type (type 4) reactions[22].

Impaired epidermal barrier and skin inflammation mutually influence each other. Intrinsic impairment of epidermal barrier stimulates inflammation through chemokine activation that attracts T cells

released from keratinocytes, cytokine mediated natural immunity (such as IL-1 family members) and cytokine mediated Th polarization as well as Langerhans cell activation (IL-25, IL-33 and TSP)[23-27]. When epidermal barrier with an impaired function interacts with this immune environment, also percutaneous allergen sensitivity occurs[28]. With an inadequate arrangement of antimicrobial peptides specific to epidermal barrier with impaired function, *S. aureus* colonization increases. Production of *S. aureus* proteases results in exacerbations and chronicity through stimulation of natural signal pathways and release of enterotoxins that activates superantigens, which in turn activate T cells. This condition is responsible for IgE-mediated sensitization and direct mast cell degranulation[1,26,29,30]. Thymic stromal protein seems to have two functions, to establish direct relationship between somatosensorial nerve endings and to produce Th2 cytokines such as IL-13 and IL-31 that directly stimulate nerve endings and regulate them in a way to increase release of cellular pruritogens[31,32]. The resulting neurogenic inflammation completes the vicious circle with the support of Th2 responses, keratinocyte proliferation and epidermal thickening[33].

Itching occurs often in AD and usually this itching cannot be controlled with antihistaminics. Histamine, substance P and their receptors have been shown to play an important role in peripheral itching. Recently, attention has been drawn to the role of endogen opioids such as beta-endorphin and their receptors in itching at a central level and morphine has been reported to cause itching through gastrin releasing peptide receptors[16].

Clinical findings

Eczematous lesions may be acute, subacute or chronic. Lesions show age-related morphology and distribution.

Infancy (below 2 years of age): In babies and small children, vesicles are seen on the cheeks or hairy skin and extremity extensor surfaces in acute lesions and serous exudates and crusting in severe cases. In the chronic phase, itchy, erythematous, squamous and crusted lesions are observed. There may be trunk involvement but the diaper region is usually not involved[1-3].

Childhood/school age (2-12 years of age): Subacute and chronic eczematous lesions are seen on the flexural regions, the volar surfaces of wrists and ankles and the neck. Lichenified and excoriated plaques with less exudation are observed. Atopic reticulated pigmentation called "dirty neck" may occur particularly on both sides of the neck[1-3].

Adolescence/adulthood (13 years of age and over): The disease is much more localized in adults and chronic eczematous lesions are seen. There are lichenified lesions on the flexures in most of the patients. The head, eyelids, neck, upper trunk, shoulders, haired skin and hands are also affected by the disease, but less frequently. The disease may occur only as chronic hand eczema or prurigo-like lesions in adults[1-3].

Complications

Patients with AD have increased susceptibility to bacterial, viral and fungal infections. Infections of *S. aureus*, herpes simplex virus (HSV), molluscum contagiosum, and *Malassezia sympodialis* are seen more frequently[1,34].

Comorbidities

Some diseases including allergic rhinitis, asthma and food allergy, ichthyosis vulgaris, keratoconjunctivitis, keratoconus, infectious keratitis, blepharitis, anterior subcapsular or posterior subcapsular cataract, retina decollement, obesity, Metabolic syndrome, anemia, impaired psychosocial functions, sleep disorders, hyperactivity, depression, and anxiety may be seen more often[1,35].

Diagnosis

The diagnosis of AD is made on the basis of clinical characteristics and anamnesis[1-4]. Although many diagnostic criteria have been proposed for the diagnosis of AD, there is no diagnostic criterion that is accepted by everyone (Tables 1, 2, 3, 4). From these criteria, the Hanifin and Rajka criteria (Table 1) and the criteria of the British Workgroup (Table 2) come to the fore.

Differential diagnosis

Skin biopsies and laboratory tests also including IgE are not routinely used in the diagnosis of AD and are not recommended. However, skin biopsies, appropriate laboratory tests (serum IgE, potassium hydroxide examination, patch tests) and genetic tests may be performed in selected cases (Figure 1)[2,3,12].

The leading chronic dermatoses (contact dermatitis, xerotic eczema, lichen simplex chronicus, psoriasis), infectious diseases and congenital immunodeficiencies, keratinization disorders, and nutritional deficiencies should also be considered in differential diagnosis (Tables 5, 6, 7).

Atopic dermatitis scoring systems

Various scoring systems are being used to determine the clinical severity of AD[36-38]. In 1993, the European Task Force defined SCORing

Table 1. Diagnostic criteria of Hanifin and Rajka

Major criteria (at least 3 should be present):
1. Itching
2. Typical morphology and distribution of skin lesions (involvement of flexural areas in adolescents and adults, of extensor regions and face in babies and small children)
3. Chronic and recurrent dermatitis
4. Personal or family history of atopy
Minor diagnostic criteria (at least 3 should be present):
1. Xerosis
2. Ichthyosis/palmar hyperlinearity/keratosis pilaris
3. Reactivity in type-1 skin tests
4. Increased serum IgE
5. Early onset age
6. Vulnerability to skin infections
7. Vulnerability to non-specific hand and foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. "Dennie-Morgan" infraorbital folds
12. Keratoconus
13. Anterior subcapsular cataract
14. Orbital darkening
15. Facial paleness or erythema
16. Pityriasis alba
17. Front neck folds
18. Sweating-related itching
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Vulnerability to environmental and emotional factors
23. White dermographism
For diagnosis: 3 major and 3 minor criteria required
IgE: Immunoglobulin E

Atopic Dermatitis (SCORAD), a scale approved for children. SCORAD is the most commonly used measurement method among the AD severity scales. In this scoring system, first the involved body surface area is determined according to the rule of nines. This scoring system assesses the severity of lesions through: 1) The extent of lesions, 2) Six clinical findings (erythema, edema/papulation, oozing/crusting, excoriation, lichenification and xerosis) and subjective complaints such as 3) Itching and sleeplessness through the visual analog scale (Table 8, Figure 2). These 3 criteria, extent of disease, severity of disease and subjective symptoms, collect maximum 103 points in total. Although SCORAD is a combined scoring, sometimes the 3 criteria can be calculated separately[39]. The SCORAD index is interpreted as mild disease when the score is less than 25 points, moderate when it is between 25 and 50 points and severe when it is more than 50 points. The European Task Force issued a directive for using the SCORAD index in 1997. Since the severity scales were complex, took a lot of time and produced inconsistent results, an objective SCORAD (excluding patient perspective) and a Three-Point Severity Score were published in the end. The Three-Point Severity Score assesses only erythema, edema and excoriation. A certain area is selected and a scoring in the form of 0, 1, 2 is done for that area. The score varies between 0 and 83 in the Objective SCORAD which is scored excluding patient perspective[40]. Patient-oriented SCORAD uses basically the same criteria as in SCORAD, but figures adapted to the patient are utilized.

Table 2. Diagnostic criteria of British Workgroup

Main criterion: Presence of pruritic dermatosis (or in small children such a condition needs to be notified by the parents).
Other criteria: 1. Presence of flexural involvement (involvement of popliteal fossa, antecubital region, neck and front side of ankle; also, involvement of cheeks in children below 10 years of age) 2. Personal asthma or hay fever anamnesis (history of atopic disease in one of 1st degree relatives in children below 4 years of age) 3. History of widespread skin dryness (in past 1 year) 4. Apparent flexural eczema (also involvement of cheeks, forehead and outer sides of extremities in children below 4 years of age) 5. Rashes starting before 2 years of age (not used for children below 4 years of age)
For diagnosis, at least 3 of the other criteria alongside the main criterion should be present

