Consensus Report
Uzlaşı Raporu

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Atopic dermatitis diagnosis and treatment consensus report

Atopik dermatit tanı ve tedavi uzlaşı raporu

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Abstract

Atopic dermatitis (AD) is a chronic, itchy, and recurrent inflammatory skin disease. AD, which is known as a childhood disease because of its common occurrence, is also an important health problem in adults. With increasing prevalence rates throughout each year, particularly in developed countries, AD has a heterogeneous clinical presentation that varies with age and different degrees of severity. The treatment includes the use of topical or systemic agents after identifying the needs of the patients. Especially, the identification of molecules responsible for pathogenesis recently has allowed the development of tailored treatments. With a better understanding of both the disease and the economic burden of AD recently, studies have gained momentum on diagnosis, treatment, and quality of life. Guidelines and consensus reports addressing diagnostic and therapeutic approaches have been published in our country, too, in parallel to publications in various countries. In this age of rapid information sharing, all kinds of information need to be updated frequently and become further useful. For this purpose, it is planned to develop a current consensus guideline under the leadership of the Dermatoimmunology and Allergy Association, with the contributions of the Cosmetology and the Dermatology Academy Association, Kayseri Dermatology and the Venereal Diseases Association, and Manisa Dermatology and the Venereal Diseases Association, and through the participation of faculty members experienced in the diagnosis and treatment of AD. The topics and the authors were chosen in December 2020. All Medline data published in the years between 1980 and 2021, current AD diagnosis and treatment guidelines, meta-analytical studies, and expert opinions and experiences were reviewed, and section drafts were developed. Literature data and section drafts were assessed and discussed during a meeting held in March 2021 with the participation of all authors. Then, the sections were finalized via e-mail correspondences and submitted as a final consensus report.
Keywords: Atopic dermatitis, guideline, diagnosis, topical treatment, systemic treatment

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Öz

Atopik dermatit (AD) kronik, kaşıntılı ve tekrarlayan enflamatuvar bir deri hastalığıdır. Sık görülmesi nedeni ile çocukluk çağı hastalığı olarak bilinen AD, erişkinlerde de önemli bir sağlık problemi olarak karşımıza çıkmaktadır. Her geçen yıl özellikle gelişmiş ülkelerde görülme sıklığı artan AD, yaşla değişen heterojen bir kliniğe sahiptir ve farklı şiddette seyretmektedir. Tedavi, hastaların ihtiyacı belirlenerek topikal veya sistemik ajanlarla sürdürülür. Özellikle son yıllarda patogenezden sorumlu moleküllerin tanımlanması kişiye özel tedavilerin geliştirilmesine olanak tanımıştır. Son yıllarda AD'nin hem hastalık hem de ekonomik yükünün daha iyi anlaşılması ile tanı, tedavi ve yaşam kalitesine ilişkin çalışmalar hız kazanmıştır. Çeşitli ülkelerde olduğu gibi ülkemizde de tanı ve tedavi yaklaşımları içeren kılavuzlar ve uzlaşı raporları yayınlanmaya başlamıştır. Yaşadığımız hızlı bilgi paylaşımı çağında, tüm bilgilerin sık sık yenilenmesine ve daha yararlı hale getirilmesine ihtiyaç vardır. Bu amaçla, Dermatoimmünoloji ve Alerji Derneği öncülüğünde Kozmetoloji ve Dermatoloji Akademisi Derneği, Kayseri Deri ve Zührevi Hastalıkları Derneği ve Manisa Deri ve Zührevi Hastalıklar Derneği'nin katkıları ve AD tanı ve tedavisinde deneyimli öğretim üyelerinin katılımı ile güncel bir uzlaşı kılavuzu hazırlanması planlanmıştır. Öncelikle Aralık 2020'de konu başlıkları ve yazarlar belirlenmiş ve 1980-2021 yılları arasında yayımlanan tüm Medline verileri, güncel AD tanı ve tedavi kılavuzları, meta-analitik çalışmalar ve uzman görüş ve deneyimleri doğrultusunda bölümler yazılmıştır. Tüm yazarların katılımıyla Mart 2021'de gerçekleştirilen toplantıda literatür verileri ve bölüm taslakları değerlendirilmiş, tartışılmış ve elektronik posta yazışmaları ile son şekli verilerek uzlaşı raporu olarak sunulmuştur.
Anahtar Kelimeler: Atopik dermatit, kılavuz, tanı, topikal tedavi, sistemik tedavi

