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Turkish Guideline for Atopic Dermatitis 2018

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Abstract

Background: Atopic dermatitis (AD) is a common inflammatory skin disease worldwide and life-long prevalence thereof can exceed 20% in developed countries. The prevalence of the disease increases gradually in developing countries and in African and Asian countries with low income.

AD affects quality of life unfavorably in a significant manner. The cost of AD is quite high both due to healthcare expenses required for treatment and causing labor loss. Patients receive long-term treatments owing to the fact that it is a disease with a chronic course and there is no curative treatment which also cause medicine expenses and a number of toxicities.

This guideline covers etiology, clinic diagnosis, laboratory, complications and treatment approaches for atopic dermatitis in details.

Atopic Dermatitis

I. Epidemiology

Atopic dermatitis (AD) is a common inflammatory skin disease worldwide and life-long prevalence thereof can exceed 20% in developed countries. The prevalence of the disease increases gradually in developing countries and in African and Asian countries with low income [1].

Generally, atopic dermatitis affects 25% of children and 2-3% of adults [2]. Data regarding the prevalence of atopic dermatitis in adults has been reported as variable with 0.3%-14.3% due to lack of multicenter stu-

dies and well-established diagnostic criteria [**3**].

The age of onset of the disease is generally 3-6 months and clinical findings are observed in 45%, 60% and 85% of patients in the first 6 months, before the age of 1 and before the age of 5, respectively [**4, 5**]. Only in a patient group as small as 2%, the symptoms appear after the age of 20 [**6**]. Family history is observed in 70% of the patients [**7**].

The course of the disease is mild in approximately 80% of children with atopic dermatitis [**8**]. In more than 70% of case, complaints do not continue in adulthood [**8**].

II. Pathogenesis

In the last decade, substantial developments have been recorded with the importance of filaggrin, immunologic changes in subtypes (Th17, Th22) of T-helper cells other than Th1 and Th2 and identification of the effect of many cytokines mainly IL-4 and IL-13 [**9**].

Basically, two important events which are responsible for the pathogenesis of atopic dermatitis is skin barrier dysfunction and overactivation of the immune system [**4**].

Pathogenetic mechanisms set forth in the skin barrier dysfunction can be listed as impairment in the proteins of various epidermal differentiation complexes and filaggrin, decrease in skin ceramides, impairments in the pH of stratum corneum and overexpression of chymotryptic enzyme [**5**]. Filaggrin is an essential protein responsible for the prevention of transepidermal water loss and microbial invasion ensuring the natural moisturization of the skin by the breakdown products [**10**]. Reduction of filaggrin metabolites in the skin causes skin barrier dysfunction also by causing a decrease in skin acidification [**11**]. One of the most well-known causes of skin barrier impairment observed in atopic dermatitis is the mutation in the filaggrin gene and is observed in 10-30% of atopic dermatitis patients. Except the filaggrin gene mutations, in almost all moderate-severe atopic dermatitis cases, there is an acquired defect in filaggrin expression. This is explained by the fact that overexpression of IL-4 and IL-13 causes a decrease in filaggrin expression by keratinocytes [**12**].

Overactivation of the immune system is conventionally predominanted by the profile of T-helper cell 2 (Th2) in atopic dermatitis. Thymic stromal lymphopoietin (TSLP), interleukin 25 (IL-25) and IL-33 are produced by keratinocytes damaged by the protease activation developing due to barrier impairment in epidermis caused by genetic or environmental factors. These cytokines initiate Th2 cell activation. Activated Th2 cells produce IL-4, IL-5, IL-13, IL-25 and IL-31. T2 cells, along with many other immune system cells and are responsible for increased levels of IL-4 and IL-13 in atopic dermatitis lesions. IL-4 and IL-13 cause an increase in the inflammatory cell infiltration to skin and as aforementioned, cause a decrease in filaggrin expression by keratinocytes hence an impairment in skin barrier function. IL-4 induces IgE production from B cells provides IL-5 eosinophil activation [**4**].

As the lesions become chronic, differences are observed in cell infiltration; T2 cytokines dominant in the acute phase are replaced by Th1-associated cytokines such as interferon-gamma (IFN- γ) and IL-12 in the chronic phase. In late lesions of atopic dermatitis, it is acknowledged that Th2 cells are accompanied by Th22 cells producing IL-22. IL-22 is responsible for keratinocyte proliferation and acanthosis developing correspondingly. In addition IL-22, along with IL-4 and IL-13, decreases the expression of barrier-related genes, such as filaggrin, loricrin and involucrin, decreasing the skin barrier function. It plays a role in the late-stage tissue remodelling by increasing the expression of IL-17 profibrotic cytokines released from IL-13 and Th17 cells [**4, 5**].

Increase in the density of nerve fibers in epidermis and low stimulation threshold in nerves are blamed for the pathogenesis of pruritus in atopic dermatitis. It is considered that TSLP, IL-4, IL-13 and IL-31 are the cytokines playing a role in itching in atopic dermatitis [**4**].

The role of microbial pathogens in the development of atopic dermatitis have been demonstrated. S. aureus, Malassezia species and Candida albicans are the microbial pathogens which play a role in the pathogenesis of atopic dermatitis [**13**]. Bacterial colonization with S. aureus is associated with skin

barrier dysfunction associated with the increase in protease activity in skin and basophil activation in skin and increase in the proinflammatory cytokine levels such as IL-31 [**14**]. S. aureus density on lesional and non-lesional skin correlates with eczema severity [**15**].

III. Histopathology

Histologic features of atopic dermatitis show similarity to a large extent with allergic contact dermatitis. In acute lesions, intercellular edema in epidermis and marked perivascular T-cell infiltration accompanied by monocytes and macrophages in dermis are observed. Lymphocytic infiltrate is formed of activated memory T-cells carrying CD3, CD4, HLA-DR, CD25 and CD45RO. In acute lesions, eosinophils and mast cells are observed whereas basophils and neutrophils are sporadic. Epidermal hyperplasia, elongation of the rete ridges, hyperkeratosis and minimal spongiosis are observed in acute lichenified lesions. Increase in the count of dendritic cells in epidermis and monocyte-rich infiltration in dermis occur. Elevated count of eosinophils are detected in dermis with the immunochemical stain of eosinophil products such as eosinophil major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin [**5, 16**].

IV. Etiology

I. Genetic Factors

Genetic factors play a role in predisposition to atopic dermatitis. Familial history is positive in 70% of patients. The risk is increased 2-3 fold with the presence of atopic dermatitis in one of the parents and 3-5 fold in case both parents have atopic dermatitis [**2**]. In twin studies, concordance ratios has been found to be 85% in monozygotic twins and 21% in dizygotic twins [**17**].

Genetic factors play a role in immune dysfunction and skin barrier dysfunction mentioned in the pathogenesis section. A strong association has been demonstrated between atopic dermatitis and mutations causing loss of function in the gene encoding the filaggrin protein [**18**]. In the filaggrin gene, the mutation has been detected in approximately 40% of patients with moderate-severe atopic eczema. In patients carrying filaggrin mutation, risk of early-onset severe atopic dermatitis and incidence of asthma have increased [**7**]. In the genome-wide association analyses performed, common variants on 11q13 and 1q21 chromosomes have been observed. Hornerin, a protein that plays a piv otal role in the region keratinocyte differentiation on 1q21 chromosome, encodes loricrin and involucrin. The only nucleotide polymorphism on the genetic region encoding claudin-1 causes decreased gene expression of claudin functioning in the structure of tight junctions between keratinocytes [**11, 19**]. A relationship has been demonstrated between atopic eczema and mutations in SPINK5 gene encoding a serine protease inhibitor. The mutation in this gene impairs the protease-antiprotease balance that is necessary to ensure skin barrier function. It is suggested that, in the genetic studies, the variants detected in the genes encoding IL-4, IL-4 receptor and IL-13, play a role in the development of eczema [**20**].

ii. Environmental Factors

The fact that the prevalence of atopic dermatitis varies within the same country, higher incidence of atopic dermatitis is observed in people migrating from the countries with low prevalence to developed countries and the prevalence increases correspondingly with urbanization demonstrates the importance of environmental factors in etiopathogenesis [**1**]. Environmental factors causing an increase in the risk of atopic dermatitis are summarized in (**Table 1**).

It is acknowledged that climate conditions affect the prevalence of atopic dermatitis. Exposure to low humidity and low ultraviolet (UV) are among the risk factors for atopic dermatitis. When the income levels of countries are equalized, symptoms of atopic dermatitis have been found to be directly proportional with latitude and inversely proportional with ambient temperature. It is suggested that this data is related to UV light exposure which have immunosuppressive effects. However, it should be noted that exacerbations may be observed in summer season in some patients. The incidence of atopic dermatitis increases in adults migrating to temperate climate from tropical climate [**1, 8, 21**].

The incidence of atopic dermatitis is higher in cities compared to rural areas. Traffic-associated air pollution increasing with urbanization has been found to be related to the development of atopic dermatitis [**22, 23**].

High education level of families are one of the risk factors for atopic dermatitis. However, the results of the studies investigating the effects of socioeconomic level are controversial [**2, 8**].

Western style diet rich in polyunsaturated fatty acids and sugar has been reported as the risk factor for the development of atopic dermatitis. It has been demonstrated that consumption of fresh fruits has a protective effect against atopic dermatitis whereas consumption of convenience food is related with severe eczema [**8, 24**].

Even though it has been suggested that lactation has a protective effect against asthma and atopic dermatitis, in the studies conducted, it has been demonstrated that the diets of babies in the first 6 months are not associated with the risk of atopic dermatitis [**25, 26**]. Current data indicates that partially hydrolized formulae and probiotic support prevent atopic dermatitis development in babies who are not only fed with breast milk [**2, 27**]. In addition, there is insufficient data to recommend any diet in the prevention of atopic dermatitis development. There are studies setting forth the relationship between atopic dermatitis and obesity in children and adults [**28, 29**].

During pregnancy and infancy, exposure to wide-spectrum antibiotics and living with uncrowded families are related to the development of atopic dermatitis [**8**]. It is suggested that exposure to infections in the early stages of life has a preventative role in the development of atopic dermatitis. According to the hygiene hypothesis, a child with multiple siblings is constantly exposed to infections in perinatal and postnatal period and therefore manifestation of the allergic disease is suppressed [**8, 17, 30**]. In uncrowded families, increased incidence of asthma and atopic dermatitis is observed in children who live under hygienic conditions and use ant ibiotics in the early periods of life [**31**]. In addition, it has been demonstrated that presence of an older sibling increases the risk of atopic dermatitis in children with filaggrin deficiency [**32**].

As mentioned under the topic Pathogenesis, skin barrier dysfunction is the main factor responsible for the development of atopic dermatitis. Therefore, environmental factors such as frequent detergent use, use of soaps that increase the pH of skin, water hardness are also responsible for the exacerbations of the disease [**33**].

Albeit controversial studies, it is accepted that smoking and exposure to cigarette smoke have no significant effect on the risk of atopic dermatitis [**2**].

V. Clinic

I. Atopic Dermatitis in Infancy

Atopic dermatitis in infancy is observed in children between the ages 0-2 [**34**]. During this period, face and extensor region involvement is typical whereas any region may be affected [**35**]. The first signs of atopic dermatitis in infants are eczematous papulovesicular and patchy lesions generally localized on cheeks. After a few weeks, excoriations due to pruritus and crusty erosions develop. Initially, perioral and paranasal areas are mostly protected. Usually thin squamations clinically similar to seborrheic dermatitis may be observed in the scalp. In severe cases, yellowish sticky crusts may be present [**5,36**]. Persisting pruritus causes restlessness in the infant. Thereafter, arms and legs can be affected. Typically, diaper region is protected. Lichenification is rare in infants. In approximately 20-30% of cases, lesions disappear following the age of 2 [**5, 8, 35**].