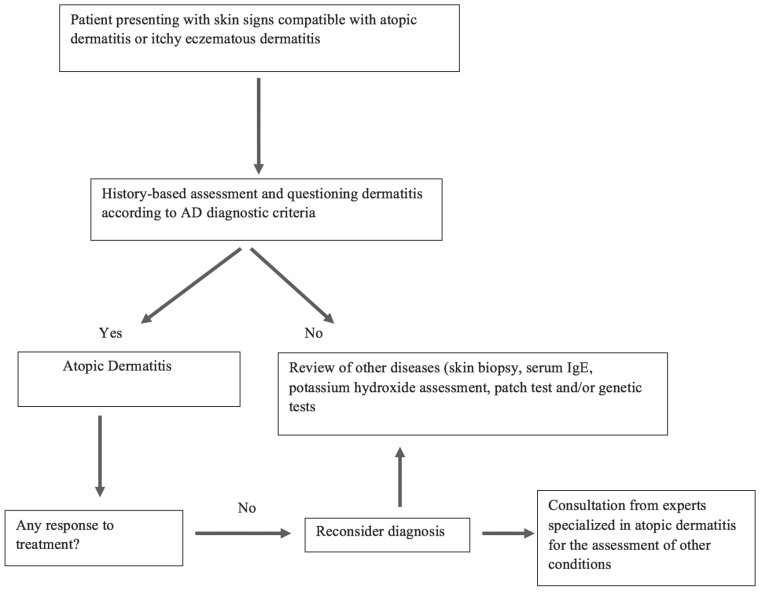

Figure 1. Atopic dermatitis diagnosis algorithm

Table 3. Atopic dermatitis diagnostic criteria of Japan Dermatology Group

1. Pruritus
2. Typical morphology and distribution a) Eczematous dermatitis - Acute lesions: Erythema, exudation, papule, vesiculopapules, squama, crusts - Chronic lesions: Infiltrated erythema, lichenification, prurigo, skuama, crusts b) Distribution - Symmetrical: Predilection sites: forehead, periorbital region, perioral region, lips, periauricular region, neck, joint sites of extremities, trunk - Age-related distribution: Infancy: Starts from haired skin and face, often spreads to trunk and extremities Childhood: Neck, flexural regions of arms and legs Adolescence and adulthood: Tends to be more severe on the upper half of the body (face, neck, front side of trunk and back)
3. Chronic or chronically recurring progression (generally old and new lesions are together): Prognosis longer than 2 months in babies, more than 6 months in childhood, adolescence and adulthood
For diagnosis: Entire 3 criteria need to be present regardless of severity. Age-related acute and chronic nonspecific eczemas should be excluded

Table 4. Diagnostic criteria rearranged by Hanifin

1) Main characteristics (must be present) a. Itching b. Eczematous changes 1. Typical morphology and age-specific distribution a. Face, neck and extremity extensors in babies and children b. Flexural lesions in examination or history (in adulthood or at any age) c. Inguinal or axillary involvement should not be present 2. Prognosis with chronic or recurrent attacks
2) Major characteristics (characteristics present in most of the subjects and supportive of diagnosis) a. Early onset b. Atopy 1. Personal and/or family history 2. IgE reactivity c. Dry skin
3) Accompanying characteristics (characteristics suggesting atopic dermatitis but inappropriate to be used for trial or epidemiologic purposes for being nonspecific) a. Atypical vascular responses (e.g. pale face, white dermographism, delayed white response) b. Keratosis pilaris, palmar hyperlinearity, ichthyosis c. Ocular/periorbital changes d. Other local signs such as perioral changes/periauricular lesions e. Perifollicular accentuation/lichenification/prurigo lesions
4) Conditions to be excluded: Scabies, allergic contact dermatitis, seborrheic dermatitis, psoriasis, ichthyosis, skin lymphomas, immunodeficiencies
IgE: Immunoglobulin E

Proposed by Hanifin et al.[41] for child and adult patients, Eczema Area and Severity Index (EASI) is the second most frequently used scoring system. It was developed by modifying the Psoriasis Area and Severity Index scoring. The body is assessed in 4 anatomic areas, head/neck, trunk, upper extremities and lower extremities. Each of these 4 body areas are evaluated separately for erythema, induration/papulation/edema, excoriation and lichenification. Each finding is scored between 0 and 3 depending on its severity. The maximum score of EASI is 72 (Table 9). Symptoms such as pruritus and findings such as xerosis and squama are excluded from the area assessment. This simple system is used for the initial assessment of eczema and its progression during follow-up. However, there is no definite distinction as to which score would mean mild, moderate or severe disease[42].

Investigator Global Assessment (IGA) is the third most frequently used scale[43]. It is used quite often in pediatric patients. Easy to use, this 6-point scale assesses dermatitis as a whole using the clinical and characteristic signs of it (erythema, infiltration, papulation, oozing and crusting skin) and scoring them in the interval from 0 (clean) to 5 (very severe disease). A total score between 0 and 25 is obtained in this way (Table 10). A limitation of the IGA scoring is that; it does not include subjective symptoms[44].

Berth-Jones[45] proposed in 1996 another simple clinical severity scoring called Six Area, Six Sign Atopic Dermatitis (SASSAD) for children and adults. This scoring rates 6 signs (erythema, exudation, excoriation, dryness, cracking and lichenification). These signs are scored as 0 (absent), 1 (mild), 2 (moderate) and 3 (severe) for each of 6 areas (arms, hands, legs, feet, head/neck and trunk). The SASSAD scoring does not assess subjective symptoms. In this way, a score between 0 and 108 can be obtained in SASSAD (Table 11)[45].

An objective method, Objective Severity Assessment of Atopic Dermatitis (OSAAD), is also used to determine severity in pediatric patients. This scoring is based on transepidermal water loss and skin hydration, but its use in clinical practice is difficult[46].

Charman et al.[47] described a Patient-Oriented Eczema Measure (POEM) scoring in 2004. This scoring system is based on patient point of view on disease severity. Simple questions are asked to child and adult patients about the frequency of 7 symptoms, itching, sleep disorders, weeping skin, oozing skin, cracked skin, flaking and dry/rough skin. How many days in the past one week these symptoms have affected the patient is

Table 5. Differential diagnosis of atopic dermatitis as compared to other dermatitis

Dermatitis type	Affected age group	Frequency	Clinical characteristics
Seborrheic dermatitis in infancy	Babies	Frequent	Salmon-red oily squamae that emerge in the first 6 weeks of life and typically disappear within weeks, are mostly seen on hairy skin and napkin region
Seborrheic dermatitis in adulthood	Adults	Frequent	Yellow, white or grayish squamous erythematous patches seen in seborrheic regions and particularly on hairy skin, in the midst of the face and chest
Nummular dermatitis	Children and adults	Frequent	Squamous patches in the shape of a coin mostly on the legs and hips generally not itchy
Irritant contact dermatitis	Children and adults	Frequent	Generally limited to the contact area, acute or chronic eczematous lesions; locally applied irritants in the history is a risk factor; possibility of being together with atopic dermatitis
Allergic eczematous contact dermatitis	Children and adults	Frequent	Eczematous lesions mostly concentrated in the direct contact area with possibility to spread; locally applied irritants in the history is a risk factor; possibility of being together with atopic dermatitis
Lichen simplex chronicus	Adults	Rare	One or more localized, limited, lichenified plaques associated with scratching due to intense itching
Asteatotic eczema	Adults	Frequent	Dry, squamous, fissured patches mostly on legs

Table 6. Differential diagnosis of atopic dermatitis as compared to infectious diseases and congenital immunodeficiencies

Infectious skin diseases	Affected age group	Frequency	Clinical characteristics
Dermatophytosis infection	Children and adults	Frequent	One or more limited squamous plaques with red raised contours, with center tending to heal; variable itching
Impetigo	Children	Frequent	Limited erythemous patches with bullae or yellow honey-colored crusts
Scabies	Children	Frequent (especially in developing countries)	Itchy superficial tunnels or pustules in palms, soles, between fingers and genital region; possibility of secondary eczematous changes
Congenital immunodeficiencies			
Hyper-IgE syndrome	Children	Rare	Pustular and eczematous rashes in the first years of life; staphylococcus infections in skin, sinuses and lungs; high serum IgE; eozinophilia
Wiskott-Aldrich syndrome	Children	Very rare	Atopic dermatitis like lesions in male babies usually in the first weeks of life; microthrombocytopenia
Omenn syndrome	Children	Very rare	Early-start erythroderma; diffused squamous lesions; chronic diarrhea

IgE: Immunoglobulin E

questioned (Table 12). The limitation of the POEM scoring system is that it consists of subjective criteria only. The total score obtainable is 28[47].

Eichenfield[48] reported in 2004 that the SCORAD index and EASI system were the two most reliable and practicable methods in clinical practice. These methods are useful in categorizing severity in daily practice and clinical studies[48]. In recent years, 20 different scoring systems have been published. However, only EASI, SCORAD and POEM are thought to be sufficient and valuable, EASI or SCORAD for being objective in assessing disease severity and POEM for measuring severity from patient point of view[49]. Although there are a number of scales involving self-assessment by the patient in AD, POEM is the only system that has been validated adequately among them. The scales rating disease severity from patient perspective have not been validated yet in Turkish. Therefore, they are presented as Turkish translations.