1. Introduction and methods

Introduction

Atopic dermatitis (AD) is a chronic, itchy, and recurrent inflammatory skin disease. It is characterized by dry skin, itch-scratch cycle, and eczematous lesions. AD, which is known as a childhood disease because of its common occurrence, is also an important health problem in adults. Other atopic comorbidities accompanying the disease and severe itching and insomnia have significant adverse effects on the quality of life (QoL) and increase the burden of the disease. With increasing prevalence rates throughout each year, particularly in developed countries, AD has a heterogeneous clinical presentation that varies with age and different degrees of severity. The treatment includes the use of topical or systemic agents after identifying the actual needs of the patients. Especially, the identification of molecules responsible for pathogenesis recently has allowed the development of tailored treatments[1].

Methods

With a better understanding of both the disease and the economic burden of AD recently, studies have gained momentum on early diagnosis, determination of severity, impacts on the QoL, and meeting actual treatment needs. Guidelines and consensus reports addressing diagnostic and therapeutic approaches have been published in our country, too, in parallel to publications in various countries. In this age of rapid information sharing, all kinds of information need to be updated frequently and become further useful. With the aim of meeting such needs, it is planned to develop a current consensus guideline under the leadership of the "Dermatoimmunology and Allergy Association", with the contributions of the Cosmetology and the Dermatology Academy Association, Kayseri Dermatology and the Venereal Diseases Association, and Manisa Dermatology and the Venereal Diseases Association, and through the participation of faculty members experienced in the diagnosis and treatment of AD. The topics, the questions to be answered considering current literature information, and the authors were chosen in December 2020. All Medline data published in the years between 1980 and 2021, current AD diagnosis and treatment guidelines, meta-analytical studies, and expert opinions and experiences were reviewed, and section drafts were developed in line with the planned task distribution. Literature data and section drafts were assessed and discussed during the second meeting held in March 2021 with the participation of all authors. Then, the sections were finalized via numerous e-mail correspondences and submitted as a final consensus report.

2. Epidemiology of atopic dermatitis

AD is generally considered to affect 20-25% of the pediatric population and 2-3% of adults. Although it is common in childhood, its incidence varies widely across countries. This difference is attributable to the use of different methods in prevalence studies, such as the use of population-based questionnaires or disease rates of the previous year or the combined use of both physical examination and questionnaires. Approximately 50% of the existing cases consist of infants aged one year[2]. In a multicenter study, the prevalence in one-year-old infants was found to be lowest in Spain and highest in Honduras at rates of 10.6% and 28.2%, respectively[3]. In that study, it was reported that the mean rate in Europe was 14.2%, whereas the mean rate in Central America was 18.2%. In a study conducted in Sweden on children aged five and six, the incidence of AD was found to be very high at a rate of 35%[4]. There are no population-based studies on the incidence of AD in our country, apart from a few regional studies and those on specific age groups. Three cross-sectional studies, which were conducted out 10 years apart on children aged 6-14 years in the Adana region (on 2,334 children in 1994, 3,728 in 2004, and 3,209 in 2014), reported a gradual increase in allergic diseases with AD incidences of 5%, 9.9%, and 7% in three different years, respectively[5]. In another study on 495 children in Erzurum, the incidence of AD in the last 12 months and the incidence of physician-diagnosed AD were reported to be 11.5% and 3.6%, respectively[6]. In Malatya, the lifetime and 12-month incidences of AD were found to be 7.5% and 6.5%, respectively, in 480 children[7]. In another study conducted in Aydın, the lifetime and 12-month incidences of AD, and the incidence of physician-diagnosed eczema were found to be 9.6%, 7.8%, and 2.9%, respectively, in children aged 6-7 years, whereas the lifetime and 12-month incidences of AD among 13-14-year-old children were reported to be 12.0% and 7.4%, respectively[8]. In an observational study conducted in Ankara, 4,025 patients in the age range of 0-16 years presenting to the pediatric dermatology department of a hospital were evaluated and the incidence of AD was found to be 7.8% in all age groups[9]. A multicenter