Table 1. Environmental factors [**2,8**]

• Living in a region of low humidity and low UV exposure
• Living in cities
• High education level of families
• Western style diet rich in polyunsaturated fatty acids and sugar
• Exposure to wide-spectrum antibiotics during pregnancy and childhood
• Living in uncrowded families
• Frequent use of detergent, use of soap which increases the skin pH, hard water

ii. Atopic Dermatitis in Childhood

Atopic dermatitis in childhood defines the clinical features observed frequently in children between the ages 2-12. In this period, involvement is observed in flexural region (antecubital fossa, neck, wrist, ankle), dorsum of the neck, hand, and foot. Reticular pigmentation also referred to as dirty neck is observed in lateral neck. Dryness and fissures behind the ear or on earlobe are typical. The lesions may be new-onset lesions whereas they may be lasting since infancy as well [**5, 6, 34**].

iii. Atopic Dermatitis in Adulthood

Even though there are authors stating that atopic dermatitis in adulthood is formed of two separate subgroups with different clinical features as cases with onset in the adulthood and cases with onset in pre-adulthood, a consensus has not been established yet [**34**]. Hand, flexural region, head and neck involvement is frequent in adulthood. Close relationship with asthma, allergic rhinitis, hand eczema and allergic contact dermatitis has been detected [**37**]. Xerosis is frequent being more significant particularly in winter time [**5**].Head-neck dermatitis in this period is typical and it should be noted that it may be an indicator for sensitivity to Malassezia furfur yeast [**6**].

iv. Types of Regional Atopic Dermatitis

Various regional atopic dermatitis types have been defined in children and adults. Genital dermatitis is frequent in infancy; atopic foot, nummular eczema and prurigo-like type in childhood and eyelid eczema in adulthood [**38**].

Nummular eczema is a type of eczema with inflamed patches or plaques having net margins and the treatment thereof is difficult. Nummular eczema is frequently secondarily infected with S. aureus. Typically, it is localized in extremities and gluteal region [**6**]. Juvenile papular dermatosis shows a course with hypopigmented lichenoid smooth papules localized on knee and elbow and commonly observed in spring and summer [**6,39**].

Atopic dermatitis is an endogenous risk factor for the development of hand eczema. Atopic hand eczema frequently involves the volar face of the wrist and dorsum of the hand and is observed more commonly with the increasing age. There is no pathognomonic evidence in the differential diagnosis of atopic hand eczema from the irritant or allergic hand eczema [**40, 41**].

Eyelid eczema with pruritus accompanied by erythema, edema and thin squamation can be observed in atopic dermatitis. With pruritus becoming chronic, development of lichenification is typical in the forthcoming period [**42**].

Chronic cheilitis with erythema, squams and fissures in both lips and commissures can be observed in atopic dermatitis [**43**].

v. Other Organ Symptoms Except Skin Signs

Atopic dermatitis is a part of the process referred to as the atopic walk and in the forthcoming periods, asthma and rhinitis can develop in patients. Asthma, allergic rhinitis and IgE-mediated food allergies, which are systemic atopic comorbidities, can be observed in approximately 40% of patients with atopic dermatitis [**20,44**]. Atopic dermatitis is among the major risk factors for the development of asthma. It has been reported that, up to 3 years of age, at least one of asthma or allergic rhinitis has been observed in 66% of children with atopic dermatitis. Besides, it has been reported that patients were predisposed to animal, food, and drug allergies [**44,45**]. The severity of eczema has been found to be correlated with the prevalence and severity of atopic comorbidities (asthma, allergic rhinitis, and food allergy); patients with atopic comorbidity in addition to eczema, it is more difficult to take the disease under control [**45,46**]. In patients with early-onset, severe atopic dermatitis, food allergy usually accompanies atopic dermatitis. IgE-mediated food allergy has been reported in 35% of children with atopic dermatitis [**44**].

In atopic dermatitis chronic pruritus and inflammation cause sleep disorders and psychiatric symptoms. Neuropsychiatric disease risks, such as depression, attention deficit, hyperactivity disorder, speech disorders in children, headaches and seizures, are increased [**47**]. Significant increase has been detected in the risk of depression in individuals with diseases such as asthma, eczema, and allergic rhinitis [**48**]. Depression and anxiety

are commonly observed particularly in cases with severe atopic dermatitis [**49**]. Severe eczema and female gender have been detected as risk factors for depression and predisposition for suicide [**50**].

It has been found that the individuals with atopic dermatitis have an increased predisposition to vitiligo, alopecia areata, rheumatoid arthritis and inflammatory bowel diseases [**51,52**]. In recent years, even though the relationship of atopic dermatitis with cardiovascular diseases is emphasized, no significant relationship has been found [**53**].

VI. Diagnosis

Clinical diagnosis is substantial in atopic dermatitis; there is no specific histological finding or laboratory test. Until today, various diagnostic criteria have been defined by many different groups. With the revision performed in 2003 on criteria determined by Hanifin and Rajka in 1980, diagnostic criteria appropriate for clinical practice has been constituted for the diagnosis of atopic dermatitis in infancy, childhood and adulthood [**2**] (**Table 2**).

In order to exclude other diseases falling within the differential diagnosis of atopic dermatitis, it may be necessary to perform, when required, skin biopsy and serum IgE level measurement, potassium hydroxide test, patch test and various genetic tests. There is no data supporting, in disease diagnosis, the use of many different cytokines and chemokines, the role of which has been demonstrated in the pathogenesis of atopic dermatitis [**2**].

VII. Laboratory

Even though high serum IgE and eosinophil values are observed in atopic dermatitis, there is no pathognomonic laboratory finding. Elevated total and/or allergen-specific serum IgE values are the most commonly observed laboratory findings. These values are normal in approximately 20% of patients. Total IgE levels do not always correlate with the disease severity. IgE levels may increase in conditions such as parasitic diseases, some cancers and autoimmune diseases [**2,54**].

Various allergens, mainly food, can be responsible for the exacerbations in approximately 30% of symptoms in children with atopic dermatitis. Children under three years of age with moderate-severe eczema should undergo skin prick test or allergen-specific IgE tests

Table 2. Diagnostic Criteria for Atopic Dermatitis [**2**]

Main Characteristics; should be present: • Pruritus • Eczema (acute, subacute, chronic): Typical morphology and age-specific distributions* Chronic or recurrent history • Face, neck and extensor region involvement in children Lesion or history of lesion in flexural regions in any age group Preserved inguinal or axillary region	**Accompanying characteristics;** Characteristics that suggest the diagnosis of atopic dermatitis, whereas due to their non-specific nature, that cannot be used for the diagnosis of atopic dermatitis in scientific studies: • Atypical vascular responses (facial pallor, white dermographism, delayed blanch response) • Keratosis pilaris (pitriasis alba/hyperlinear palm/ichthyosis • Ocular/periorbital changes • Other regional signs (perioral changes/periauricular lesions) • Perifollicular prominence/lichenification/prurigo lesions
Important characteristics; signs observed in most cases, supporting diagnosis: • Age of early onset • Atopy (Personal or familial history) • IgE reactivity • Xerosis	**Excluding characteristics;** conditions to be excluded before diagnosis • Scabies • Seborrheic dermatitis • Contact dermatitis (allergic or irritant) • Ichthyoses • T-cell lymphoma of the skin • Psoriasis • Photosensitive dermatoses • Immunodeficiency conditions • Erythrodermas due to other causes

with regard to egg white or cow milk allergies along with other food allergies observed commonly in the population. Positive results should be confirmed with food provocation tests. Food allergy tests are not recommended for children older than three years. This patient group can be investigated with regard to mite sensitivity and other common inhalant allergens [**55**].

VIII. Disease Severity Scales

There are many atopic dermatitis severity scales prepared for use in clinical studies. Among these, the statistical validity of Scoring Atopic Dermatitis (SCORAD) and Eczema Area and Severity Index (EASI) have been shown in the studies conducted [**56**].

SCORAD index is calculated by taking into account the extent, intensity and subjective complaints it causes. The extent (A) is scored by applying the rule of nine, the intensity (B) is determined by grading each of erythema, edema, effects of scratching, weepy sores, lichenification and dryness on a scale from 0 to 3 and subjective complaint (C) is scored by grading pruritus and sleep disorder on a scale from 0 to 10 followed by the calculation according to the A/5+7xB/2+C formula. Maximum score is 103 [**57**]. When EASI score is calculated, disease extent and intensity evaluated by the doctor is taken into account. As distinct from the SCORAD index, subjective complaints and signs of dryness, weepy sores are not included in the assessment [**58**].

IX. Complications

Skin-barrier impairment, immunological disorders, low antimicrobial peptide levels and long-term topical steroid use observed in atopic dermatitis, establishes the basis for serious skin infections in these patients (**Table 3**). Levels of LL-37, a cathelicidin, and b-defensin 2 (HBD-2) exerting antimicrobial activity produced by keratinocytes in normal people are decreased in atopic dermatitis. Therefore, predisposition to bacterial, viral and fungal infections is increased. Particularly, the prevalence of skin infections developing with S. aureus is significantly high. Clinically, bacterial and viral infections are observed more commonly in atopic dermatitis cases and have a sudden onset. In addition, fungal infections have an insidious onset [**36, 59**].Impetigo is frequent due to S. aureus colonization in lesions. Impetigo due to streptococci is frequent as well [**36**]. Staphylococci cause impetiginization of the lesions. Although all regions can be affected, facial, particularly perioral area involvement is typical. Recently developed and rapidly spreading weepy sores and yellowish crusts are observed [**5**].

Table 3. Complications in Atopic Dermatitis

Infective
• Bacterial infections
• Viral infections
Ocular
• Keratoconjunctivitis
• Blepharitis
• Cataract
• Uveitis
• Keratoconus
• Retinal decollement
Others
• Growth and developmental delay
• Erythrodermia

The most serious infectious complication eczema herpeticum is defined as disseminated herpes simplex virus infection arising from eczema. Monomorphic vesicles and erosions with sudden onset disseminating rapidly in 1 or 2 weeks are observed in cases with severe eczema. It is associated with grouped vesicles and extensive crusty plaques localized on face, neck and sometimes on extremities. Secondary bacterial infections and in severe and disseminated cases, meningitis and encephalitis can develop. Mostly, fever, fatigue, lymphadenopathy and lymphopenia in blood accompany skin signs. Tzanck smear can be used to support diagnosis [**36, 60**].

Molluscum contagiosum with raised papules in skin color is another viral infection developing in children with atopic dermatitis. Even though localized on flexural regions mostly, it can be observed everywhere since it is easily spread through autoinoculation [**36**].

In lesions unresponsive to treatment or showing peripheral spread gradually, superficial fungal infections should be considered. Tinea pedis and tinea faciale can be observed [**36**].

Blepharitis, keratoconjunctivitis, keratoconus, uveitis, cataract, and retinal decollement and ocular herpes simplex are the ocular complications of atopic dermatitis. The inci-

dence of ocular complications has been reported as between 25% and 50%. Seasonal allergic conjunctivitis, perennial allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis, atopic blepharoconjunctivitis, and giant papillary conjunctivitis fall under the title of chronic allergic conjunctivitis. Seasonal and perennial allergic conjun ctivitis are the most common allergic ophthalmologic diseases observed.

In general, severe pruritus, burning sensation, watering and erythema are observed bilaterally. Corneal involvement and permanent loss of vision are very rare. Vernal keratoconjunctivitis and atopic keratoconjunctivitis are more serious diseases with corneal involvement and can cause loss of vision. Vernal k eratoconjunctivitis is a disease observed usually in prepubertal period in atopic children in spring. It is associated with severe pruritus and when there is corneal involvement, photophobia, foreign object feeling and watering are observed. Atopic keratoconjunctivitis starts at the age of twenties and is a conditio n causing vernal keratoconjunctivitis-like symptoms. As distinct from vernal keratoconjunctivitis, eyelid and periorbital skin involvement are more significant. Development of cataract has been reported in 5-35% of patients [**42,61**].

In severe cases, erythrodermia as well as growth and develomental delay can be observed [**6,7**]

X. Prognosis

Atopic dermatitis has a chronic course and affects the life of patients unfavorably. However, in some patients, it has also been observed that atopic dermatitis with early age onset remits with the advancing years. 10-30% of those who have atopic dermatitis in childhood have the disease at later ages [**62**]. It has been claimed that remission rates in patients appropriately treated and followed up are higher. In addition, it has been reported that remission rates in patients with mild-moderate disease is higher than those in patients experiencing a severe disease. Another prognostic factor is that remission rates were lower in patients who were required to be hospitalized [**63**]. Predisposition to bacterial, viral and fungal infection is increased in patients with atopic dermatitis. Eczema herpeticum, a serious manifestation and a common herpes simplex virus (HSV) infection, is observed in a ratio up to 3%. Predisposition to molluscum contagiosum infections is also increased in child and adult atopic dermatitis patients. It has been reported that colonization of Malassezia sympodialis fungus is increased in patients in whom dermatitis is observed in the facial and neck region and that allergic sensitivity develops against this fungus in patients [**64,65**]. In a recent meta-analysis in which studies investigating the association between AD and lymphoma development wer e reviewed, it has been observed that lymphoma risk is somewhat increased in serious AD patients. In adult-type atopic dermatitis patients, a mild clinic with generally mild attacks and remissions, a course with mild symptoms and sometimes with severe attacks, or a course with consistently severe symptoms can be observed [**66**].