Table 7. Differential diagnosis of atopic dermatitis as compared to keratinization disorders and nutritional deficiencies

Keratinization disorders	Affected age group	Frequency	Clinical characteristics
Ichthyosis vulgaris	Children and adults	Rare	Thin squamae together with dry skin mostly in lower abdomen and extensor areas; perifolicular skin papules; palmar hyperlinearity; progressing with filaggrin mutation, rare forms, often together with atopic dermatitis
Netherton syndrome	Children and adults	Very rare	Eczematous skin lesions showing linear serpiginous pattern together with double-edged squamae; hair shaft anemia (bamboo hair); high serum IgE; eozinophilia
Nutritional deficiencies			
Zink deficiency	Children	Rare	Often erythematous squamous patches and plaques around mouth and anus; its rare congenital form may accompany diarrhea and alopecia
Neoplastic diseases			
Cutaneous T cell lymphoma	Adults	Rare	Pink-brown thin squamous macules and plaques; weak response to topical corticosteroids; varying itching (at early stages)

IgE: Immunoglobulin E

Role of skin tests in diagnosis

Skin prick tests [skin prick test (SPT) with food allergens or food cuttings, prick to prick test (PPT)] and serum-specific IgE tests are widely used methods when an IgE-mediated food allergy is suspected.

In recent years, atopy patch tests (APT) have been introduced for assessing IgE-dependent and IgE-independent late phase skin reactions in AD. There are no standardized challenge tests to reveal the relationship of SPT, IgE-specific and APT results with the condition and to clarify the role of aeroallergens.

No easy-to-use *in vivo/in vitro* tests with high sensitivity and specificity

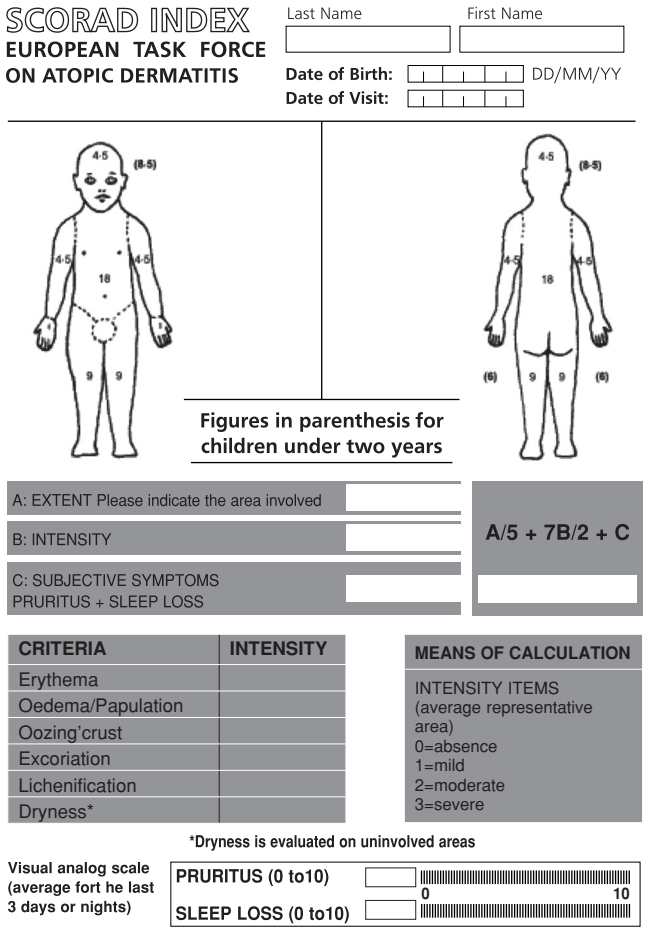

Figure 2. SCORing Atopic Dermatitis index

Table 8. SCORing Atopic Dermatitis

SCORAD criteria
Clinical signs
Erythema 0-3 Edema/papule 0-3 Oozing/crusts 0-3 Excoriation 0-3 Lichenification 0-3 Xerosis 0-3
Subjective complaints
Visual analog scale (sleep loss-itching) 1-10
Mild eczema if less than 25 points, moderate if between 25-50 points and severe if over 50 points SCORAD: SCORing Atopic Dermatitis

are available at the present which can be used in the diagnosis of AD and identification of the triggering factors. Despite the high sensitization rates achieved with the tests applied in daily practice, weak relationship of these allergens with the clinic of AD makes the process even more complicated. The age-based variance of the factors affecting AD prognosis is shown in Figure 3[50].

Food allergy

The allergic sensitization process, which is called atopic march in AD, is thought to emerge as food allergy in early childhood[50-53]. Chicken eggs, cow milk, wheat, soya and peanuts are the most accused foods in infancy; fish, seashells and nuts in later periods; and pollen-related food allergies (e.g. apples, celeries, carrots and hazelnuts in those who have a birch pollen allergy) in late childhood, adolescence and adulthood[54-57]. While tolerance to these allergens may develop in time (e.g. eggs and cow milk), peanut and seashell allergies may prevail lifelong. For this reason, it is recommended to reassess patients in regular intervals[51,58,59]. Food allergies may manifest with different symptoms and signs in patients with AD[59,60].

Early type reactions: Urticarial lesions (local, generalized), angioedema and flushing occur mostly within the first 2 hours and may be accompanied by gastrointestinal system (GIS), respiratory and cardiovascular signs. They do not cause inflammation in AD lesions.

Combined reactions: Pruritus emerges 2 hours after food intake. It leads to secondary inflammation in AD lesions due to itching.

Late type reactions: They develop within 6-48 hours after exposure to the responsible food. They result in worsening of AD lesions (eczema response)[61].

Diagnosis of food allergy[57,62,63]

- Detailed anamnesis, physical examination,
- Skin prick tests (SPT, PPT),
- Skin application food test,
- Food-specific IgE antibodies,
- APT,
- Oral challenge test and elimination diet.

The skin tests in AD are performed optimally in cases resistant to treatment, in cases where skin symptoms aggravate after food intake and in the presence of both of these[55].

Serum-specific immunoglobulin E measurement: It is preferred in cases where distinct dermographism and eczematous lesions are present, where antihistaminic therapies that may affect SPT cannot be discontinued and where test compliance and histamine response are decreased such as in early childhood (>2 years of age)[60,64]. The diagnostic value of food-specific IgE is lower in children older than 2 years compared to infancy, the reason being that although food allergy diminishes with advancing age, specific IgE remains detectable[51].

Atopy patch test: It has started being used in AD in recent years to assess IgE-dependent and IgE-independent late phase skin reactions. As in patch test, allergens are assessed after a closed application in this test[51,62,65-68]. In the report published by the European Allergy and Clinical Immunology Academy APT application with foods is recommended in the following cases[69]:

1) In patients suspected of having a food allergy but whose SPT was not positive or who did not have a significantly high serum-specific IgE,

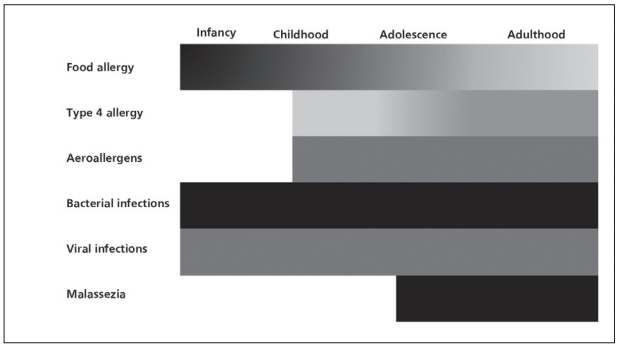

Figure 3. Variation of triggering and disease-complicating factors in atopic dermatitis by age

Table 9. Eczema Area and Severity Index

EASI criteria	Body regions
Erythema Induration Excoriation Lichenification Total score	Head/neck, trunk, upper extremity, lower extremity

Severity of each sign will be scored between 0-3. Maximum score is 72
EASI: Eczema Area and Severity Index

Table 10. Investigator global assessment

IGA criteria	
Erythema Infiltration Papulation Leakage Rough skin	0 (clear)-5 (very severe disease)

Total score is between 0-25
IGA: Investigator global assessment

Table 11. Six Area, Six Sign Atopic Dermatitis

SASSAD criteria	Body regions
Erythema Exudation Excoriation Dryness Cracking Lichenification Total score	Head/neck, trunk, arms, hands, legs, feet

Scoring 0 (absent), 1 (mild), 2 (moderate) and 3 (serious)
Total score is between 0-108 SASSAD: Six Area, Six Sign Atopic Dermatitis

Table 12. Patient-Oriented Eczema Measure: It is calculated based on answers given to the question how many days in a week do the symptoms occur

POEM criteria
Itching Sleep disorders Weeping skin Oozing skin Skin cracks Scaling Dry/rough skin

Total score is 28. No days: 0 points, 1-2 days: 1 point, 3-4 days: 2 points, 5-6 days: 3 points, everyday: 4 points
POEM: Patient-Oriented Eczema Measure

2) In patients with severe and/or treatment-resistant AD with unidentified disease triggers,
3) In AD patients who do not have evidenced clinical findings although they had multiple IgE sensitization.