study on 6,755 pediatric patients in the age range of 10-11 years, using the ISAAC phase II protocols, reported rates of 17.1%, 8.1%, and 2.6% for the lifetime, 12-month, and physician-diagnosed incidences of AD, respectively[10].

It is generally assumed that 30% of childhood-onset AD cases persist into adulthood. However, in a prospective study conducted in Denmark, children diagnosed with AD were followed up from school age until adulthood (in the years between 1995 and 2010)[11]. That study showed that the persistence of AD into adulthood could occur at a rate as high as 50% and persistent AD was associated with early onset, allergic rhinitis, and hand eczema.

3. Factors involved in the development of atopic dermatitis

A complex mechanism with the interplay of genetic and environmental factors occurs in the development of AD. The increasing incidence of AD, especially in developed countries, cannot be exclusively based on genetic factors, but the lifestyle of modern life (hygiene hypothesis and the exposure to cigarette smoke, fast food, air pollution, etc.) contribute largely to the development of the disease[12].

Genetic factors

The epidermal barrier plays a very important role in natural immunity with its structure and functions by forming the first physical barrier in the organism against the environment. This complex structure consisting of corneocytes, matrix proteins and corneodesmosomes also provides hydration of the skin. Disorders in the structure and functions of this barrier are known to be responsible for developing AD[13]. A large number of proteins involved in this barrier function are encoded and synthesized by a gene region known as the Epidermal Differentiation Complex located on chromosome 1q21[14]. Among these proteins, filaggrin (FLG), is major involved in the natural moistening of the skin. An FLG gene mutation is present in 10-40% of AD patients[15].

Environmental factors

Environmental factors may cause changes in the expression of genes without any alterations in the genetic sequence (DNA nucleotide sequence). DNA methylation, specific histone modification, and overexpression of non-coding mRNAs induce epigenetic modifications. Diet, medications, environmental pollution, exposure to cigarette smoke, and infections facilitate the occurrence of AD through epigenetic changes. Recent studies have shown that the epigenome is dynamic and undergoes changes under the effects of environmental conditions and age[16].

4. Immunopathogenesis of atopic dermatitis

The immunopathogenesis of AD is complex and multifactorial. Genetic predisposition, epidermal-barrier dysfunction, immune dysregulation, and skin dysbiosis take part in the pathophysiology of the disease[17]. However, it is not easy to name one as the inducer among these factors. The outside-in hypothesis suggests that epidermal barrier dysfunction is the primary factor, triggering immune dysregulation and inflammation. However, the inside-out hypothesis suggests that immune dysregulation and associated inflammation are the primarily preceding events leading to impaired epidermal barrier function. It is likely that the pathogenesis of the disease is cyclical rather than unidirectional, as advocated by these hypotheses. In other words, the factors involved in the pathogenesis mutually interact with each other and contribute to the development of the disease[18]. The pathogenesis of AD is summarized in Table 1.

Genetic predisposition

There were 32 susceptibility loci identified for AD. These loci contribute to the pathophysiology of the disease in less than 20% of patients. The strongest genetic risk is the presence of FLG null mutations. However, most patients do not have this mutation and 60% of those with the mutation do not develop the disease. Other genetic loci contribute little to the disease pathophysiology. These include mutations associated with innate immune system signaling, T-cell activation, and T-cell specification[19].