XI. Risk Factors

The development risk of atopic dermatitis starts within the mother's womb. The issue that cow milk, egg in the mother's diet, exposure to house mites in a setting constitute a risk during pregnancy and lactation is still controversial. Despite the publications with regard to the possibility that breast milk may be protective in infancy, there are controversial results such as long-term lactation increases the incidence of AD. In a Cochrane review carried out in 2006, it has been emphasized in the studies conducted that foods such as cow milk, eggs and nuts ingested during pregnancy do not increase the risk of atopic disease. Nevertheless, American Academy of Pediatrics (AAP) recommends diet during lactation period and states that peanut, walnut, egg, cow milk, and fish increase the risk [**64, 65, 67**]. It has been stated in two studies conducted that AD risk was low in a baby whose mother did not ingest foods such as milk, egg, and fish during lactation. However, the Cochrane review stated that there was no clear evidence regarding that protection from antigens during lactation period prevented atopic dermatitis in breastfed babies. They stated that, in the diet of babies who have a high risk of developing atopic dermatitis before six months of age, eating fish, eggs, nuts, and cow milk, which have a high allergic potential, increases the risk. However, there is

paucity of evidence as to the efficacy of diet in protection after six months of age. Even though protection from allergens is recommended in sensitive people, being protected from allergens during pregnancy may not be preventive since specific Th2 cells may develop in the baby in the postpartum period. It has been emphasized that nutrition rich in antioxidants, fibers and minerals during pregnancy decreased the development of allergic rhinitis however, Ca, F, and Mg decreased the risk of atopy. It has been detected that B-carotene increased the risk of atopy. Smoking increased sensitization in experimental animals [**64, 65**].

Smoking and alcohol consumption elevates the level of IgE developing against respiratory allergens in humans. Smoking and alcohol are accepted as factors increasing the risk of atopic dermatitis. Atopic disease is high in babies delivered via Caesarean section or who are premature or have low birth weight. Probiotics reduce the antigen absorption by changing the intestinal flora and support Th1 immune response which decreases in AD. Receiving probiotics during pregnancy and infancy decreases the incidence of AD between 2-4 years of age. Omega-3 and omega-6 oils have been investigated and no specific effects thereof have been detected. The subject regarding that natural life and avoiding chemical exposure decrease atopic dermatitis risk is controversial. Atopic dermatitis has been more commonly observed in children under five years and diagnosed with obesity for more than 2,5 years [**64,65,67,68**].

XII. Differential Diagnosis

The age group of the patient is very important in the differential diagnosis of AD. Since clinical symptoms differ according to age groups, diseases falling within the differential diagnosis change considerably as well. Seborrheic dermatitis is the first disease mistaken for and it is sometimes impossible to differentiate [**69**]. Even though axillary and inguinal involvement is in favor of seborrheic dermatitis, in case this differentiation is not possible, some of the clinicians recommend that diagnosis of infantile dermatitis be made. In addition, syndromes with immune system findings such as Netherton, Omenn, Hyper-IgE, Wiskott-Aldrich and, although rare, lymphoproliferative diseases such as histiocytosis should be considered in this age group. Nummular eczema is important due its coexistence and being mistaken for the disease. Also in this age group, impetigo, scabies, pyridoxine, niacin, riboflavin, essential fatty acids and biotin deficiency, phenylketonuria, and nutritional deficiencies like acrodermatitis enteropathica fall within differential diagnosis. When we examine diseases falling within differential diagnosis in both children and adults, irritant and allergic contact dermatitis are the diseases which rank first. In addition, diseases like dermatophyte infections and ichthyosis vulgaris may be mistaken for in both child and adult patients. Diseases falling within differential diagnosis only in adults are mycosis fungoides, xerotic eczema, lichen simplex chronicus, and psoriasis [**69, 70, 71**]. The diagnosis is made by diagnostic criteria and in the case of a suspicion, in order to differentiate it from other skin diseases, skin biopsy and laboratory tests such as IgE are routine ly performed [**64, 65**]. However, in selected cases, apart from these tests, screening for mycosis, patch test and genetic tests can be performed. In most of the clinical and experimental studies, it has been detected that there is a decrease in contact sensitization in AD patients. However, it is recommended that skin patch test be performed to detect and avoid the related allergens in persistent cases. Causes of other erythematous-squamous diseases, Langerhans cell histiocytosis, collagenous tissue diseases and erythrodermia and particularly T-cell lymphoma should be excluded [**64, 65, 66, 67, 68**].

XIII. Treatment

i. Non-pharmacological Methods

a. Education and Support

Atopic dermatitis is a common disease and affects quality of life unfavorably in a significant manner. The cost of AD is quite high both due to healthcare expenses required for treatment and causing labor loss. Patients receive long-term treatments owing to the fact that it is a disease with a chronic course and there is no curative treatment which also cause medicine expenses and a number of toxicities [**64**]. It can be considered that AD has preventable characteristics since the disease has triggering factors. Triggers vary for different patients and among these are various foods,

aeroallergens, irritants and contactors, hormones, stress, climate, house mites and microorganisms like S. aureus. Eliminating the allergens, diet, skin care and protection and assessment of many proven or unproven controversial subjects and performing the accurate applications are critical [**68**]. The pat ient and family thereof should be well-informed in order to ensure the most appropriate conditions in the follow-up of patients and minimize the medical treatment need. They should be informed about the critically important matters that the disease can be triggered by stress, the skin of patients is drier than normal and moisturizing has a critical importance, triggers such as chemicals and wool having allergen characteristics should be avoided; cloth selection, bed and pillow choices, minimizing the house mites and subjects as such have critical importance. Other than these, particularly in children, the patient and the families should be informed about many subjects such as the benefits of diet, choice of baby food and benefits of bathing and, in order for bathing to not be harmful, ideal bathing and what should be done after the bath; and access to reliable sources regarding this information should be ensured. Support programs and patient societies can be useful to consult and patient information brochures and similar educational instruments can be helpful as well [**64, 65, 68**].

b. Skin barrier repair

The most significant difference in the skin of atopic dermatitis patients is that their skin is very dry. With this dryness, the barrier fun ction of epidermis is impaired. Barrier dysfunction eases the entrance of allergens and irritants and dryness escalates pruritus [**72, 73**]. Therefore, the basis of treatment is to moisturize the skin and enhance the barrier functions. Regular daily use of moisturizers should be recommended to all patients. In patients with mild symptoms, only moisturizers are sufficient, however in moderate and severe patients they are used as adjuvants to treatment. After the attacks are taken under control with systemic and topical medicines, moisturizers stand out in maintenance. Thus toxicities to emerge are prevented by allowing us to lower the dose and duration of medication, mainly the corticosteroids. When used alone, moisturizers increase hydration and decrease pruritus. They decrease erythema, fissuring, rhagade and lichenification as well. It is suggested that reinforcing the epidermal barrier with moisturizers prevents atopic walk, however this has not been proven [**64, 65, 67**]. In infants in whom pre-natal atopy risk has been calculated to be high, use of regular moisturizers decreased the chance of atopic dermatitis development in these infants. This study demonstrated that moisturizers not only decrease the symptoms in AD but also have disease preventing effects and emphasized the importance of moisturizer use [**74**].

We can divide the moisturizers in three groups as emollients, occlusives and humectants. Emollients are comprised of glycol, glycerol stearate, soy sterols and their main effect is to ensure that the skin is softened. Occlusives, on the other hand, are comprised of vaseline, dimethicone and mineral oils and their main duty is to form a layer which prevents the evaporation of water. Preventing the evaporation of water enhances emollience as well. Humectants are comprised of agents drawing and retaining water such as glycerol, lactic acid, and urea [**64, 73, 74**]. Other than the classical classification, in order to enhance the skin barrier repair, there are products comprising ceramides, free fatty acids and cholesterol which are present in the natural structure of epidermis. Even though they have advantages for the epidermal repair, the superiority of these moisturizers over the conventional ones has not been proven [**75**]. In fact, there is no data or study demonstrating which type of moisturizer is ideal for which atopic dermatitis patient. Currently, the most essential feature of a moisturizer is that it is not an allergen. Since testing the moisturizers before use is not common, odorless moisturizers with less preservative ratio and less risk of sensitivity are ideal and these should be preferred. Ideal moisturizer varies for each patient and whether or not it is entirely ideal is realized after use. Ease of use and cosmetic disturbances may be important in moisturizer selection as well. Presenting various options to the patient and continuing with the most satisfying one is the best approach. Using moisturizers comprising propylene glycol and urea should not be preferred in patients under the age of two and in children, respectively. The application method of moisturizers is as essential as their type. It is

recommended that they be used after bath and 1-3 times/day depending on the need. Concomitant use with topical medicines is not recommended since it may cause dilution problems and inactivity [**64, 65, 67, 68**].

ii. Topical Treatment

a. Topical Corticosteroids

Topical corticosteroids (TCS) have been the basis of atopic dermatitis treatment for more than 50 years.

Mechanism of Action: It is suggested that topical steroids suppress the release of proinflammatory cytokines by disrupting their antigen processing mechanisms [**76, 77, 78**].

Administration: Topical steroids are administered twice a day, in the morning and night, during the acute exacerbation period in the treatment of atopic dermatitis. When inflammation regresses or remission is ensured, it may be administered once a day. There are many randomized, controlled studies and systemic reviews demonstrating that there is no difference in efficacy between once or twice daily administration [**79**]. When acute period regresses, side-effect frequency may be decreased with once daily administration. The dose of administration should be gradually reduced or switched to intermittent administration (proactive treatment) when the treatment dose is being reduced. In the acute period, steroids with moderate-high potency for 3-6 days and in the maintenance period steroids with low potency are preferred. Principles of using topical steroids in atopic dermatitis are summarized in (**Figure 1**) [**65**].

With regard to the choice of topical steroids for infants and children, a topical steroid with a lower potency compared to that of adults is preferred (**Table 4**). However, in case a response is not ensured, switching to a topical steroid with higher potency is possible by careful monitoring. In some countries, only hydrocortisone acetate and butyrate are the approved steroids for use in children under one year of age. Mometasone furoate and fluticasone propionate can only be used in chil dren older than 2 years. Other topical treatments can be used in patients above 12 years of age. Since side-effects can develop in facial and neck regions where the drug absorption is high, topical steroids with medium to low potency should be preferred [**65**].

Compliance to treatment is reduced during topical steroid use due to steroid phobia and the expected effect may not be achieved. Therefore, the families should be trained in terms of treatment and accurate topical steroid use.

Efficacy: Their use is indicated in case non-pharmacological methods are inadequate and the response is very goog when used concomitantly with moisturizers. Ointment forms are used due to dryness of the skin, however, in exudative lesions other forms may be preferred. The use of topical steroids also reduces the Staphylococcus aureus colonization on the skin [**80**].

Side-effects: Well-known side-effects such as skin atrophy, petechiae, striae, telangiectasia, color changes, acneiform eruptions, and local infections may occur; additionally as a result of sudden discontinuation of treatment, exacerbations or, despite the treatment, loss of efficacy referred to as tachyphylaxis may develop [**65**].

Topical steroids are safe during pregnancy and lactation, however, it should be of note that use on an extensive skin area may incur unfavorable effects on fetal growth. Steroid should not be administered on breasts shortly before lactation and should be cleaned if there is any.

Combination with topical antibiotics: There is no data as to the superiority of topical steroids plus antimicrobials to monoth erapy [**65**]. Therefore, topical steroids are sufficient in AD as monotherapy. In the case of infection on the involved area, infection treatment principles should be complied with.

b. Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (TCI), tacrolimus and pimecrolimus (**Table 5**) [**76, 77**], are steroid-free agents with anti-inflammatory effects in both acute exacerbations and mai ntenance treatment of AD in adults and children above 2 years of age [**76, 77**].