In the diagnosis of AD, only 1/3 of the suspected foods cause real food allergy that is evidenced with double-blind placebo controlled food challenge (DBPCFC)[70-75] and the relationship of allergens found in positive skin tests with the condition should be verified with elimination diets and oral challenge tests. Although diminished symptoms after an elimination diet confirm the diagnosis of food allergy, the diagnostic value of an elimination diet and/or keeping a symptom/food diary has not been demonstrated in a sufficient number of studies[55].

The oral challenge test: It is used to verify a diagnosis of food allergy or to find out whether or not a tolerance has developed to that food. Oral challenge tests can be performed in 3 different ways, open-label, single-blind and double-blind[71]. DBPCFC is the gold standard in the diagnosis of food allergy[53-55,60,70]. As double-blind tests are not practical, open-label and single-blind food challenge tests are used more often in clinical practice. Provided that these two tests are negative and the objective symptoms that develop when they are positive in conformity with the anamnesis and laboratory tests, they have a diagnostic value without a need for DBPCFC. Food challenge tests should be performed by medical staff specialized in this area and in the presence of emergency equipment[55,60,70].

Besides the conventional methods, many other tests have been introduced in recent years including basophil histamine release test, lymphocyte stimulation, facial thermography, stomach fluid analysis, endoscopic allergen challenge, hair analysis, kinesiology test, allergen-specific IgG (particularly IgG_4) measurement, cytotoxicity test, electrodermal test (Vega) and mediator release assay (LEAP diet). Since there is not enough evidence to show the effectiveness of these tests, their use in the diagnosis of food allergy is not recommended. Although not a routine test in the diagnosis of IgE-mediated food allergy, the basophil histamine release test is reported to be a test that can be used for research purposes[55,59].

Inhalant/aeroallergens

Sensitization to aeroallergens is frequently seen in AD patients, and contrary to foods, their prevalence increases with advancing age. House dust mites, pollens, animal epithelium and fungi are the most known aeroallergens[50,60]. The IgE-mediated sensitization to aeroallergens found in those with a respiratory tract allergy through anamnesis and physical examination is usually compatible with the clinical condition. However, positivity found in patients with AD may be the cause of an accompanying respiratory tract allergy and may not be associated with the skin lesions of AD[72]. Inhalation of aeroallergens may lead to release of pro-inflammatory cytokines from the skin in sensitized individuals, but the effectiveness of avoidance measures has not been shown in a consistent way in studies, nor could the effectiveness of immunotherapy with those allergens in AD be clearly demonstrated[49,60,73]. While a positive result is obtained only rarely in APTs performed with aeroallergens in patients with a respiratory tract allergy and healthy subjects, the rate ranges between 30-50% in patients with AD[49,66,74,75]. In summary, there are no standardized challenge tests in AD to determine the relationship of SPT, specific IgE and APT results with the condition and to clarify the role of aeroallergens. Therefore, the results of SPT, specific IgE and APT, which are frequently used in daily practice despite their low predictive values, should be evaluated in combination[70,76].

Standard patch test

The prevalence of allergic contact dermatitis (ACD) in patients with AD (6-60%) is at similar levels as the general population. In the presence of the anamnesis and physical examination findings mentioned below, possibility of ACD should be considered and a patch test should be performed[60].

1) Vesicular dermatitis on the eyelids and/or face, neck folds, dorsal hands and finger tips,
2) Extraordinary/atypical lesion localization areas (e.g. localization on feet),
3) Newly emerging dermatitis,
4) Patients not responding to standard AD treatment,
5) Patients with AD without a family history of late-onset and atopy.

Although it is well known that allergens play a role in varying degrees in patients with AD, as stated in international guidelines, if there is no suspicion of food allergy in an anamnesis, it is not appropriate to perform allergy tests. Extensive efforts to discover allergic grounds should not lead to performing unnecessary tests and ignoring proper skin care, classical treatment and patient education approaches, which are the essence of patient management.

Treatment

Topical treatment

Since a complete cure cannot be achieved in AD, the main purpose of a treatment is to suppress the acute attacks and symptoms and to put the disease under long-term control. Topical agents are greatly involved in the treatment as epidermis and epidermal barrier assume the major role in the pathogenesis of the disease[1].

The topical treatment of AD can basically be divided into 3 main groups:
1) Reinforcement of the barrier function,
2) Controlling inflammation,
3) Treatment of *Staphylococcus* colonization

1) Reinforcement of the barrier function

In patients with AD, the barrier function of epidermis is impaired and xerosis emerges as a major finding. Therefore, reinforcement of epidermal barrier and elimination of xerosis is the most important step of the treatment in all patients with AD. Regular daily use of moisturizers should be recommended to all patients. While moisturizers assist the treatment in all forms of AD, they alone are remedial agents in the mild forms[77,78]. Besides increasing the hydration of the skin, moisturizers also decrease the symptoms and signs of AD such as itching, erythema, fissuration and lichenification[79-81]. The moisturizers marketed recently contain ceramides, free oil acids and cholesterol, which are present in the natural structure of epidermis. Although these moisturizers are known to have positive effects in both preventing dryness and reinforcing epidermal barrier in AD, sufficient data is not available to say that they are superior to other moisturizers[1,82]. The crucial point in the selection of a moisturizer is to choose an odorless and reliable one that has a small percentage of preservatives and a low possibility of producing sensitivity. It should be noted that the efficacy of a moisturizer may change from person to person depending on many factors including

the degree of skin dryness and daily activities of the patient and the contact agents to which he/she is sensitive. Proposing options to the patient in this matter and determining a patient-specific frequency of use may facilitate compliance with the treatment. Moisturizers containing urea are not appropriate for children[1]. Use of a moisturizer containing propylene glycol should not be recommended for patients less than 2 years of age as it may cause irritation[83]. Moisturizers should be applied to the whole body once to three times daily, that is, as often as necessary to eliminate skin dryness. The best application would be the one done within 5 minutes immediately following a bath after toweling the excess water. If a moisturizer is being used together with another topical medicine, it should not be applied at the same time to avoid diluting that medicine[84]. Patients should wait at least an hour after applying a moisturizer before they apply an anti-inflammatory agent[1]. Use of moisturizers in AD is summarized in Table 13.

2) Controlling inflammation

Topical corticosteroids

Topical corticosteroids (TCSs) remain to be the first agents preferred in both the treatment of attacks and achieving long-term remission in AD. Their effect on AD occurs due to their inflammation-suppressing properties. They suppress many genes and particularly the genes coding proinflammatory cytokines by binding to corticosteroid receptors in cells. The most important point that should be considered both to achieve an effective result and to protect the patient from side effects in corticosteroid use is the selection of a corticosteroid of a correct strength with an appropriate carrier. In such selection, factors such as the characteristics and localization of the lesion and the age of the patient should be taken into consideration. Very strong TCSs should not be preferred for the face, eyelids, genital areas, neck, and intertriginous regions as they are more sensitive to local side effects. Since babies and children are at more risk than adults for both local and systemic side effects, very strong steroids should also not be used for patients in this age group[3,82]. The problems that can arise from uncontrolled use of steroids should be explained to the patient and their loved ones who apply the treatment without creating a fear of steroids and the safety of controlled use should be stressed for the patient group that declines to use them due to a fear of steroids. TCSs are applied twice a day for the treatment of acute attacks. However, some studies have shown that results equivalent to the application of TCSs twice a day are obtained when they are applied once a day. In order to facilitate patient compliance and to avoid unnecessary drug use, it can be recommended to start with an application of twice a day at least during the first few days of the treatment in acute attacks and bring it down to once a day as response is obtained. Rubbing a fingertip unit (the area from the distal interphalangeal joint to the fingertip in an adult index finger) of TCS into an area as broad as 2 adult palms is a sufficient application. This amount corresponds to approximately 0.5 mg[82]. After the active disease is brought under control with daily applications, a long-term TCSs application twice a week on the region with prior dermatitis has been observed to enable a longer remission time without any side effects[3,85,86]. Using these agents together with the wet-wrap method has been reported to be both effective and reliable in the treatment of resistant attacks that do not respond to TCSs[82]. The possible local side effects include atrophy, acneiform eruptions, rosacea, perioral dermatitis, hypertrichosis, telangiectasia/purpura/stria formation, hypopigmentation, aggravation in skin infections, delayed wound healing, and ACD. Recommendations to minimize possible side effects after clinical improvement is achieved include transition to another less strong medicine, intermittent use (2 days in a week) and combination therapies with other non-steroid medication. The possible systemic side effects associated with TCSs include Cushing syndrome, femoral head necrosis, development of cataract or glaucoma, and suppression of hypothalamic pituitary axis. This risk emerges as a result of using strong or very strong TCSs on broad body areas for extended periods of time or under occlusion. It is recommended to use such strong corticosteroids at most twice a day for 2-4 weeks without exceeding 50 grams a week for very strong drugs or 100 grams a week for strong ones[86-88]. Use of TCSs in AD is summarized in Table 14.