Epidermal barrier disorder

The main epidermal-barrier structure is the stratum corneum (SC). SC prevents the loss of water and water-soluble substances and inhibits the entry of pathogens or harmful substances from the external environment. FLG dysfunction and impairments in the zonula occludens (tight junction) are causes of epidermal-barrier dysfunction[20]. FLG dysfunction leads to structural changes in the SC, resulting in increased water loss and enhanced passage of substances through the skin. FLG is involved in the production of urocanic acid and pyrrolidine carboxylic acid in the upper layers of SC. Urocanic acid maintains the acid pH of the skin, while pyrrolidine carboxylic acid is the major component of the natural moisturizing factor and enables SC to retain water. Therefore, FLG dysfunction impairs the skin pH, allowing the colonization of pathogenic bacteria on the skin surface. Consequently, antigen presentation increases, and inflammation is induced. Additionally, pH disturbance activates the serine protease enzyme. The activation of serine protease results in the cleavage of the corneodesmosomes, lipid degradation, reduced lipid synthesis, and impaired barrier function. Inflammation is triggered as there will also be a conversion from pro-interleukin-1 (IL-1) to IL-1a and IL-1b. Reduced pyrrolidine carboxylic acid synthesis due to FLG dysfunction reduces the water retention capacity of SC resulting in dry skin[21,22].

Immune dysregulation

Dysfunction or reduced quantities of antimicrobial peptides (AMP) (cathelicidins and defensins) and pattern recognition receptors (toll-like receptor; NOD-like receptor) occur, which are the components of the innate immune system[23]. As a result, the colonization of pathogenic microorganisms (particularly *Staphylococcus aureus (S. aureus)* increases.

The expression of thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 in keratinocytes is increased. TSLP increases OX40L expression in dendritic cells (DC), which lead OX40+$CD4^+$-naive cells to divert to T-helper 2 (Th2). IL-33 (external sensor of allergen proteases) and IL-25 not only support the TSLP-OX40 axis but also impair the skin barrier and aggravate FLG dysfunction.

TSLP, IL-25, and IL-33 also activate Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC)[24]. LCs and IDECs have high-affinity receptors for immunoglobulin E (IgE) on their surfaces. Thus, they enhance affinity for the allergen and perform IgE-facilitated antigen presentation. LC cells predominate in the acute stage and this

presentation stimulates Th2 cells. In the chronic stage, the response switches to Th1 as IDECs increase considerably[25].

Cytokines

IL-4 and IL-13 reduce the synthesis of filaggrin, keratin, and ceramides, promoting IgE production by B-cells. IL-31 reduces FLG expression and is a major pruritogenic cytokine. IL-5 enhances the development, differentiation, and migration of eosinophils. IL-22 promotes keratinocyte proliferation[26].

Microbial dysbiosis

Reduced diversity of the cutaneous microbiome occurs in AD. *S. aureus* colonization is detected in most patients. It's debatable whether this is a cause or an effect. The Th2-dominant response inhibits the synthesis of AMP. Colonization may occur as a result. However, the reduction of commensal bacteria may further inhibit AMP synthesis, leading to increased colonization. Furthermore, increased pH in the diseased skin increases the expression of fibronectin and fibrinogen. This allows *S. aureus* to adhere directly to the skin. The relationship between the gut microbiome and AD is controversial[27].

5. Clinical manifestations of atopic dermatitis

Symptoms and signs

General symptoms and signs: AD is characterized by an early age of onset (85% under the age of five), widespread skin dryness, persistent itching throughout the day, nocturnal aggravation of pruritus, and itchy eczematous skin lesions[28-30]. Itching may be aggravated by sweating, dermal contact with certain textile articles (especially woollen textiles), cold-heat differences, and stress.