Mechanism of Action: TCIs show their anti-inflammatory effects by suppressing the calcineurin dependent T-cell activation hence the production of proinflammatory cytokines and mediators. Antipruritic effects thereof de-

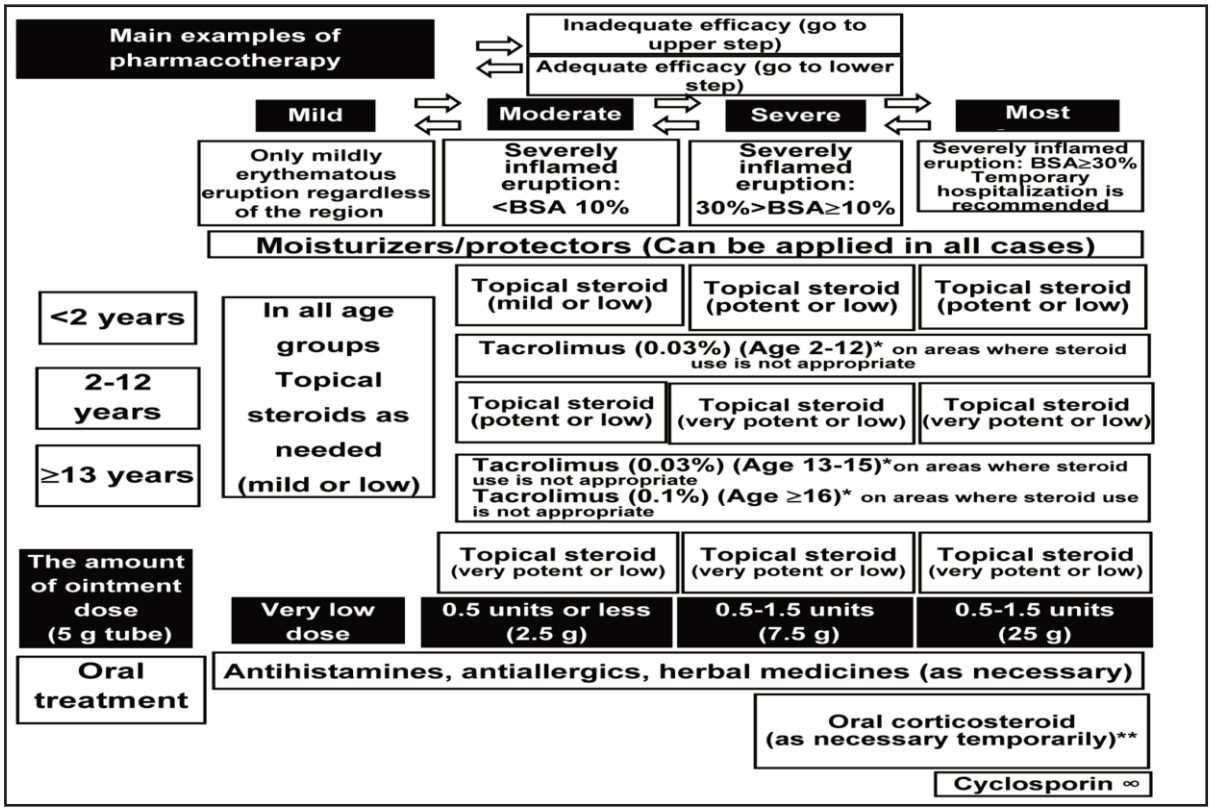

Figure 1. Administration method of topical steroids in atopic dermatitis. **This medicine should be applied upon consultation with specialists. ∞Indicated so as to be discontinued within 3 months in patients aged >16 with very severe symptoms. *This drug should be administered according to the prescribing information [**81**].

Table 4. Topical steroid use according to the severity of eruptions [**65**]

Severity	Eruption characteristics	Topical steroid choice
Severe	Severe edema, lichenification with erythema or infiltration	Potent or very potent
Moderate	Many papules, dry flakes, crusts, vesicles, erosions, excoriations, and itchy nodules	Potent or moderate
Mild	Moderate erythema, dry flakes, few papules, and excoriation	Moderate, weak
Very Mild	Pruritus, dry flakes, and mild erythema No dryness, no inflammation	Agents, such as moisturizers, other than topical steroids

Recommendations

Topical steroids should be recommended taking into account the efficacy and safety profile.

Once or sometimes twice daily administration is sufficient, however, long-term use is not recommended.

Patient's age, how extensive the lesion is and severity thereof should be considered in the choice of potency in steroids.

Babies and areas such as head-neck, skin folds and genital regions, which are problematic in terms of side-effects, should be monitored closely and occlusion should be avoided.

When remission is ensured, maintenance treatment twice a week is continued.

Table 5. TCI Formulations [**76,77**]

Formulations for tacrolimus ointment in moderate-severe AD
• 0.03% formulation in children with ages 2-15
• 0.1% formulation in children with ages ≥16
Pimecrolimus 1% cream is indicated in mild-moderate AD patients ≥2 years

pend on inhibiting mast cell degranulation [**82**]. Therefore, due to lack of side-effects such as skin atrophy, TCI use is superior to TCS use in sensitive and thin skin areas [**76, 77**].

Administration: Twice daily administration of tacrolimus ointment or pimecrolimus cream is effective in treating inflamed lesions and resolving pruritus. In the administrations of TCI, there are different restrictions than TCS. Tacrolimus ointment cannot be applied onto erosive or ulcerative surfaces and the efficacy of the drug is limited [**77, 83**]. It is recommended that tacrolimus ointment be applied once a day after bath and UV exposure be avoided afterwards. It is also recommended that tacrolimus ointment be applied up to a maximum of twice daily with 12-hour intervals [**8**].

Efficacy: It has been demonstrated in the USA that application of TCI once-twice daily per day or one to three times weekly onto the recurring skin decreased relapses [**76, 77**]. Japanese and American guidelines reported that 0.03% or 0.1% forms of tacrolimus demonstrated similar efficacy and safety profiles in children and 0.1% form was superior in children. Anti-inflammatory potency of steroids with moderate potency has been found similar to 0.1% tacrolimus ointment and higher than 1.0% pimecrolimus cream [**65, 79**].

TCI is not recommended in children younger than two years old and in pregnant and lactating women [**65**].

Side-effects: The most common localized side-effects of TCI is generally burning and stinging sensation and pruritus. In order to prevent early withdrawal, the patients should be informed about these potential side-effects [**76, 77**]. Japanese and American guidelines reported a correlation between AD severity and increased lymphoma risk regardless of TCI use. Whereas EADV eczema group reported that lymphoma, other malignancy types and photo-carcinogenicity are unrelated with TCI, however, that sunscreen can be applied during TCI use considering the increased photo-carcinogenicity with systemic calcineurin inhibitors [**78**]. In 2011, FDA (US Food and Drug Administration) reported that there was paucity of evidence supporting that tacrolimus ointment increased the risk of T-cell lymphoma [**65**].

Even though there are publications regarding that TCI may increase the prevalence of local viral infections (eczema herpeticum or eczema molluscatum) [**83, 84**], information is contradictory [**76,78**]. In case local viral infection develops during the treatment, the treatment should be discontinued.

It is recommended that age limitations should be considered during TCI use. TCI can be individually preferred in infants and babies who have severe facial and cheek eczema. In this case, it is important to inform parents with regard to off-label use and effect-side effect profile [**80**].

American guideline does not recommend routine control of tacrolimus blood levels since the systemic absorption amount after topical application is very low so as to be ignored [**6**]. However, in another guideline, in order to prevent the elevation of the drug in blood concentration and protect the safety of the drug, the upper limit of the 0.1% form has been determined as 5 g in adults. Similarly, the upper limit of the 0.03% form in children with ages 2-5 (<20 kg body weight), 6-12 (20-50 kg body weight) and 13 years and above (≥50 kg body weight) has been determined as 1g, 2-4 g and 5 g, respectively [**65**].

c. Topical Antimicrobials and Antiseptics

In the studies conducted in the skin microbiome of AD patients [**85**], increase in S. aureus gene copies and decrease in microbial variation have been demonstrated. And this

brings forefront the notion that TCS and antimicrobial combinations might be effective in patients with high S. aureus colonization [**78**]. Topical antiseptics are particularly recommended in acute AD exacerbations with clinical manifestation of bacterial impetiginization characterized by leakage, pustules and fissures [**78**].

Proactive antimicrobial bleach baths (twice a week with 0.005% sodium hydrochloride) can be used in patients who have recurrent skin infection [**76, 77**]. In these group of patients, intranasal mupirocin can be applied along with bleach baths [**7**]. In case there is no response to TCS and TCI and/or in the presence of superinfection, addition of antimicrobial therapy (topical antiseptic) may be considered [**84**]. Even though chlorhexidine, octenidine, 0.3% crystal violet, diluted potassium permanganate baths (100 ml of 1% KmnO4 stock solution to an entire bathtub) are applied, there is no sufficient evidence as to their efficacy [**78**].

Recommendations

TCI is the first line option in acute and chronic treatment of AD patients who do not respond to topical treatments or in whom these treatments are not administered.

TCIs are recommended as first line treatment in "problematic areas" (face, intertriginous regions, genital region, scalp in babies) since they lack the adverse, side effects of glucocorticoids.

TCIs can be used in maintenance treatment for the prevention of recurrences.

In recent years, the efficacy of antimicrobial clothes covered with silver nitrate or a quaternary ammonium composition is contradictory. Antimicrobial underwear (for example consisting of silver nitrate) can be considered in chronic AD patients [**80**].

In a meta-analysis published by Birnie et al., it has been demonstrated that topical corticosteroid preparations consisting of an antimicrobial or antifungal have no superiority over the ones not consisting them [**86**]. The general opinion does not favor long-term use of topical antibiotics (including fucidic acid) [**78, 80**].

Clinically, antifungal treatment should be considered in cases of face-neck-shoulder dermatitis. This is particularly recommended in patients with predisposition to Malassezia species [**80**].

d. Topical Antihistamines

Topical antihistamines are not recommended in the treatment of AD due to absorption risk and the risk of photoallergic contact dermatitis development [**76**].

Recommendations

Topical antiseptics are particularly recommended in acute AD exacerbations with clinical manifestation of bacterial impetiginization characterized by pustules and fissures.
Topical antibiotics should not be used for prolonged periods.

Clinically, antifungal treatment should be considered in in cases of face-neck-shoulder dermatitis.

There is paucity of studies with regard to the efficacy of antiseptic baths.

e. Other topical agents

1) Coal Tar

Despite being one of the oldest therapies in the treatment of AD, topical coal tar has fallen into disfavor due to lack of controlled-randomized trials demonstrating its efficacy in treatment [**76, 77**]. Even though the evidence is inconsistent, there are publications recommending coal tar in AD with scalp involvement or lichenification [**77, 78, 80**].

Mechanism of Action: Coal tar can restore filaggrin expression by aryl hydrocarbon receptor (AHR) activation and STAT6 dephos phorylation and counteract Th2-mediated downregulation of skin barrier proteins thus

Recommendations

Due to difficulty of cosmetic tolerance of tar, it can only be applied in selected cases where lichenification is observed.

Use in babies is controversial.

diminish spongiosis, apoptosis and CCL-26 expression [**87**].

2) Topical Phosphodiesterase Inhibitors

Various novel PDE4 inhibitors are under research in clinical trials of mild-moderate AD treatment.

Mechanism of Action: Crisaborole ointment is a 2% boron-based benzoxaborole PDE4 inhibitor. It has been demonstrated that it resolved the severity of the disease in AD patients. Boron chemistry in this compound mimics the phosphate in cAMP. Therefore, PDE4 inhibition and weakening of cellular inflammation are targeted [**88**]. The fact that it has a small molecular structure, is a lypophylic compound and has unique physiochemical properties, crisaborole can penetrate dermis and be active in the inflamed area. However, it is converted to its inactive metabolites AN7603 and AN8323 during its absorption to systemic circulation [**89, 90**]. Crisaborole also has an inhibitory effect on Th2-originated cytokines such as IFN-γ, TNFα, IL-2, IL-5 and IL-10 [**91**].