Table 13. Moisturizers in the treatment of atopic dermatitis

Effects	Reduces water loss from epidermis Enhances barrier function Reduces the need for corticosteroids Palliates symptoms of erythema, squama, xerosis, fissuration and itching Delays development of AD
Indications	Every patient with AD should use
Dose	1-3 times daily, frequency may be increased until xerosis disappears Application within the first 5 minutes after a bath increases effectiveness
Side effects/ contraindication	Contact sensitivity, irritation
Pregnancy and lactation	Safe
Pediatric use	Those containing urea should not be used Those containing propylene glycol should not be used below 2 years of age
Follow-up in long-term use	Safe

AD: Atopic dermatitis

Topical calcineurin inhibitors

Topical calcineurin inhibitors suppress synthesis of inflammatory cytokines in tacrolimus and pimecrolimus T cells, keratinocytes and Langerhans cells which show their effects by inhibiting calcineurin phosphatase, a cytoplasmic enzyme[82]. Pimecrolimus 1% cream is suitable for use in patients over 2 years of age with mild and moderate AD. Tacrolimus is used in patients with moderate and severe AD; its 0.03% form in patients between 2-16 years of age and its 0.1% form in those over 16 years of age. Neither tacrolimus nor pimecrolimus has been approved for use in children below 2 years of age[82,86]. Initially they are applied twice a day. After active dermatitis signs recede, they may be used further 2-3 times a week on the area where dermatitis recurs most often[82-84]. They should not be recommended in occlusion form. Its combination with phototherapy is also not appropriate[13]. The most frequently seen side effects associated with these agents are mild local side effects such as itching, tingling and burning that are more distinct during the first few days of the treatment and fade away in

time. Patients should be informed about these side effects to avoid interruptions in the treatment because of them. Vulnerability to viral infections such as herpes simplex may also occur. ACD and rosaceous granulamatous reactions are among rarely reported side effects. To avoid increasing the risk of carcinogenicity, exposure to ultraviolet light should be avoided after the application and they should not be used together with phototherapy[3,82,88]. Whether its long-term use lead to a tendency to malignity is one of the most debated issues in relation to the use of calcineurin inhibitors. Although quite a few, some reports on patients who were diagnosed with skin cancer and lymphoma during their treatment with these agents have led United States Food and drug Administration (FDA) to impose a container alert in 2006[82,89]. However, such association was not supported by the follow-up studies that have been conducted for 10 years[90]. In a recent meta-analytic study reviewing the studies investigating the relationship between AD and lymphoma occurrence, the risk of lymphoma was observed to increase a little in patients with serious AD but this risk had no significant correlation with the topical therapies used[91]. Even so, in order not to increase the amount passing into the systemic circulation, topical calcineurin inhibitors should not be recommended to erythrodermic patients and occlusion-type applications should be avoided[3]. Furthermore, patients and/or their loved ones should be informed about the alert on the drug container to prevent unnecessary worries about it. Use of topical calcineurin inhibitors in AD is summarized in Table 15.

Table 14. Topical corticosteroids in the treatment of atopic dermatitis

Effects	Treatment of mild-moderate-severe attacks
Indications	Short-term treatment of mild-moderate-severe acute and chronic dermatitis Long-term treatment by applying intermittently to the area with prior dermatitis (proactive treatment)
Dose	In treatment of attacks, once or twice daily until clinical signs remit, Afterwards twice a week for maintenance
Side effects/ contraindication	Local side effects: - Risk increases with long-term use and highly strong steroids and in areas where the skin is thin - Atrophy - Acneiform rashes, rosacea, perioral dermatitis - Hypertrichosis - Talengiectasia/purpura/stria formation - Hypopigmentation - Aggravation in skin infections - Delayed wound healing - Allergic contact dermatitis - Glaucoma, cataract (when used around eyes) Systemic side effects: - Seen rarely. Risk increases with long-term use of highly strong steroids in larger areas - Cushing syndrome - Femur head necrosis - Suppression of hypothalamic pituitary axis
Pregnancy and Lactation	Category C
Pediatric use	Sensitive to systemic absorption (broad surface area according to weight) Avoid using very strong steroids
Follow-up in long-term use	Follow up on side effects

Combined use with topical corticosteroids

Starting with a steroid of medium or high strength and applying tacrolimus pomade on the healing area occasionally has been shown to be an effective practice for protection from the next attack and for avoiding the necessity of using TCSs again[92].

Wet-wrap application

Described in 1987, the application of wet-wraps is an effective treatment method that can be recommended for the treatment of patients with moderate and severe AD; it aims at increasing the absorption of a topically applied agent[93]. In this practice, the skin is wetted through having a bath, the topical agent (moisturizer, TCS or topical calcineurin inhibitor) is spread on the area of concern and a piece of gauze or cotton cloth wetted with warm water and then squeezed is wrapped

Table 15. Topical calcineurin inhibitors

Effects	Suppresses synthesis of inflammatory cytokines from T cells, keratinocytes and Langerhans cells by inhibiting calcineurin phosphatase
Indications	*Pimecrolimus:* - Short-term treatment of mild attacks in patients for whom topical corticosteroids cannot be used due to side effects - Treatment of the face, intertriginous areas and eyelids - Long-term treatment by applying intermittently to the area with prior dermatitis (proactive treatment) *Tacrolimus:* - Short-term treatment of mild-moderate-severe attacks in patients for whom topical corticosteroids cannot be used due to side effects - Lesions resistant to topical corticosteroids - Treatment of the face, intertriginous areas and eyelids - In long-term uninterrupted corticosteroid use - Long-term treatment by applying intermittently to the area with prior dermatitis (proactive treatment)
Dose	In treatment of attacks, twice daily until clinical signs remit afterwards 2-3 times a week for maintenance
Side effects/ contraindication	Burning, pricking (more during the first days of treatment, then fading away) vulnerability to herpes simplex infection
Pregnancy and lactation	Category C
Pediatric use	No FDA approval for under 2 years of age Tacrolimus %0.1, approved for over 16 years of age
Follow-up in long-term use	Increased risk of developing lymphoma and cutaneous malignity (questionable)

FDA: United States Food and Drug Administration

around the area. This wet layer is then wrapped again with a dry piece of gauze that will be kept there for about 8 hours. The humid medium formed by a wet-wrap procedure increases both the hydration of the skin and the absorption of the topical agent. It also helps break the itching-scratch circle as it forms a physical barrier. The efficacy of this treatment method has been supported by a number of studies[94-96]. It should be applied at most for a period of 2 weeks[88,97]. This method can be used in our country for an in-patient treatment of severe attacks or resistant lesions before starting a systemic treatment.

Topical antimicrobials, antiseptics

Both inadequate physical barrier and impaired antimicrobial peptide production result in more frequent occurrence of skin infections in patients with AD. Particularly *S. aureus* is the most important factor leading to colonization and clinical infection in these patients. Even its colonization alone without causing clinical infection triggers inflammation in patients with AD. This happens because the toxins they secrete act like superantigens and exogenic protease inhibitors increase allergen penetration by damaging the epidermal barrier[82]. To avoid drug resistance, routine use of antimicrobials is not recommended in the treatment of AD[82]. Antimicrobial agents should be reserved only for the cases involving clinical infection findings. Diluted bleach baths have become a popular method recently against *S. aureus* colonization and infection[98,99]. In this method, half a glass (120 mL) of domestic 6% bleach is diluted in a fully filled bathtub (150 liters) to have a concentration of 0.005%. A 5-10 minute bath without sinking the face and neck into the tub is repeated twice a week[86]. The use of intranasal mupirocin cream, an anti-inflammatory agent and a moisturizer in combination with bleach baths is reported to be a good treatment regimen especially in patients having staphylococcal skin infections frequently[100]. However, it was shown in another study that bleach baths were not superior to baths with plain water with respect to colonization or AD clinic[98]. Therefore, to be able to say that they are effective, further scientific data is needed.

Failure in topical treatments

The major reason for failure in treatment is the problem of patient compliance with treatment. The possible causes of such incompliance are listed in Table 16. The problem can be solved by arranging the treatment in line with the patient's living conditions and verbally explaining and/or schematizing the medications to be used according to the patient's sociocultural level.