Signs and symptoms related to eczema: Erythematous-oedematous, weeping/oozing, papular, vesiculopapular-like lesions, and excoriation predominate in the acute stage, whereas lichenification and scaling predominate in the chronic stage[28-30]. Unlike contact dermatitis, intact vesicles are not observed in AD. Subacute eczema lesions exhibit transitional forms between acute and chronic eczema lesions. Itching and dryness accompanied the lesions. Lesions show age-related morphology and distribution patterns[31] (see below). The disease may manifest in chronic persistent or chronic residual (as episodes with remissions/aggravation) courses. AD usually follows a seasonal

Table 1. Pathogenesis of atopic dermatitis

		Molecular results	Clinical results
Genetic mutations	- Filaggrin, - Innate immune system signaling, - T-cell activation, - T-cell specification.		- The most important mutation is the filaggrin mutation. - Its contribution to the disease is limited.
Epidermal barrier dysfunction	Filaggrin dysfunction.	Structural defects in the stratum corneum.	- Water loss, - Macromolecule entry.
		Reduced urocanic acid synthesis.	Disturbed dermal pH: - Pathogenic bacterial colonization and induction of inflammation - Increased serine protease activity: - cleavage of corneodesmosomes, - lipid degradation, - reduced lipid synthesis, - conversion from pro IL-1 to IL-1a and IL-1b and induction of inflammation
		Reduced pyrrolidine carboxylic acid synthesis.	Depletion of natural moisturizing factors.
	Dysfunctional zona occludens	Decreases in claudins and occludins.	- Loss of water and solutes, - Increased passage of macromolecules and microorganisms.
Immune dysregulation	Reductions in pattern recognition receptors (TLR, NLR)		Increased colonization by pathogenic bacteria (*S. aureus*).
	Depletion or dysfunction of anti-microbial peptides (cathelicidin, defensins)		Increased colonization by pathogenic bacteria (*S. aureus*).
	Increased expression of thymic stromal lymphopoietin, IL-25, and IL-33 by keratinocytes.	Th2 diversion: Increases in IL-4, 5, 13, 22, 31	- Microbial dysbiosis, *S. aureus* colonization, - Reduced filaggrin, ceramide, keratin synthesis, - Increased IgE, - Increased maturation, differentiation, and migration of eosinophils, - Pruritus.
		Langerhans cells and inflammatory dendritic epidermal cells increase.	- Increased affinity for the allergens, - IgE-facilitated antigen presentation, - Different clinical manifestations in the acute and chronic stages.

IL-1: Interleukin-1, TLR: Toll-like receptors, NLR: NOD-like receptor, IgE: Immunoglobulin E

course, with improvement in the summer and exacerbations in the winter. photosensitivity may be observed in some cases. AD may cause erythroderma in its most severe form.

Signs and symptoms associated with atopic skin structure: Secondary skin changes are major indicators of atopic skin structure and such changes may include xerosis keratosis pilaris, follicular/perifollicular accentuation (goosebumps), pulpitis sicca/winter foot, pityriasis alba, hyperpigmentation [post-inflammatory, frictional (dirty neck appearance) or periorbital], prominent creases and folds (Dennie Morgan lines/palmoplantar hyperlinearity/anterior neck fold), shiny nails due to scratching, thinning or loss of the outer third of the eyebrows (sign of Hertoghe), pale or red facial appearance, white dermographism, earlobe rhagades, perleche, and nipple eczema[30].

A significant part of such findings constitutes the "minor criteria" of the Hanifin and Rajka diagnostic criteria system, which is the gold standard tool in making the diagnosis of AD (see section 8). For cases, where these changes predominate without eczema, scoring systems have been developed to determine the atopic skin structure[32].

Clinical phenotypes

Age-related phenotypes: AD is classified under different categories based on the patient's age or the age at disease onset. The most accepted classification includes the following infantile (<2 years), childhood (2-12 years), and adult (over 12 years) categories[30]. Adult-onset (>18 years) AD is considered a separate entity[33,34].