Efficacy: Crisaborole ointment has achieved a good efficacy profile in all studies for the treatment of mild-moderate AD. Two pioneer trials, AD-301 and AD-302, were designed similarly and Phase 3 trials primarily researched the efficacy of crisaborole ointment 2% applied twice daily for 28 days on each atopic lesion. Crisaborole ointment attained treatment success before the control group (placebo-treated patients) and resulted in the regression of IGA (Investigator's Global Assessment) severity scores in patients receiving crisaborole treatment. Both trials set forth remission in disease severity based on diminished AD signs and symptoms including pruritus, erythema, exudate, excoriation, induration/papule and lichenification [**90**].

Side-effect: Crisaborole ointment demonstrated a favorable safety profile with regard to treatment emergent adverse events (TEAEs) and application site reactions (pain, dermatitis) in most of the mild-moderate AD cases. The incidence of these reactions in the treatment group is higher than that of the control group whereas the side-effects are short-term. Additionally, no clinically significant difference has been observed in any treatment group in vital findings, electrocardiograms and laboratory values. The side-effects reported are exacerbation of AD (3.1%), pain in the application site (2.3%) and infection in the application site (1%) [**90**].

Crisaborole ointment 2% provided therapeutical benefit with its favorable safety profile and drug application was submitted to FDA in 2016 [**92**].

3) Application of Wet-wrap Dressing

Application of wet-wrap dressing may be beneficial in the treatment of resistant AD [**76, 77, 93**]. In acute, oozing and erosive lesions, wet-wrap dressing is recommended primarily during the period until oozing stops. On the other hand, caution should be exercised against folliculitis, skin maceration and secondary infections that might develop due to long-term use of wet-wrap dressing [**78**].

4) Polydocanol

It has an anesthetic and antipruritic effect. No systemic side-effect has been reported except rare contact allergy. Since there are no controlled trials, it can be used as an adjuvant for antipruritic effect in AD [**80**].

5) Tannins

Their activity results from their astringent properties. Since there are no controlled trials, it can be used as an adjuvant for antipruritic effect in AD [**80**].

6) Zinc

Albeit the astringent, anti-inflammatory and cooling effect of topical agents comprising zinc, there are no controlled trials demonstrating its efficacy in AD [**80**].

7) Topical Non-steroidal Anti-inflammatory Drugs

There is no publication demonstrating the effect of non-steroidal anti-inflammatory drugs (NSAIDs) in the eczematous lesions of AD. NSAIDs are not included in the AD treatment guidelines in Europe and USA [**87**].

iii. Phototherapy

Photo(chemo)therapy is a good therapeutic option to resolve skin lesions, pruritus and insomnia in AD patients with remission durations up to 6 months without serious short-term side-effects [**94**].

Mechanism of Action: Various factors such as suppression of the antigen-presenting function of Langerhans cells, stimulation of antimicrobial peptides, stimulation of apoptosis in T-lymphocytes [**95**], decrease in S. a ureus and Malassezia spp. colonization, diminished antigen presentation in phototherapy-mediated stratum corneum thickening [**96, 97**].

Efficacy: Considering its low risk profile, relative efficacy, availability, and patient comfort level, db-UVB is emphasized as the most effective option. Additionally, UVA1 for acute exacerbations, UVB for chronic AD and PUVA only in severe, extensive AD are recommended [**76, 77**]. The American guideline states that phototherapy can be used as maintenance therapy in chronic disease.

S2k AD guideline states that phototherapy (UVA-1, db-UVB, broadband UVB, balneophototherapy) can be recommended as an adjuvant therapy in AD patients above 18 years of age in the acute period. In the same guideline, it has been expressed that phototherapy might be considered in children ≥12 years [**81**]. It should be of note that TCI use along with phototherapy is still controversial [**78**].

Side-effect: In the presence of oozing, early lesions, UV therapy is not recommended due to poor treatment response [**78**]. In addition, use of TCS and emollients is recommended in order to prevent exacerbations before phototherapy [**78**].

Recommendations

Phototherapy is recommended in the treatment of AD in chronic phase and resistant to topical treatments.

Except for UVA1 effective in acute exacerbations, phototherapy is rather recommended in chronic, lichenified AD cases.

iv. Systemic Agents

a. Systemic Antihistamines

In the controlled studies, there is no data demonstrating that antihistamines contribute to the atopic dermatitis severity scores and diminish pruritus significantly [**98,99,100, 101**]. Therefore, long-term treatment with sedative or non-sedative antihistamines has no place in the management of AD. On the other hand, non-sedative antihistamines may contribute to treatment in patients with additional manifestations related to AD such as urticaria, allergic rhinitis or conjunctivitis[**77, 102, 103**]. Decision should be made according to patient characteristics for short-term adjuvant treatments targeting pruritus in acute AD attacks.

In patients with sleep dysfunction due to severe pruritus, even though short-term sporadic use of sedative antihistamines such as hydroxyzine is appropriate, it should be of note that they affect sleep quality. Long-term use thereof is not recommended particularly in children [**78, 104**].

Recommendations

There is no data as to the contribution of long-term use of oral H1 antihistamines to the management of AD.

Short-term use according to patient characteristics may be appropriate in the management of severe AD attacks.

b. Systemic Antimicrobials

It is well known that genetic and environmental defects in the natural immune system of the skin and insufficiencies in the local antimicrobial defense mechanism lead to colonization of many pathogens, mainly S. aureus, in AD patients. This incidence reaches 90% for S. aureus in moderate and severe AD patients [**105**].

Routine use of systemic antimicrobial treatment is not recommended in the management of AD. Oral antimicrobial treatment appropriate for active bacterial, viral, or fungal infe ctions defined with clinical findings contributes to the treatment of AD [**106**].

Microscopic examinations should be performed and cultures be taken to support the clinical signs. Superinfections of S. aures and beta-hemolytic streptococci on the bacterial side, herpes simplex on the viral and Malassezia on the fungal side should be the firsts that come to mind. Particularly a streptococcal infection should be investigated in a child suffering from an AD attack accompanied by intense, bright red erythema in skin folds [**78**]. Again, in resistant eczemas on face, neck and shoulders, examination for Malas-

Recommendations

Systemic antibiotic treatment should be recommended only if clinical findings clearly show that there is bacterial superinfection.

Resistant eczemas of face, neck and shoulders should be evaluated in terms of Malassezia superinfection and antifungal treatment.

Herpes infections should be carefully evaluated in terms of manifestation of eczema herpeticum and systemic antiviral treatment.

sezia followed by oral or topical antifungal treatment may be necessary [**107**].

In herpes infections with increased incidence and higher dissemination risk, if this dissemination (eczema herpeticum) has occurred, use of systemic anti-virals is mandatory. Caution should be exercised with regard to eczema coxsackium or eczema vaccinatum manifestations as well [**104,108**].

c. Immunomodulatory Agents

1) Cyclosporine

Cyclosporine, an immunosuppressive drug, is the first-line option for systemic treatment in children, adolescents and adult patients with extensive and severe AD. Cyclosporine, a calcineurin inhibitor, suppresses T-lymphocytes strongly through proinflammatory cytokines including interleukin-2 [**12**]. Cyclosporin has been approved about 20 ago for use in adult AD patients. It has been demonstrated in randomized, controlled studies and meta-analyses that cyclosporin reduced severity scores and increased quality of life [**109, 110, 111, 112, 113, 114, 115**].

A dosing range of 2.5-5 mg/kg/g can be selected as the starting dose. The treatment a dministered as being divided into two is m aintained as a dose reduction of 0.5-1 mg/kg/g every two weeks after disease control is ensured which is usually 6 weeks. It is essential that, along with general examination before treatment, blood pressure control, particularly nephrology tests be performed and basal creatinine levels be recorded [**109**].

Optimal treatment duration should be considered as 3-6 months in patients responding well to treatment. It is known that with 3- to 4-month treatments repeated intermittently, the disease is well-controlled [**11**]. The intermissions can be determined according to severity evaluation of the patient and other features. In patients who tolerate the drug well and have a long history of severe disease before the treatment, treatment period can be prolonged to a maximum of 1-2 years with relatively low maintenance doses, without intermissions [**116**]. However, caution should be exercised for side-effects that may occur during the uninterrupted treatment particularly with high doses.

In the routine monitoring of cyclosporine, which is a drug with a narrow therapeutic index, close monitoring of blood pressure, creatinine, liver enzymes and lipid levels in blood tests are important parameters. In addition, infections and increase in malignancies due to immunosuppression and other considerable side-effects such as gingival hyperplasia and hypertricosis should be carefully monitored [**104,109**].

Recommendations

Cyclosporine is the first-line option for systemic treatment in the management of extensive and severe AD.

A dose of 2.5-5 mg/kg/g can be selected as the starting dose. The treatment is maintained as a dose reduction of 0.5-1 mg/kg/g every two weeks after disease control is ensured which is usually 6 weeks.

Optimal treatment duration is recommended as 3-6 months. In patients who tolerate the drug well and have a long history of severe disease before the treatment, treatment period can be planned as 1-2 years with the lowest dose possible, without intermissions. Patient follow-up is mandatory in uninterrupted treatment for side-effects.

Blood pressure control, nephrologic parameters and blood lipid levels are important parameters of follow-up.

Cyclosporine should not be administered in combination with phototherapy due to increased risk of carcinogenesis. Live vaccination is not recommended during cyclosporine use. The appropriate time is two weeks after the treatment is discontinued. The earliest restart can be possible after 4-6 weeks [**106,109**].

2) Azathioprine

In the treatment of disseminated and severe AD, in cases when cyclosporine is ineffective and contraindicated, azathioprine can be evaluated as a second-line option. Although its efficacy has been demonstrated in randomized, controlled trials, long-term efficacy and safety data are limited [**117,118**]. Even though it is not a licensed treatment in AD yet, it can be used in children as well [**119,120**]. Azathioprine, which is a purine analog, suppresses both B- and T-lymphocytes that demonstrate high proliferation in inflammatory conditions by inhibiting DNA synthesis [**102**].

The onset of action is slow and reaches the peak efficacy in 8-12 weeks. Although the optimal dose range is 1-3 mg/kg/g, the starting does is usually selected as 50 mg/g in the first 1-2 weeks. The risk of myelosuppression is high in individuals with low thiopurine methyltransferase (TPMT) activity [**78,118**]. Even though controlling the enzyme activity can indicate that the person is under risk, since access to this test is not common, low starting doses are selected and dose is escalated in time.

Increase in the risk of leukopenia, gastrointestinal side-effects, elevations in liver enzyme levels, non-melanoma skin cancers and lymphoma are the possible side-effects [**102**]. An important point with regard to drug interactions is that the applicable dose should be reduced up to its 1/4 in concurrent use with xanthine oxidase inhibitors like allopurinol. Azathioprine should not be used in combination with phototherapy due to increased risk of carcinogenesis [**109**]. It can be used very cautiously during pregnancy in limited indications with dose reduction [**78**].

Recommendations

Methotrexate is the third option after cyclosporine and azathioprine in the treatment of extensive and severe AD.

Optimal dose is 7.5-25 mg/week in adults and 0.2-0.7 mg/kg/week in children. The onset of action is slow and reaches peak efficacy in 8-12 weeks.

Gastrointestinal side-effects, hepatotoxicity, bone marrow toxicity are prominent parameters in patient follow-up.

3) Methotrexate

AMethotrexate can be evaluated as the third option after cyclosporine and azathioprine in the treatment of extensive and severe AD. Even though its efficacy has been demonstrated in limited number of studies, two of which were randomized and controlled, carried out in adults and children, there is paucity of data regarding its long-term efficacy and safety [**121, 122, 123, 124**]. Although it is not a licenced treatment for AD, it can be used in children as well [**78,122**]. Methotrexate, which is a folic acid antagonist, shows immunosuppresive effect by inhibiting purine and pyrimidine synthesis [**104**].

Its onset of action is slow and reaches peak efficacy in 8-12 weeks. The optimal dose range is between 7.5-25 mg/week in adults and 0.2-0.7 mg/kg/week in children. Oral or subcutaneous forms can be used [**78,102**].

In the follow-up of the drug which is usually well-tolerated, hepatotoxicity, bone marrow toxicity, pulmonary toxicity, gastrointestinal side-effects are prominent parameters. In order to decrease the risk of these side-effects,

Recommendations

In case cyclosporine is ineffective or contraindicated, azathioprine can be selected in the treatment of extensive and severe AD.