Systemic treatment

A need for systemic treatment may arise in patients with moderate and severe AD which cannot be fully controlled with topical treatment (Table 17). To start a systemic treatment, it should be observed that the skin signs of the patient result in significant physical, emotional and

Table 17. Systemic therapies in the treatment of atopic dermatitis

- Phototherapy and photochemotherapy
- Systemic antihistaminics
- Systemic antimicrobials
- Immunomodulator agents
- Systemic steroids
- Cyclosporine A (CsA)
- Azathioprine
- Mycophenolate mofetil
- Methotrexate
- Interferon gamma
- Leukotriene inhibitors
- Oral calcineurin inhibitors
- Crisaborole (phosphodiesterase inhibitors)
- Biological agents
- Dupilumab
- Omalizumab
- Ustekinumab
- Rituximab
- TNF-α inhibitors (etanercept infliximab)
- Other treatments

TNF-α: Tumor necrosis factor-alpha

Table 16. Problems in compliance with topical treatment and proposals for solution

Problems in compliance with topical treatment	Proposals for solution
1. Running out of prescribed drug before the time sufficient for treatment has passed, being unable to get new prescription	- Inform patient about the length of treatment - Increase number of boxes prescribed depending on the area of lesions
2. Application in wrong frequency and amount. (applying more than needed and running out of drugs in a short time or applying inadequate amounts)	- Explain patient how the treatment should be used
3. Procedure being time consuming and tiring	- Find formulas suitable to patient (reducing treatment frequency, keeping drugs at work, obtaining help from family members when applying, motivation with frequent checks)
4. Thinking that treatment would render useless	- Inform patient about the disease and treatment options
5. Ineffective application (bath after drug use, applying insufficient amounts or use of moisturizers at the same time with an anti-inflammatory agent)	- Explain patient how the treatment should be used
6. Discomfort from applying topical products (feeling of oily skin, oiling of clothing, odor, etc.)	- Find formulas suitable to patient (preferring lotion-type moisturizer, replacing it with another agent or night-time use)
7. Not knowing where to apply each of more than one topical product prescribed	- Explain patient how the treatment should be used, provide patient with treatment schemas
8. Being unaware that the disease is a chronic one	- Inform patient about the disease
9. Not using due to fear of steroids	- Inform about steroids

social effects. These medicines should be used in their lowest doses that are enough to control the disease and maintenance should also be done in the lowest doses possible. The most widely used therapies with known efficacies in the treatment of AD are cyclosporine (Cs), methotrexate (MTX), mycophenolic acids and azathioprine (AZA). Data on leukotriene inhibitors and oral calcineurin inhibitors are limited and their place in routine use is small. Although systemic corticosteroids are important agents used to suppress acute enfls and exacerbations, they are not preferred much even for short periods due to their side effects and the fact that they lead to rapid enfls when the therapy is stopped. Their long-term use is not recommended at all. Despite their widespread use, adequate data on the use of systemic immunomodulator drugs is not available with respect to appropriate dose, length of treatment and follow-up protocols. IFN-γ is used in patients with resistant AD for whom systemic treatment and phototherapy are used or other treatments are not appropriate and its efficacy varies from patient to patient with a moderate level of success. There have been a lot of expectations from biological drugs. Except for a few new agents, satisfactory results have not been obtained from those that have been tried. They are used rarely in AD because they are new and studies showing their efficacy are not adequate. When deciding on the treatment, patient-specific decisions should be made taking into consideration the disease history, accompanying health conditions and the situation at that moment[83,101].

Phototherapy-photochemotherapy

Due to the increased photocarcinogenesis effect of ultraviolet (UV) A and UVB, narrowband-UVB is the most preferred therapy today in terms of effectiveness and safety[102-104]. Phototherapy is recommended as a second line treatment in the case of failure in the first line treatment composed of moisturizers, TCS and topical calcineurin inhibitors. It can also be used as a maintenance treatment to control the chronic disease. The light method selected should be under physician supervision and management considering the factors such as practicability, cost, patient skin type, history of skin cancer and use of light-sensitive drugs. A domestic type phototherapy may be advisable for patients who are unable to receive phototherapy from healthcare institutions due to social reasons. The treatment protocols and parameters for the use of phototherapy in patients with AD are implemented under the rules used for psoriasis patients by way of a similar method[102-104]. Phototherapy may be implemented as a maintenance treatment or as a continuous or intermittent treatment for patients with refractory or chronic disease. Those who use a calcineurin inhibitor together with phototherapy should be warned that the possible side effects of phototherapy will increase. Actinic damage, local erythema and sensitivity, itching, burning, and prickling are the most frequently reported side effects. Its rarer side effects include non-melanoma skin cancer, lentigo, light eruption (particularly polymorphous light eruption), folliculitis, photoonycholisis [particularly with psoralen + UVA (PUVA) use], melanoma, HSV reactivation and facial hypertrichosis. Cataract formation is also a known side effect in an UVA therapy[102-104]. Studies have evidenced safe and effective use of both UVA and UVB phototherapies in children and adolescents. Psychosocial factors may be effective in a successful treatment in child patients as lamps and machinery may be seen as frightening. There is no study reporting long-term outcomes of phototherapy use in children with AD. The risk of non-melanoma skin cancer has been reported for children receiving PUVA therapy for psoriasis. Sites using narrowband UVB between 311-313 nm are agreed to be a first line agent for children as they are safe and effective in the treatment of light-sensitive dermatosis. Therefore, phototherapy is appropriate for the treatment of children with AD that does not respond to topical treatments[105].

Home phototherapy

The most important factor restricting the widespread use of phototherapy is the frequent travels of the person who implement this therapy. Home phototherapy is an excellent alternative prior to systemic treatments. However, there are no studies on the effectiveness and safety of home phototherapy in patients with AD; similarly, there are no studies on office phototherapy. Home phototherapy under the supervision of a physician may be advisable for patients who are unable to receive phototherapy in an office setting[102-104,106].

Lasers and extracorporeal phototherapy

Various laser methods including excimer, diode and pulse-dye lasers have been tested in patients with AD for their properties in the improvement of some parameters such as itching and quality of life. However, the number of publications is very limited and considering its quality, lasers are not recommended for the treatment of AD yet[107]. Extracorporeal phototherapy is used to control the severity and symptoms of severe and erythrodermic AD. Various rates of response among patients range from complete remission to no response. Extracorporeal phototherapy is not recommended for a routine treatment of AD[108].

Oral antihistaminics

Patients with AD often describe severe itching that affects their quality of life. Oral antihistaminics are used to treat itching in patients with AD to improve their quality of life, but there is not sufficient evidence to recommend their use. The cause of itching in AD is linked more to the increased skin temperature than histamine degranulation. Short-acting sedative antihistaminics may be useful to prevent secondary sleep loss due to itching, but topical antihistaminics should not be preferred[109]. It has been concluded that antihistaminics not leading to sedation are ineffective in the management of AD and only their sedative forms can improve the quality of sleep[13]. Non-sedatives are recommended at level A and sedatives at level C and the evidence level is 2 for non-sedatives and 3 forr sedatives[110,111]. Oral antihistaminics are used in conventional doses, but the dose can be increased up to 4-fold particularly for itching. Their common side effects are sedation, dry mouth, blurred vision and tachycardia[109-111].

Oral antimicrobials

S. aureus and HSV infections may be seen more frequently and extensively in patients with AD. Presence of purulent exudes and pustules may suggest diagnosis of a secondary bacterial infection on top of dermatitis-related inflammation. Use of systemic antibiotics is not recommended in the treatment of AD without infection, but it can be recommended for patients with bacterial infection related clinical signs. "Eczema herpeticum" associated with HSV infection increases patient morbidity, in which case systemic antiviral agents are used. Antibiotics are recommended at level A if there is infection and their evidence level is 1; if not, they are recommended at level B, evidence level being 2[112,113].

Immunomodulators

Systemic steroids

Systemic steroids are used orally and intramuscularly in the treatment of AD to achieve fast clinical recovery. However, it is important to administer them to limited patient groups for short periods and in a controlled way. The side effects associated with the use of systemic steroids include many short- and long-term signs and particularly the well-known and frequently seen conditions of hypertension, glucose intolerance, gastritis, weight gain, decreased bone intensity, adrenal suppression and emotional instability. It has not been shown that they cause an increase in the risk of infection[99]. Due to side effects, rebound effect and the possibility of recurrence of the disease in a more severe form, systemic steroids are not preferred today as much as they used to be in both adults and children. Their use for fast disease control in a short time may be acceptable in case the efficacy of other systemic drugs starts late. Systemic steroids are recommended at level B in the treatment of AD and their evidence level is 2. Their most common forms of use are oral prednisolone and intramascular triamcinolone acetonide. Oral prednisolone is used in doses of 0.5-1 mg/kg/day. It is not preferable in the first two trimesters of pregnancy as it may cause congenital anomalies. It can be used with confidence in the last trimester and particularly after the 28th week. All potential side effects of systemic steroids seen in adults can also be seen in children. The impacts of corticosteroids on growth are more apparent in the prepubertal period; therefore, care should be taken when using them in that period.