Morphological phenotypes: Morphological phenotypes include nummular, follicular, papular-lichenoid (like juvenile papular dermatosis), prurigo-like (Besnier's prurigo), inverse (knee-elbow), and seborrheic (scalp and behind the ear) manifestations[35-39]. Studies investigating the relationship between age and morphological phenotype have reported the presence of papular-lichenoid and seborrheic morphologies in infantile AD, nummular and prurigo-like morphologies in childhood AD, prurigo-like morphology in adult AD, and nummular, prurigo-like, seborrheic, and follicular morphologies in adult-onset AD[34-36,39].

a. Infantile atopic dermatitis

This term refers to the period of life between two months and two years after birth. Acute eczema morphology is the predominant manifestation. Lichenification is unlikely to occur during this period. Initial findings usually include symmetrical, weeping eczema lesions on the cheeks, starting around the second month of life. The areas around the mouth and nose were spared. Lesions may occur on the forehead and chin and seborrheic morphology may be observed on the scalp[28,30,31,40]. The glandular area is usually spared. Lesions may occur on the neck, extensor faces of extremities, and the trunk. Moreover, it is emphasized that flexural eczema may be observed in the infantile period and in other age groups[41].

b. Childhood atopic dermatitis

This term refers to the period of life between the ages of two and twelve. Weeping-oozing lesions are less common but lichenification is more prominent[28-31,40]. Bend-type eczema predominates on flexural regions (antecubital and popliteal areas, the neck, wrists, and ankles)[30]. Facial periorbital eczema may be observed[42]. Atopic dirty neck appearance and earlobe rhagades may occur, too.

c. Adult atopic dermatitis

The disease period refers to age over twelve years. Lesions of the flexural region are most common[28-31,40,43]. Hand eczema is also common in this age group and is included in the differential diagnosis of contact dermatitis. Furthermore, head and neck lesions are characteristic and are named "portrait/bust type eczema"[30]. Head and neck lesions are considered to be caused by increased Malassezia sympodialis colonization and IgE-mediated sensitization to this agent. Lesions on the eyelids may be seen on the face.

d. Adult-onset atopic dermatitis

It includes patients who are more than 18 years of age at onset[33,34]. Although it is considered a separate entity, there are also controversial aspects. Although infantile/childhood AD lesions may recede and remain asymptomatic in some patients, such lesions may recur in adulthood. It may be challenging to distinguish this picture from AD that starts primarily in adulthood[43].

Localized types of atopic dermatitis

Localized lesions of AD have been described and may include eczema of hands, feet, genitalia, eyelids, fingertips, and nipples; cheilitis/perleche on lips, and infraauricular/retroauricular/infranasal fissuring[39,40]. The involvement of genitalia is more common in infancy; atopic foot eczema occurs more commonly in childhood, and eyelid and nipple eczema is seen more commonly in adolescents[39].

Extracutaneous manifestations of atopic dermatitis

During AD, other atopic diseases may develop, including food allergy, allergic rhinitis/rhinoconjunctivitis, and bronchial asthma, respectively. This condition is called the atopic march.

Allergic keratoconjunctivitis, keratoconus, and anterior subcapsular cataract are the most important ocular findings associated with AD[31]. Allergic conjunctivitis is often accompanied by itching and photophobia. Other comorbidities are described in section 7.

Complications

Infections: The susceptibility to bacterial, viral, and fungal infections is increased in patients with AD. As a result, many types of infections may occur, including skin infections such as erysipelas and cellulitis due to *Streptococci* and *Staphylococci*, methicillin-resistant *S. aureus* infections, meningitis, encephalitis, herpes simplex infections, eczema herpeticum, molluscum contagiosum, Malassezia sympodialis infections (especially in patients with head and neck involvement), and tinea pedis[28,31,40]. Infections such as aspergillosis and tuberculosis have also been reported, but less commonly.