Although the optimal dose range is between 1-3 mg/kg/g, according to TMPT enzyme activity, use of lower doses may be required. If the enzyme activity cannot be measured, the starting dose is low such as 50 mg/g and the dose is incremented in 1-2 weeks. Its onset of action is slow and reaches peak efficacy in 8-12 weeks.

Myelosuppression and liver enzyme levels are prominent parameters in patient follow-up.

folic acid support should be recommended. It is contraindicated in pregnancy [**78,106**].

4) Mycophenolate Motefil /Mycophenolate Sodium

Mycophenolate motefil (MMF) or Mycophenolate sodium (MPS) is an option to be evaluated in patients unresponsive to phototherapy and other systemic treatments particularly in the treatment of adult patients with extensive and severe AD. In a single, controlled trial, MPS has been found to have a similar efficacy with cyclosporine [**125**]. In addition, limited number of uncontrolled trials and case series support its efficacy [**126, 127**]. MPS impairs purine synthesis by inhibiting inosine monophosphate dehydrogenase and affects B- and T-lymphocytes selectively [**102**].

In adults, MMF and MPS can be used up to their optimal doses of 2 gr/g and 1440 mg/g, respectively. Onset of action is slower than cyclosporine (78). It can be used in children in selected cases. The dose can be selected as 30-50 mg/kg/g [**128**].

As an immunosuppressive drug, its side-effect profile is more moderate. The most common reported side-effects are gastrointestinal effects such as nausea, diarrhea and hematological disorders. Its use in pregnant women is contraindicated [**78**].

Recommendations

Mycophenolate motefil (MMF) or Mycophenolate sodium (MPS) is an option to be evaluated in patients unresponsive to phototherapy and other systemic treatments particularly in the treatment of adult patients with extensive and severe AD.

5) Interferon-γ

In the management of severe and disseminated AD, interferon-γ (IFN-γ) can be evaluated as an alternative treatment option in patients not responding to phototherapy or other systemic treatments. However, the results of relatively old, limited number of controlled trials are controversial [**129, 130, 131, 132**]. A relatively new trial reporting a successful result is not a controlled trial [**133**]. IFN-γ is TH1 cytokine active in natural and acquired immune system by increasing natural killer cell proliferation and macrophage oxidation [**102**].

There is no classic dose scheme due to studies conducted in different dose schemes. Headache, fever and muscle pains have been reported as the most common side-effects [**106**]. Even the fact that it is among the last options in systemic treatments due to high costs and side-effects is controversial [**104, 106**].

Recommendations

IFN-γ is among the last options in patients not responding to phototherapy or other systemic treatments in the management of severe and extensive AD.

6) Systemic Steroids

Common clinical dermatology experiences support the only controlled trial reporting that corticosteroids, the first of immunosuppressive treatments which spring to mind, demonstrate similar efficacy in AD patients [**134**]. However, well-known important side-effects make their use unadvisable when profit-loss balance is considered. They can be evaluated in terms of short-term use in severe acute attacks in adult AD patients resistant to other treatments [**78, 106**].

Methylprednisolone can be selected with an initial dose of 0.5 mg/kg/g and the treatment duration may be a short attack treatment of one week or be extended to a maximum of one month with a tapering schedule according to the severity of the disease. In uses where dose reduction is not possible, relapse/rebound risk is high [**78, 106, 134**]. It may serve as a bridge in order to switch to other systemic treatments in selected severe cases [**102**]. When compared to adults, it may be an option for a short-term with caution in children suffering

Recommendations

Systemic steroids can be evaluated in terms of short-term use in extensive and severe acute attacks in adult AD patients. It should be used very cautiously in child patients.

Methylprednisolone can be used in a starting dose of 0.5 mg/kg/g. It can be discontinued complying with the tapering scheme.

It is not recommended as a long-term treatment in in the treatment of AD.

from extensive and severe attack. It is not recommended as a long-term treatment in the treatment of AD [**106**].

d. Biologic Agents

1. Omalizumab

Omalizumab is a recombinant humanized IgG1 monoclonal antibody binding to free IgE in circulation from the Ce3 region of the Fc fragment. Omalizumab binds to free IgEs in circulation and prevents them from cross binding to the high-affinity FcER-IgE complex on the surface of mast cells and from being degranulated. In addition, decreasing the level of IgE level in circulation, omalizumab decreases the amount of high-affinity IgE receptors on mast cells and basophils, therefore suppresses the activation of those cells and mediator release [**135**]. Omalizumab is indicated in allergic asthma and chronic urticaria. Its use in atopic dermatitis is off-label and the number of patients reported in literature is limited and efficacy results are controversial. When the literature is reviewed, it is emphasized that some features relating to the patients and use of the drug are the factors determining the efficacy of the drug [**136, 137**].

Patient Characteristics

Age: Efficacy in children is higher than adults. The reason for this might be that AD follows a natural course in passing from childhood to adulthood and during this course it demonstrates some differentiations [**138**].

Serum IgE levels: In patients with very high baseline serum IgE level, inefficacy or limited efficacy is more common. The reason for this might be that the dose adninistered may not be sufficient to reduce the free IgE level in circulation. Therefore, it is emphasized that higher dose of omalizumab might be appropriate in these group of patients [**139**]. However, contrary to this, there are cases with high IgE level responding very well to the treatment. This may be due to the fact that omalizumab demonstrates some other immune regulating functions regardless of IgE in AD. Even these mechanisms can be ahead of IgE-mediated mechanism [**140**].

Skin barrier disorders: Omalizumab is more effective in patients without filaggrin mutation and with no disorders in lipid metabolites such as fasting serum glycerophospholipids, phosphatidylcholines, and sphingomyelins. Namely, this drug seems to be more effective mainly in AD occurring due to immune dysregulation rather than skin barrier disorder. Evaluating the metabolic profiles of lipids before treatment can guide to determine the appropriate omalizumab patient [**141**].

Features Regarding the Drug

Drug dose: In distinct cases, omalizumab has been administered in a dose of 150-600 mg/once in 2 weeks. It has been reported that efficacy is better in high doses in some of these cases and it was emphasized that this is related to the amount of the drug to decrease the serum free IgE level [**138**]. However, in some other studies, it has been demonstrated that omalizumab dose as low as 150 mg/once in 15 days is sufficient for the treatment of AD. It has been emphasized that this is an important evidence that main mechanism of action of this drug is immune regulation and it has even been emphasized that there should not be a target such as decreasing the serum free IgE level in these patients [**142**]. In a manner supporting this, in some of the trials, even though total serum IgE level has been seriously suppressed with the omalizumab treatment, its clinical efficacy has not been demonstrated. It has been emphasized that, the main indicator demonstrating the clinical efficacy is decreased serum IgE/IgG and IgE/IgG mRNA ratio rather than decreased IgE level [**140**].

Treatment duration: It seems like one of the factors determining the efficacy of omalizumab in AD is the treatment duration. In general, it is not possible to evaluate the efficacy of treatment before 3 months. As the period progresses, treatment success increases. Even in some studies, it has been demonstrated that main efficacy is achieved after a period as long as 7-10 months. The cause for this has been shown as the prolonged time of elimination of IgEs, which omalizumab binds to, from serum and as incomplete efficacy as a result of insufficient elimination [**143**].

There is paucity of case presentations regarding the concurrent use of omalizumab with some other agents in AD. It is considered that these combinations both increase efficacy and reduce drug doses. One of these combinations is combination with ivig. Low dose omalizumab (150-300 mg) and very low dose ivig (10 g/week) have been found to be effective in AD

[**144**]. Another combination is the combination of omalizumab with extracorporeal photopheresis. An effective result has been achieved in a resistant AD patient in whom extracorporeal photopheresis has been administered [**145**]. Due to the paucity in number of patients in whom combination treatments are administered, these treatments can only be applied in very resistant, severe cases.

Use of omalizumab in AD is safe. No significant side-effect has been reported with its use in these patients [**146**].

Although omalizumab is not one of the standard treatments administered in AD, it may be an effective treatment method in a group of patients. Further studies are required to determine the dosing of the drug and subtypes of patients in whom the drug can be used.

Recommendations

Omalizumab's use in atopic dermatitis is off-label and the number of patients reported in literature is limited and efficacy results are controversial.

Omalizumab has been administered in a dose of 150-600 mg/once in 2 weeks in AD patients.

It is not possible to evaluate the efficacy of treatment before 3 months. As the period progresses, treatment success increases.

Use of omalizumab in AD is safe. No significant side-effect has been reported with its use in these patients.

2) Dupilumab

Dupilumab is a human monoclonal antibody that binds to and blocks the alpha subunit of the IL-4 receptor found as a common structure in IL-4 and IL-13 receptors. Inhibition of this structure leads to the blockade of both of IL-4- and IL-13-mediated signalizations and therefore to the suppression of Th2 inflammatory response which has an important role in the pathogenesis of AD [**147**].

Phase 1, 2 and 3 trials have been carried out with dupilumab regarding its use AD and it has been approved in Match 2017 by FDA to be used in "moderate and severe AD in adult patients in whom topical treatments were not successful or use thereof is not recommended [**148**]. There is no study or data as to its use in children. Therefore it cannot be used in childhood AD.

Efficacy: Dupilumab relieves both the skin signs and symptoms and improves the quality of life index in AD with regard to general health dose-dependently. Pruritus, that is the most important sign suffered from, attenuated in a ratio of 55.7% at the end of a 12-week treatment and significant improvement has been observed in pruritus according to NRS (pruritus numeric rating scale) and 5D pruritus scale. Suppression of pruritus is the main cause of increase in the quality of life. In addition, in patients receiving dupilumab, significant improvement has been observed in EASI (Eczema Area and Severity Index), SCORAD (SCORing Atopic Dermatitis), IGA (Inve stigator's Global Assessment), PRO (patient-reported outcomes) sleep pattern, depression, anxiety and quality of life index [**149, 150**].

It has been demonstrated that dupilumab achieved an improvement of %74+/-3.6 in EASI and 82,5-85%, 60-62% and 36% of patients reached EASI-50, EASI-75, and EASI-90, respectively [**149,151**].

Also an acceptable improvement of 38-40% has been detected in IGA score [**152**]. Despite the lack of one-to-one comparative trials with regard to efficacy, dupilumab seems to be more effective than cyclosporine [**153**].

Dosage and Administration: In the studies conducted, when 300 mg/week, 300 mg/2 weeks, 200 mg/2 weeks, 300 mg/ month and 100 mg/month are compared, it has been detected that efficacy increased with dose. Due to the fact that the most effective doses are 300 mg/week and 300 mg/2 weeks and there is no significant difference between these two doses and this dose has been approved by FDA [**150**], the dosage was determined as 300 mg/2 weeks.

The initial dose is administered as 600 mg and repeated doses continue as 300 mg/2 weeks. The administration is via subcutaneous injection. It is a treatment that the pa-

tients can administer at home once the route of administration is taught to the patient. In case a dose is missed, it can be administered in 7 days without disrupting the protocol. However, in case the dose is missed for more than one week, that dose should be skipped and the dosing is withheld until normal dosing time on the 14th day [**148**].

Dupilumab can be used alone or in combination with topical treatments. When used in combination, topical calcineurin inhibitors should be restricted so as to be applied only onto the problematic areas. When combined with topical corticosteroids, the efficacy of the drug increases [**148, 154**].

Side-effects: Dupilumab is a safe drug. The side-effects are mild or moderate in severity and generally not different from those of plasebo. The most common side-effects are nasopharyngitis, exacerbation of the disease, headache, injection reactions, conjunctivitis, blepharitis, oral herpes infection, keratitis, itching of the eyes, other herpes simplex virus infections and dry eye [**148, 155**]. Serious side-effects such as exacerbation of the disease and skin infections are more common with placebo than dupilumab [**149**].

In many cases, conjunctivitis and keratitis ameliorate during the treatment or when the treatment is discontinued. Conjunctivitis emerging with the use of dupilumab is an infectious conjunctivitis or a conjunctivitis of unknown origin and does not seem to be an allergic conjunctivitis. It is not common and even in some studies, the frequency has been found even below 0.5% [**148,156,157**].

Herpes virus infections have not been detected in all studies. In the studies it was detected, the entire herpes simplex virus infections are mild or moderate and observed in the form of herpes labialis [**149**].

İnjection reactions are observed in 7% of patients. The incidence and severity is not dose-dependent [**149**].