Cyclosporine

CsA is an immunomodulator that has an effect on T cell differentiation and IL-2. It was first introduced for the treatment of AD in 1991[114]. CsA is an effective treatment option for patients with AD that is resistant to conventional topical treatments. CsA shows its effect in weeks 2-6 of the treatment at the earliest; in that period, a recovery more than half of the disease activity scores is expected. The efficacy of CsA in the treatment of AD is at a moderate level. Cyclosporine is recommended in the treatment of AD at level B and its evidence level is 1-2[115-117]. Similar to its use in other diseases, the CsA dose used for the treatment of AD is 3-6 mg/kg/day. In adults, 150-300 mg/day divided into two may be administered daily. Starting with a low dose and increasing it later is not usually recommended. Trying to gradually decrease the dose after the symptoms are controlled rapidly is a more preferable method. It may be necessary to adjust and change the initial and maintenance doses of CsA depending on many factors including disease severity and other medical diseases. Using general treatment principles, the dose should be decreased and stopped in the case of full or nearly full recovery in the CsA therapy, which should then be replaced by emollients, topical agents and proper care. Infection, nephrotoxicity, hypertrichosis, hypertension, hypomagnesemia, tremor, headache, gum hyperplasia, and increased risk of skin cancer and lymphoma are its side effects that first attract attention and are considered significant. At the beginning, blood pressure, kidney and liver functions, potassium, magnesium and uric acid levels, complete urinalysis, fasting lipid levels, complete blood count, tuberculosis (Tbc) tests, and if needed, Human Immunodeficiency Virus (HIV) and pregnancy tests should be performed. Follow-ups should be done once in two weeks in the first 2-3 months and then once a month and blood pressure, kidney and liver functions, potassium, magnesium and uric acid levels, complete urinalysis, fasting lipid levels and complete blood count should be checked at each check-up, and Tbc and pregnancy tests should be repeated when necessary. If creatinine level has gone up above 25%, the drug dose should be lowered to 1 mg/kg/day and it should be checked again after 1-2 weeks; if the elevation continues to be above 25% compared to the baseline, the drug should be discontinued, but if it has returned to the baseline values or the elevation is less than 25%, the lowered dose should be continued. Drug interactions are common with CsA. If an additional drug will be used especially in children, it must be questioned for interaction and the dose should be rearranged according to the patient's weight. Although long-term use of it is well known in other dermatologic diseases, information on its long-term use in AD is limited and for this reason the longest time recommended for using CsA in AD is 1 year[20]. Its pregnancy category is C. As in adults, CsA is an effective treatment method for AD also in children. Both of the dosing schemes for uninterrupted long-term use (up to 12 months) and intermittent short-term use (3 or 6 months) have been found effective in the treatment of AD. Continuous use has been reported to produce more side effects than intermittent use. As in adult patients, treatment with the lowest effective dose and maintenance should be prescribed to achieve the desired results[114-119].

Azathioprine

AZA is an imidazole derivative of 6-mercaptoprine and a purine analog inhibiting DNA production. For this reason, it is used more in inflammatory diseases with high proliferation rates. It affects both T and B lymphocytes. It is also used off-label in the treatment of AD. When used as a monotherapy in patients, AZA has been reported to improve both the skin lesions and symptoms of AD. AZA is recommended at level B in the treatment of AD and its evidence level is 2[102-104]. Studies on the use of AZA in AD have used a dose of 1-3 mg/kg/day. The drug can be given once or three times a day. Although these doses are appropriate for patients with AD, studies have not shown which doses are effective and safe. Using doses according to the activity level of thiopurine methyl transferase (TPMT) may be useful. AZA usually shows its effect late; this delay may be more apparent in some patients. To achieve full clinical recovery, treatment longer than 12 weeks may be required. When complete or nearly complete recovery is obtained, AZA should be decreased or stopped and then further remission should be achieved using topical agents and moisturizers. Using high doses of it leads to nausea and vomiting in most of the patients, making them unable to continue the treatment. A combination treatment with phototherapy is not recommended due to increased risk of DNA damage associated with exposure to UVA and possible photocarcinogen effect. Although there are liquid forms of AZA, only its tablet form is available now in our country[120]. In the process of using AZA, nausea, vomiting and other GIS symptoms (boating, loss of appetite, cramps) may be seen. Its other side effects involve various systems; headache, hypersensitivity reactions, increased liver enzyme levels and leucopenia may occur. Although increased infections, lymphoma and non-melanoma skin cancers have been observed in some patients treated with AZA, these patients were usually the ones who had been using several medications for their accompanying diseases; thus, it is arguable whether they were due to AZA use or not.

There are no studies showing such an increased risk in patients with AD who used AZA for a long time. The tests that are required before starting to use AZA include TPMT enzyme level, complete blood count, liver and kidney function tests, hepatitis B and C, Tbc tests and when necessary HIV and pregnancy tests. It is recommended to perform check-ups every 15 days in the first 2 months, once a month in the next 4 months and every 2 months afterwards and complete blood count, liver and kidney functions should be checked during each check-up, and if necessary, HIV and pregnancy tests should be repeated. Dosing can be arranged according to the TPMT level. Although the TPMT enzyme level does not change the risk of GIS intolerance or hypersensitivity syndrome, a high level of TPMT reduces the risk of myelotoxicity. Its pregnancy category is D and its use in pregnant women is strictly not recommended. No literature is available on AZA use in the treatment of AD in children[121]. Its use is recommended only in children whose dermatitis is persistent or who significantly influence the psychosocial integrity of the patient and their family. Information on the length of treatment, the rate of relapses after treatment and appropriate dose interval is not adequate[122].

Methotrexate

MTX is an antineoplastic drug that shows its effect as a folic acid antimetabolite. There are many off-label uses of it including AD. MTX is recommended as a systemic agent in treatment-resistant AD. The studies investigating the efficacy of MTX in AD largely differ from each other in terms of methodology; therefore, its efficacy could not be demonstrated fully. A remission reducing a 24-week severity score by 52% has been observed. A 34% remission continued during the 12-week follow-up period. In a study comparing it to AZA, a score reduction of 42% was found in the MTX group and 39% in the AZA group[123]. MTX is recommended at level B in the treatment of AD and its evidence level is 2[102-104]. MTX is usually given as a single weekly dose. A weekly dose of 7.5-25 mg is recommended for AD treatment in adults. There are no studies on its effective dose for AD and the doses mentioned are based on the doses used for psoriasis. The average time for the effect to occur is week 10 and if no effect is seen in weeks 12-16, the dose may be increased. Cessation of the treatment should be considered at the end of weeks 12-16 in patients who do not respond to the treatment at a sufficient MTX dose. Oral MTX is in the form of 2.5 mg tablets and it is recommended to give them every 12 hours divided into 3 doses. Use of MTX is contraindicated in pregnant women, those with serious kidney and liver disorders, bone marrow hypoplasia, leucopenia, thrombocytopenia, anemia, alcohol addiction and AIDS. Its side effects that come to mind first are hepatotoxicity, GIS symptoms, bone marrow suppression and pulmonary fibrosis. Besides these, rarely seen side effects such as kidney function disorders and changes in the sense of smell have also been reported. Although increased risk of skin cancer and lymphoma has been reported, they are associated with the use of high doses. The cumulative MTX doses given to a person should be put in medical records. The cumulative dose for liver toxicity is not known for AD and the doses applicable to patients with psoriasis are also accepted here. While liver biopsy was recommended above 1.5 gm in the old data, it is recommended today in patients who reached 3.5-4 gm of cumulative dose. Folic acid supplementation is recommended for all patients with AD who are receiving MTX to reduce possible hematologic and GIS toxicity. Although not definite, its applicable dose is 1 mg/day except on days MTX is taken. Pulmonary fibrosis may develop after its long- or short-term use; therefore, its use should be avoided in those with an underlying pulmonary disease such as asthma and chronic cough. Both female and male patients must take contraceptive measures during MTX therapy and at least 3 months after the therapy. The tests required at the onset of treatment include complete blood count, liver and kidney function tests, hepatitis B and C, Tbc tests and when necessary HIV, pregnancy and pulmonary function tests. Follow-up is weekly in the first month, every two weeks in the next month and once a month afterwards; complete blood count and liver function tests are sufficient in these checks[124]. Its category in pregnancy is X and its use is definitely not recommended. It is also not recommended during breast feeding as it mixes with mother's milk. There are no prospective studies on MTX use in children with AD. A single retrospective study comparing 12-week MTX use to low-dose cyclosporine has concluded that MTX is a slow-starting and effective therapy causing rare relapses. Calculation of cumulative doses and liver biopsy are not recommended in children. After the desired effect has been obtained, its reduction and discontinuation is recommended. Data on child patients with psoriasis show that MTX is safe in children[125].