Ocular complications: Besides the potential of accompanying eye findings (see above) other complications may occur, such as infectious keratitis, ocular herpes infection, blepharitis, uveitis, cataract, and retinal detachment[28,40].

Other complications: Although rare, complications such as infectious arthropathy and endocarditis have also been reported[28,31]. In its most severe form, AD may cause erythroderma.

6. Socio-economic burden in atopic dermatitis

AD is a chronic, recurrent disease with exacerbations and may have a restraining effect on the life of the patient and lives of other members

of the family. The disease not only causes physical symptoms such as itching, skin disturbances, and sleep disturbances but also may lead to decreased work productivity, mental problems, social dysfunction, and a decline in the QoL. Treatment-related costs and decreased productivity associated with the disease impose an economic burden[28]. The disease burden associated with AD should be evaluated in the QoL domain and the social, academic, professional, and economic domains[44].

Symptom burden

The symptom burden includes itching, sleep disturbance, and painful skin.

Itching and sleep disturbance: Itching is a symptom that is difficult to cope with in the vast majority of patients[28]. In an electronic questionnaire-based study, 91% of the patients reported that they experienced itching every day and 68% reported that they experienced itching more than four times a day[45]. In another questionnaire-based study, 73.9% of patients with moderate and severe AD and 51.9% of patients with mild AD reported that they experienced itching every day[46]. In the same study, the percentage of patients experiencing itching-associated sleep problems almost every night of the week was found to be 42.4% in patients with moderate and severe AD and 22.4% in patients with mild AD. The high rate of itching, pruritus-associated issues such as insomnia, and effects of itching even in mild AD prove that AD causes severe disturbances in the QoL of patients. In many ways, AD unfavorably acts on sleep in both adults and children. Difficulty falling asleep, a shorter overall duration of sleep, and frequent awakenings may be seen in patients. Sleep disturbances were found in 47-60% of AD patients[47]. Sleep disturbances may occur in the early stages of the disease, and this should be considered when evaluating the efficacy of the treatment in infants[47].

Sleep disturbances not only affect children with AD but their parents as well. Sleep disturbances of parents and sleeping with their children were directly related to AD severity[48].

The painful skin: Painful skin has recently been recognized as a separate complaint among AD symptoms. It has been pointed out that painful skin along with itching should also be considered when evaluating the treatment response. Painful skin and AD severity were associated with each other[49].

Social burden

The physical and psychosocial health of patients with AD may be unfavorably affected due to symptoms and skin changes caused by the disease. School/work success, career/friend choice, social relationships, and QoL may undergo untoward changes because of causes associated with the disease[28]. Psychosocial disorders are more common in patients with severe AD compared to patients with moderate AD[50].

Economic burden

Estimations of the economic burden of AD cover the AD-associated health expenditures of the patient and family along with indirect costs such as reduced productivity at work and school, a decrease in the QoL, and other costs resulting from comorbidities (atopic diseases, alopecia areata, cutaneous and extracutaneous infections, depression, anxiety, etc.)[28]. Among skin diseases, AD is the one that results in the highest figure of disability-adjusted life years[51]. According to a study conducted in our country, one-third of AD cases visit a physician no less than once a year due to eczema and 10% miss at least one day of school[10]. Comorbidities, rates of using health centers, and health expenditures of AD cases were found to be significantly higher than the control group and comparable to those of psoriasis patients[52].

Disease burden and quality of life

AD places a large burden on patients and families. Disease burden is evaluated based on the QoL measurement methods. Researchers and clinicians should use validated methods appropriate for the age of the patients for measuring QoL. Besides the recommendations for researchers for the use of generic and dermatology-specific or AD-specific methods, clinicians, too, should apply no less than one of these dermatology-specific and AD-specific methods[53]. Impairment in QoL is consistent with disease severity, pruritus severity, and sleep disturbance[54]. Many studies have shown that patients with AD, as well as their caregivers and family members, have low levels of QoL[28].