Laboratorically, no evidence was observed suggesting hepatic, renal or any organ toxicity. The only laboratory disorder detected is mild eosinophilia occurring in around Week 12 in patients receiving dupilumab [**157**].

Onset rate of efficacy: Dupilumab symptoms are taken under control rapidly. There is a significant improvement in symptoms in the first 4 weeks; this even more rapid than cyclosporine [**153**].

Evaluation of the efficacy of the drug according to the factors related to patients: Serum dupilumab concentrations has been found to be lower in overweight patients, however, dose regulation is not required according to body weight in adults. Being elderly, child, one of two genders or concurrent use of topical corticosteroids do not affect the pharmacokinetics of dupilumab [**152**].

Dupilumab is an effective and safe drug in the treatment of AD. Due to being common in children, there is an urgent need for clinical trials regarding the use in these patients and efficacy and safety of this drug [**154**].

Recommendations

Phase 1, 2 and 3 studies have been carried out with dupilumab in AD and it has been approved in Match 2017 by the FDA to be used in “moderate and severe AD in adult patients in whom “topical treatments were not successful or use thereof is not recommended”.

Dupilumab is a safe drug. The side-effects are mild or moderate in severity and generally not different from those of placebo.

3) Ustekinumab

Ustekinumab is a human monoclonal antibody targeting the p40 subunit of IL-12/23. How ustekinumab acts in AD is not definite. However, it is considered that with the inhibiton of IL-23, T17 and T22 cells are blocked. The pathways that these cells play a role on are important in the pathogenesis of AD[**158**].

Ustekinumab is an agent indicated only in psoriasis in dermatology and its use in AD is off-label. Data regarding the use of this agent in AD is extremely limited and in which patients, in which dose and for how long this drug will be used are yet unknown. In current studies and case reports, ustekinumab has only been used in patients who were resistant to other treatments and who had severe AD.

Efficacy: While in some patients good results were achieved both clinically and laboratorically, in some patients adequate responses were not achieved despite improvements in

laboratory values. Also in another group of patients, no improvement has been achieved either clinically or laboratorically and even exacerbation of the disease has been observed [**159, 160, 161**]. A significant improvement has been observed in pruritus and lesions after the second or third injection in almost all patients in whom the drug was effective. Namely, ustekinumab can be evaluated as an agent, the efficacy of which is not definitely predicted in AD, however as an agent that achieves rapid success in patients it has been effective [**161, 162**].

Age: Ustekinumab has been used in children above 12 years and in adults [**163**]. There is no study demonstrating whether or not the age of the patient is important regarding efficacy.

Dose: In most of the cases, dose regulation has been applied as 45 mg or 90 mg according the weight of the patient as in psoriasis (164). However, 45 mg and 90 mg doses have been compared with each other independent of the weight of the patient and no difference was observed between each other with regard to efficacy [**160**].

Administration protocol and dose range: In current cases, the treatment was administered by following the protocol used in psoriasis. However, 12-week interval was long even in patients in whom the drug was effective and the disease exacerbated in around Week 8. Therefore, probably, it will be more appropriate that the dose range in AD be shorter [**158, 163**].

Side-effects: No serious side-effects have been detected in any cases reported in literature [**163, 164**].

Recommendations

Ustekinumab is an agent indicated in psoriasis and its use in AD is off-label. Data regarding the use of this agent in AD is extremely limited and in which patients, in which dose and for how long this drug will be used are yet unknown.

V. Maintenance Treatment of Atopic Dermatitis

Due to the fact that atopic dermatitis is a recurrent chronic disease and affects the qu ality of life unfavorably, maintenance treatment has become a current issue to prevent the development of new attacks or to lengthen the remission period It is considered that there is a subclinical inflammation in skin areas without lesions since histopathologic hyperkeratosis, epidermal hyperplasia, structural changes such as intercellular and endothelial edema on the treated skin or on the skin with normal appearance as well as epidermal barrier dysfunction, dendritic cell population similar to that in lesional skin, local proinflammatory cytokines, lymphocytic infiltration and RNA expression profile are observed [**165**]. Therefore, proactive approach has become a current issue in the maintenance treatment of AD. In proactive treatment, there is the matter of long-term intermittent administration of topical antiinflammatory treatments on areas where lesions were formed along with moisturization of the entire body including the skin areas without lesions [**165**]. In fact, maintenance treatment in AD can be defined for two different conditions. According to this, the disease is divided into two as mild or moderate in severity. Patients whose disease is taken under control with the main treatments are accepted as mild those who cannot be taken under control as moderate [**166**]. Maintenance treatment of mild AD includes appropriate skin care and general precautions. It should be preferred that the moisturizers contain oil and additives with inactive ingredients to repair the skin barrier and be applied to the moisturized skin taking into account the warnings that glycerol additive is tolerated better than urea, sodium chloride and propylene glycol can cause irritation in children under 2 years of age and moisturizers containing peanut can cause allergy and products containing urea can cause irritation in children. In addition, bath with addition of 1 ml/L sodium hypochlorite (bleach) twice a week is also recommended for reducing Staphylococcus aureus colonization and not causing bacterial resistance [**64, 65, 76, 78, 82, 102, 109, 167**]. In the maintenance treatment of moderate-severe atopic dermatitis, topical calcineurin application 2-3 times a week upon the appearance of the first symptom or on skin areas appearing to be normal but predisposed to make an attack or regular appl ication of moderately potent topical corticosteroids not containing antimicrobials 1-2 times a week are recommended [**166**]. TCS

with low potency or primarily TCIs are recommended for the facial region. In the clinical trials, no side-effects have been reported in the moderately potent maintenance treatment 2 times a week for 16 weeks. In literature, it has been reported that no side-effect has been observed with 1-year proactive treatment with TCIs [**64, 65, 76, 78, 81, 102, 109, 167**].

There are some differences with regard to recommendations for moisturizer, TCS and TCI use in current treatment guidelines; for example, in the Polish treatment guideline, TCS maintenance treatment has not been recommended; most of the guidelines do not mention any discrimination or superiority among TCIs whereas Japanese guideline only recommends tacrolimus and in the European guideline it is stated that tacrolimus is more effective than pimecrolimus.

It has been stated in Japanese and Polish guidelines that phototherapy can be used in the maintenance treatment. Narrow-band UVB is preferred due to its efficacy, low risk profile and easy application. It has been expressed that, after 95% improvement during the maintenance treatment, in the final dose it can be applied once a week for 4 weeks, decreasing the dose by 25% every two weeks for 4 week or decreasing the dose by 50% once a month [**64,81,167**]. Phototherapy is combined with other treatments except the TCIs; other guidelines do not recommend however, in the Polish guideline it is stated that TCI-phototherapy combination can be performed but caution should be exercised. Proactive treatments in current treatment guidelines are summarized in (**Table 6**) [**64, 76, 81, 102, 109, 167**].

Recommendations

Phototherapy, mainly narrowband-UVB, can be used in maintenance treatments.

Recommendations

Daily moisturization of the body and protective measures comprised in the main treatment of maintenance treatment of atopic dermatitis should be considered. It is preferred that the moisturizers contain oil and additives with inactive ingredients to repair the skin barrier. Products containing urea should not be preferred in children due to the possibility of irritation.

Bath with addition of sodium hypochloride twice a week is also recommended for reducing Staphylococcus aureus colonization and not causing bacterial resistance

Tacrolimus ointment or pimecrolimus cream can be applied for twice a week upon first symptom or on skin areas in normal appearance with predisposition to have an attack.

Class I TCS can be applied in the facial areas upon the first symptom and Class II TCS, not containing antimicrobials, can be applied on other body areas but it should not be preferred primarily.

Vi. Adjuvant Treatment in Atopic Dermatitis

Atopic dermatitis is a chronic disease affecting the quality of life of patients unfavorably in which epidermal barrier dysfunction, immune dysregulation and environmental factors play a role. A search for alternative and adjuvant treatments comes to forefront due to the chronic course of the disease, insufficiency of topical or systemic treatments from time to time or development of side-effects.

a. Diet

1) Probiotics, Prebiotics and Simbiotics

Live microorganisms which are beneficial by regulating the microbial balance in a certain concentration are called probiotics. Probiotics are microorganisms that are found naturally in human body or that resemble these microorganisms. “Pro” means “for” in Greek and “biotic” means “bios” i.e. “life”. Prebiotic is a non-digestible food ingredient that promotes the growth of beneficial microorganisms and increases the activity thereof selectively. When taken alone, prebiotics provide the growth of beneficial bacteria present in the natural flora of the colon. Simbiotics are products comprised of both prebiotics and prebiotics [**168,169**].

Normal intestinal flora both helps digestion and affects local and general immune system. It has been reported that lactobacilli are predominant in a healthy child whereas in children predisposed to allergies, Gram(-) bacteria and Staphylococcus aureus are increased. The aim is to reestablish this balance with

probiotics in the intestinal flora of AD patients. In addition, it is suggested that probiotics induce Th1-weighted lymphocytes more than Th2 and decrease IgE production [**168, 169, 170**].

Probiotics received with foods or for supplementary purposes are bacteria and yeasts. Lactic acid bacteria are Lactobacilli acidophilus, L. casei, L. fermentum, L. gasseri, L. johnsonii, L. lactis, L. paracasei, L. plantarum, L.reuteri, L. rhamnosus, L. salivarius, L. bulgaricus; bifidobacteria are Bifidobacterium breve, B. bifidum, B. infantis, B. lactis, B. longum, B. adolescentis, B. animalis; yeasts are Saccaromyces boulardii and others are Enteroccocus faecalis, Streptoccocus thermophiles, Bacillus cereus, Clostridium butyricum, Lactococcus lactis. It is desired that oral probiotics show pathogenic or toxic effects in the host, hang on to the intestinal cells, grow, produce antibacterial products, produce a mucosal and systemic immune response, be colonied temporarily, and not replace but be added to the existing natural flora. Their mechanism of action is to diminish the number of pathogenic and harmful bacteria, produce antimicrobial components, compete for food elements and colonization regions, ensure the activation of enzymes providing digestion, decrease the production of amine or toxic enzymes and improve immune system [**168, 169, 170**].

Table 6. Comparison of Current Guidelines

Treatment	Guidelines				
	America	**Europe**	**Japan**	**German**	**Polish**
Maintenance Treatment (Proactive)	Eichenfield et al. Section 2. 2014)69 (Sidbury et al. Section3,4. 2014)64	ETFAD/EADV Task Force (Wollenberg et al.2016)78	(Katayama et al. 2017) (Saeki et al 2016)65	(Werfel T, et al. 2016)80	(Nowicki et al. 2015)167
Proactive treatment approach	TCS or TCI application 1-3 times a week to the previously affected areas	TCS or TCI application twice a week to the previously affected areas, concurrent with a moisturizer for the whole body	TCS or TCI application 1-3 times a week on previously affected areas, concurrent with a moisturizer for the whole body	TCS application twice a week or TCI, average of 3 months to the previously affected areas	TCI use with certain intervals
TCS	Application to the previously affected areas 1-2 times a week	Application to the previously affected areas twice a week Class II and III are more appropriate, Class I is not effective enough There is data regarding 3-month use	1-3 times a week up to 6 months	Application to the previously affected areas 1-2 times a week Lower efficacy than Class III	Has no place in maintenance treatment
TCI	Application to the previously affected areas 2-3 times a week	Tacrolimus is more effective There is data regarding its clinical use for one year	0,03% and 0,1% tacrolimus up to 6 months	Compliance to age restriction Combination with phototherapy is not recommended, concurrent use with sunscreen recommended	To the previously affected areas Tacrolimus, twice a week up to 12 months; pimecrolimus once a day up to 3 months, longer if intermittent

Phototherapy	Has no place in maintenance treatment	Not discussed	Can be used in maintenance	Not discussed	db-UVB once a week (For 4 weeks, same as the last dose, followed by reduction in the dose by 25% every 2 weeks – for 4 weeks, then once a month a dose equal to 50% of the highest dose. PUVA treatment can be applied as well. Moisturizers can be combined with TCS, combination with calcineurin inhibitors is possible (however caution should be exercised)
Anti-histamines	Has no place in maintenance treatment	Not sufficient to resolve pruritus. Sedatives are preferred for helping sleep problems however they have no place in maintenance Blockade against alternative receptors such as H4R may be more beneficial	They are considered to be ameliorating pruritus since H1 receptors are on C nerve fibres. Contrary to many guidelines, they are recommended in treatment but has no place in maintenance.	Since they are considered to be ineffective in normal treatment, they are not recommended in the maintenance treatment	First-generation sedative antihistamines are preferred; if there is concurrent allergic rhinitis/conjunctivitis second generation is preferred but has no place in the maintenance treatment
Mast cell stabilizers	Not discussed	Not discussed	Not discussed	Since they are considered to be ineffective in normal treatment, they are not recommended in maintenance.	Not discussed
Bath with bleacher addition	Effective due to Staphylococcus aureus decolonization	5% bleach, 100 ml for 100L, full bath tub	Not discussed	Not discussed	Not discussed
Moisturizers	In the maintenance treatment, the frequency and amount of use are recommended according to age; it is recommended that oily moisturizers be applied to moist skin after bath	Emollients, bath oils, barrier creams are recommended	It is recommended that hydrophilic oils be applied to skin after bath. Urea, lactate, collagen addition is beneficial	It is recommended that oily moisturizers be applied. Urea and glycerin additive may be beneficial, however products comprising urea is not recommended in children due to irritation.	Should be used for more than once a day; the ones with barrier properties are preferred; glycerol additive is tolerated better than urea and sodium chloride; propylene glycol may result in irritation under 2 years of age; moisturizers containing peanut should not be used for the possibility of allergy.