Mycophenolic acids

Mycophenolic acids are immunosuppressive drugs that block the purine biosynthesis pathway through inhibition of inosine monophosphate dehydrogenase. Mycophenolic acids selectively affect B and T cells, and owing to this, they have a mechanism directly treating inflammatory disorders. They can be used off-label in AD for resistant cases[102-104]. Mycophenolate sodium is a form with less gastrointestinal side effects, but the trials with mycophenolic acids in AD involve only mycophenolate mofetil; however, its efficacy in AD is also ambiguous. It has been observed to have a late-starting effect, it is effective only at high doses and its clinical remission takes a long time[102-104,126]. Mycophenolate mofetil is recommended at level C in the treatment of AD and its evidence level is 3. The mycophenolate mofetil dose is 0.5-3 gm/day in AD and since there is no information on the use of mycophenolate sodium in AD, its treatment doses for other diseases (360-1440 mg/day) may be recommended. The relapse rate after discontinuing the treatment is not known. Mycophenolate mofetil is available in the forms of oral suspension, capsules and tablets and is used twice daily[127]. Mycophenolate mofetil is usually tolerated well. Nausea, vomiting and abdominal cramps are its widely known side effects. These side effects can be reduced by using its enteric coated tablets. Development of GIS symptoms, headache and fatigue are not dose-dependent and make compliance with treatment difficult. Less frequently, hematologic (anemia, leucopenia and thrombocytopenia) and genitourinary (urge incontinence, frequent urination and dysuria) disorder have been reported. No increased risk of bacterial and viral infection has been reported. They carry a potential risk of skin cancers and lymphoma as in other immunosuppressive agents. The tests required at the onset of treatment include complete blood count, liver and kidney function tests, hepatitis B and C, Tbc tests and when necessary HIV and pregnancy tests. Follow-up is every 2 weeks in the first month, every month in the next 3 months and once in 2-3 months afterwards; complete blood count and liver and kidney function tests are sufficient in these checks. Their pregnancy category is D and their use is not recommended. They have been used in the form of mycophenolate mofetil monotherapy in child patients aged 2 and over with severe AD. Due to increased hepatic

metabolism, the dose is calculated according to body surface area to be between 600 and 1200 mg/m^2. This calculation corresponds to 40-50 mg/kg/day in small children and 30-40 mg/kg/day in adolescents. Although it has been used in children with AD up to 24 weeks without any harmful effects, it has no long-term efficacy or safety profile[128,129].

Oral calcineurin inhibitors

Tacrolimus and pimecrolimus are topical agents that have been used topically for many years in the treatment of AD with evidenced effectiveness. Tacrolimus is being used also in our country in formulations of oral capsule and intravenous suspension for the prophylaxis of transplanted organ rejection. There is no systemic form of pimecrolimus. There are no studies on systemic calcineurin inhibitors in the treatment of AD. Available data is not sufficient to recommend use of systemic calcineurin inhibitors[99,102-104].

Interferon-gamma

It induces production of natural killer cells and increases oxidation of macrophages. IFN-γ has been found effective in severe AD in clinical studies, but it should be considered as an alternative treatment in patients with treatment-resistant or severe AD[2]. There are only a few studies showing the efficacy of IFN-γ in the treatment of atde[130,131]. IFN-γ is recommended at level B in the treatment of AD and its evidence level is 2. There is no optimal dose suggested for IFN-γ for the treatment of AD. It is generally administered 3 times a week[132,133]. Its major side effects seem to be fatigue, fever, nausea, vomiting, and muscle soreness. Pre-treatment tests include complete blood count, kidney and liver function tests and urinalysis; they should be repeated every 3 months during the treatment. Its teratogenic effect is not known in pregnant women and use of it is not recommended. Only follow-up is suggested in those who became pregnant while using the drug. Its use in breastfeeding periods is not recommended. There are no specific suggestions for children.

Biological agents

Dupilumab

It is an anti-IL-4 monoclonal antibody. It was approved by FDA for the treatment of AD in March 2017 and it is the first and only biologic agent approved for the treatment of AD. It was seen in two phase 3 studies, SOLO1 and 2, to achieve a 75% improvement in the AD lesion severity index in half of the patients (50% and 48%). No serious conditions were observed among its side effects other than conjunctivitis and local injection site reactions. It is found comparable to the first biological agents for the treatment of psoriasis in terms of its success rate and novelties it brought to the treatment. It is recommended in the treatment of severe and resistant AD where other agents have not been effective or could not be used due to side effects. It has not been authorized in our country yet[134].

Rituximab

It is an anti-CD-20 antibody. It prevents B cell proliferation and differentiation. It is used successfully in lymphomas, autoimmune diseases and pemphigus group of diseases. It was found effective in AD in the first 5-6 cases and its effect was reported to last up to 5 months. However, later publications have shown that its effect is small[135].

Omalizumab

There are limited number of data to assess the efficacy of omalizumab in the treatment of AD. The efficacy of omalizumab in adult patients with AD was investigated in a placebo controlled double-blind study and no clinical recovery was observed in the patients although their high free IgE levels dropped[136].

Anti-tumor necrosis factor agents

A noticeable decrease has been seen in the acute inflammation and itching scores, but their long-term effects have not been found satisfactory. They have lost their importance as acute exacerbations and aggravations in symptoms and itching have been reported in some subjects[135].

Other treatments

Tofacitinib, a JAK inhibitor, has been found effective in only a few patients. *Tocilizumab*, an anti-IL-6 monoclonal antibody, has also been found effective in only a few patients. Intravenous immunoglobulin therapy has been found effective in a few subjects, but it proved ineffective later in most of the patients who used it. Phosphodiesterase inhibitor apremilast is another therapy tried for AD. The therapies that

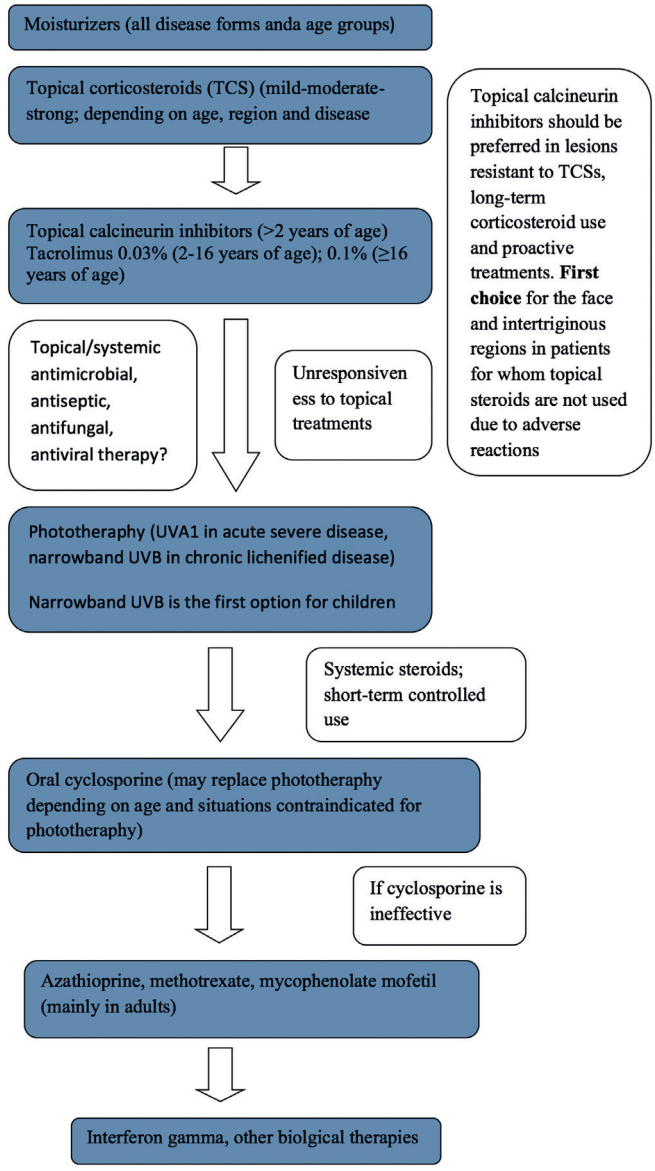

Figure 4. Treatment algorithm proposed for atopic dermatitis
UV: Ultraviolet

had been tried previously including efalizumab, alefacept, thymopentin, propylthiouracil, theophylline and papaverine are no longer in use[101-104,135]. The treatment algorithm we recommend in AD is shown in Figure 4 as a summary.

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