Table 6. Comparison of Current Guidelines (Continued)

Treatment	Guidelines				
	America	**Europe**	**Japan**	**German**	**Polish**
Other treatments	There is evidence regarding their safety and efficacy, however, which one, when, and which dose should be preferred are not clear				
Probiotic/prebiotic	No sufficient evidence to recommend	TThere is evidence however, when, in which dose and which should be preferred are not clear	Stating that there are publications as to their safety, however there is no comment for recommendation	Lactobacilli cannot be recommended according to the studies	Not discussed
Fatty acids	Fish oil is rich in n-3 fatty acid, competes with n-6 fatty acid and has an anti-inflammatory effect, however there is paucity of data for their efficacy in AD	Not discussed	Recommended in case n-6/n-3 ratio increases in blood	No sufficient study for any recommendation	Not discussed
Vitamin D	No sufficient study for recommendation	No sufficient study for recommendation	Not discussed	Not discussed	No sufficient study for recommendation
Elimination diet	Diet if any food allergy is detected, Supports a diagnostic elimination diet for 4-6 weeks and a controlled challenge	Diet if any food allergy is detected, if not normal diet	Diet if any food allergy is detected, if not normal diet	Diet if any food allergy is detected, there is no “special AD diet”	Not discussed
Specific immunotherapy	Generally not recommended	Generally not recommended In selected cases in which severe disease and patch test are positive, particularly against house dust mites, grass and pollen	Not discussed	Recommended if respiratory allergic disease coexists or any allergen is detected.	Recommended if respiratory allergic disease coexists or any allergen is detected.
Chinese herbal therapy	No sufficient evidence for recommendation	Not discussed	According to the guideline of the previous year (Saeki et al. 2016) it can be recommended; in this guideline herbal therapies are not recommended due to likelihood of severe side-effects	Not discussed	No sufficient evidence for recommendation

Borage Oil	No sufficient evidence for recommendation	Not discussed	Generally herbal therapies are not recommended	Not discussed	Not discussed
Primrose oil	No sufficient evidence for recommendation		Generally herbal therapies are not recommended	Not discussed	Not discussed
Environmental Factors	Against standard approach such as protection against house dust mites or special clothes routinely	Not discussed	No annex	Detection of potential occupational triggering factors, if any	Avoiding allergens and irritants (cigarette smoke, infections, wool clothes, stress)
Psychological Approach	Not discussed	Not discussed	Recommended	Recommended Particularly in cases triggered by psychologic state	Not discussed

Probiotics are available in capsule, tablet, cachet or powder forms. They may be found in various fermented foods, yoghurt and milk beverages. The most commonly used probiotics are Bifidobacterium lactis, Streptococcus termophilus, Lactobacilli reuteri, Lactobacilli rhamnosus, and Lactobacilli acidophilus. Their side-effects are limited. Even though bronchitis, infections, intestinal ischemia are mentioned among the side-effects, many studies reported that side-effects are not different from those of placebo [**168,169**].

The efficacy of probiotics in prevention and treatment of allergic diseases is controversial. Lactobacillus and Bifidobacterium species have been investigated. There are studies and evidence supporting that probiotics may be beneficial in the treatment and prevention of atopic dermatitis. They are necessary for the stimulation of intestinal flora intestine-related lymphoid tissues and a healthy immune system in the newborn. The intestinal flora of the babies who have allergic diseases has been found to be more different and the variety of the intestinal flora has been found low. It is envisaged that the intervention on intestinal flora by probiotics, prebiotics or simbiotics will regulate immune response, prevent the development of allergic diseases and can contribute to the treatment of the disease. In a meta-analysis published in 2014, it has been reported that mixture of different bacterial products and bifidcobacterum species of lactobacillus species have been found to be effective in decreasing the AD SCOARD index [**170**]. In a meta-analysis published in 2016, it has been reported that oral probiotic administration for 8 weeks was effective in the treatment of AD in children above 1 year of age. [**171**]. In the same study, it has been reported that probiotic use longer than 8 weeks did not provide an additional benefit. Mixtures containing different probiotic and prebiotic bacteria or lactobacillus species have been found to be more effective than other probiotic alternatives whereas due to low number of patients enrolled in the randomized, controlled trials and presence of methodologic and biologic differences between the trials suggest that the results are very optimistic[**172**]. With regard to current guidelines, it has been stated, in the current American [**64**] and German [**109**] guidelines, that there was no sufficient evidence for them to be recommended; in the European guideline [**78**]. that there is some evidence as to their safety and efficacy w hereas when, how much and which bacteria/yeast should be preferred were not clarified; in the Japanese guideline [**81**]. that there was some evidence with regard to their safety and efficacy;and in the Polish guideline [**167**].

Recommendations

According to current data, routine use of probiotics is not recommended in the prevention of development of AD or its treatment. On the other hand, they can be used in selected cases due to the presence of evidence regarding their safety and efficacy.

the subject was not discussed (**Table 6**) [**64, 76, 78, 81**].

2) Fatty Acids

Delta-6-desaturase activity has been found to be low in AD (173). Since decreased level of fatty acids has been found in the patients with eczema, it has been suggested that essential fatty acids play a role in the pathogenesis of AD however, the efficacy of essential n-6 fatty acid supplement has not been demonstrated in the studies carried out. Later, n-3 fatty acid, considered to be demonstrating antiinflammatory properties by competing with n-6, has become a current matter [**64, 168, 169, 173**]. Fish oil is rich in n-3 fatty acid. In case n-6/n-3 ratio increases in blood, n-3 fatty acid supplement has been recommended [**81**]. Gamma linoleic acid (GLA) is a kind of essential fatty acid and a precursor of some mediators such as prostaglandin E1. Even though it has been reported that it resolved inflammation and immunity in some of the trials regarding GLA, different sources have been used for GLA in these studies; borage oil (23% GLA) and primrose oil (8-10% GLA) (168,169). Oral supplement of these both oils has been evaluated as inert for eczema in Cochrane review[**14**]. Borage oil and primrose oil have not been recommended in currentguidelines [**64, 76, 78, 102, 109, 167**].

Recommendations

Standard use of fatty acids in AD treatment is not recommended, however, in case n-6/n-3 ratio increases in blood, n-3 fatty acid supplement has been recommended.

3) Chinese Herbal Treatment

Treatments of herbal origin can be administered as topical or systemic in AD. Among these, Chinese Herbal Treatments (CHT) are generally mixtures with special names in which many herbs are combined. Along with Zemaphyte, Xiano-Feng-San, Hochu-ekki-to, the efficacies of which are demonstrated in randomized, controlled studies, there are many other products prescribed in general dermatology clinics in Japan [**65,81**]. 28 randomized, controlled trials have been reviewed in 2013 Cochrane review and it has been stated that oral or topical CHT is not beneficial in the treatment of childhood or adulthood AD [**174, 175**]. Side-effects such as diarrhea, elevation in transaminases, disease exacerbation and reversible cardiomyopathy along with very serious side-effects such as fatal hepatic necrosis, nephropathy caused by CHT have been reported in literature [**65, 81**]. On the other hand, it has been pointed out that there may be non-herbal ingredients along with herbal flowers and herbal seeds under the name of CHT [**175**]. Although it has been stated in 2016 Japanese Guideline that CHT in combination with other treatments in resistant patients can be considered, in 2017 Japanese Guideline and Polish Guidelines, there is the opinion that there is no adequate evidence to recommend their use; it has not been discussed in European and German Guidelines (**Table 6**) [**64, 76, 78, 81, 102, 109, 167**].

Recommendations

There is no adequate evidence to recommend CHT.

4) Oral Vitamin D

There are various results achieved in the studies conducted regarding the serum vitamin D levels of SAD patients. In the studies, the effect of vitamin D replacement to disease activity score varies in AD patients [**168**]. Vit amin D replacement has not been recom mended in current guidelines (**Table 6**) [**64, 76, 78, 81, 102, 109, 167**].

Recommendations

Even though there is no adequate evidence to recommend vitamin D, replacement thereof is recommended in case of deficiency.

5) Elimination Diet

Food allergy is not rare in AD and food allergy test should be performed in suspected cases [**65, 168**]. Most of the current guidelines do not recommend a special diet if there is no food allergy detected. However, American guideline supports a diagnostic elimination diet and controlled elimination diet for 4-6 weeks if there is a suspected case and no positivity in the test [**64, 76, 78, 81, 102, 109, 167**].

Recommendations

Food allergy should be investigated in suspected cases in AD. If food allergy is not detected, in order to avoid malnutrition, elimination diet is not recommended.

b. Environmental Factors

It is considered that skin barrier function is impaired in AD and therefore allergens penetrate through the skin and activate the i mmune system and this leads to the development of atopic diseases such as hay fever, asthma which is known as atopic walk. Therefore, it is suggested that long-term control of skin inflammation and barrier function will prevent the development of atopic diseases in the future. Moisturizing the skin is one of the main treatments in AD. Again for the same reasons, environmental factors that may impair the barrier function of the skin should be avoided. The main allergens and irritants are soaps, detergents, house dust and mites, solvents such as formaldehyde and toluene, infections, cigarette, wool clothes. Since the threshold of AD patients are low, it is recommended that they avoid these general allergens and irritants, use soaps with neutral pH, prefer soft and cotton clothes, wear the new clothes after washing with liquid cleaners and rinsing very well and avoid extreme heat and extreme moisture. In addition, it is recommended that, if any, occupational potential trigger functions be detected. Along with these precautions, patient-based approach is recommended [**64, 76, 78, 81, 102, 109, 167**]

Recommendations

Avoiding irritants that may impair skin barrier function, detection of potential triggers and patient-based approach is recommended.

c. Psychological Factors

As well as causing predisposition to atopic diseases such as hay fever and asthma, AD causes sleeping problems not rarely due to chronic pruritus and inflammation, and comorbid mental health problems such as speech disorder and hyperactivity disorder in childhood [**47**].

Sleeping disorders in AD are characterized as diminished quality of sleep, waking up during the night and daytime sleepiness. A relationship has been detected between sleeping problems and AD severity. It has been reported that sleeping problem is the main factor affecting quality of life in childhood AD. Tiredness, fatigue and mental diseases such as depression can be observed in patients with sleeping problems [**47, 176, 177**]. One or more depression symptoms are observed in one third of AD patients. Anxiety, impairment of concentration along with depression have been reported in AD patients and even depression or injuries or fractures due to antihistamine use could have been observed. Assessment of systemic treatment alternatives such as cyclosporine and methotrexate have been recommended in patients suffering from sleeping problems [**47, 176, 177**]. In German and Japanese guidelines which are the recent ones, psychiatric consultation has been recommended in cases in which mental diseases play a role in etiology in AD patients (**Table 6**) [**64, 76, 78, 81, 102, 109, 16**].

Recommendations

Psychiatric consultation should be requested with regard to comorbid mental diseases in which psychological factors trigger AD.

Systemic alternative treatments should be evaluated in patients suffering from sleeping problems despite appropriate topical treatment.

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