a. Quality of life of children

In a study on children, cerebral palsy (38%) has ranked first among all types of chronic diseases and followed by extensive AD (33%), renal disease (33%), cystic fibrosis (32%), urticaria (28%), asthma (28%), and psoriasis (27%)[55]. QoL is affected more adversely in those suffering from severe diseases[56].

b. Quality of life in adults

Impaired QoL is associated with itching and sleep disturbances, which worsen in parallel with the increasing severity of the disease. However, it has been reported that the relationship between QoL and disease severity is moderate and that QoL is affected more with the involvement of genitalia or visible areas of the body such as the face[57]. Besides the severity of AD, the characteristics of the area of involvement contribute to the impairment in QoL in adults[44].

c. Quality of life in the families of patients

Having a child with AD can sometimes be wearisome for parents emotionally and because of sleep quality disorders. In a study conducted in Poland, QoL was considerably impacted in parents having a child with AD, with higher magnitudes of QoL impairment in mothers[58].

7. Non-atopic comorbid diseases associated with atopic dermatitis

Allergic diseases

Asthma: AD is caused by disorders in mediators such as IL-4, IL-13, IL-5, and IL-31, particularly in the type 2 immune pathway. Later stages of AD may be accompanied by comorbidities originating from similar pathways[59]. AD is the initial step of such disease progression, also called the "atopic march." The disease may progress to asthma and allergic rhinitis[60]. Therefore, AD is considered among the biggest risk factors to be evaluated for developing asthma[61]. It has been reported that half of the children diagnosed with AD develop asthma by the time they reach adolescence[62]. Other studies report that 80% of children with AD may develop asthma or allergic rhinitis or both at a later age[63]. In a real-life study examining the comorbidities in approximately 34,000 children with AD, the highest correlation was found between AD and asthma[64]. To investigate the prevalence of asthma in patients with AD, Ravnborg et al.[65] conducted a review and meta-analysis study by reviewing 39,500 publications. In a recent study, they found that the prevalence

of asthma was 25.7% [95% confidence interval (CI): 23.7-27.7] in patients with AD and 8.1% (95% CI: 7.0-9.4) in the control group.

There are genetic risk factors associated with asthma and AD. there is a strong correlation between both AD and asthma and between mutations in the gene encoding the FLG protein[60,66]. The risk of severe AD and the incidence of asthma were found to be high in individuals carrying this mutation[67].

In addition to genetic risk factors, environmental triggers, too, play a significant role in the development of asthma. Hypersensitivity or intolerance to food or airborne allergens may develop. Allergic respiratory diseases such as asthma and rhinitis and food intolerance may develop because of the entry of such allergen molecular components to the body through the skin or the respiratory tract[60,61].

The risk of developing asthma increases in direct proportion to the severity of AD. Although the risk of developing AD is 8% in healthy individuals, this figure may rise to 30% in patients with mild AD and up to 70% in patients with severe AD[68-70]. In a study that included 10,000 young men with AD in the age range of 19-21 years, who were conscripted in Korea, the relationship between AD severity and atopic manifestations (asthma, allergic rhinitis, food allergy, etc.) was examined[71]. The results revealed that atopic comorbidities were substantially associated with AD severity. Therefore, the disease burden and morbidity were reported to be high in patients with chronic and severe AD.

Allergic rhinitis: AD often progresses to allergic rhinitis, asthma, and food allergy. In the literature, 45-75% of patients with AD develop allergic rhinitis[72-74]. AD is usually the first disease to occur in patients, in whom allergic rhinitis develops[75-77]. The hypothesis on this subject is that the skin barrier function is impaired in individuals with high sensitivity, and therefore, type 2 inflammatory responses occur against environmental, nutritional, and bacterial allergens[78-81].

A study on 114 children with AD, with a follow-up period of 5 years, reported that children with AD had a higher risk of developing asthma and allergic rhinitis[82]. Additionally, the best predictors of asthma were aeroallergens and food allergens, while the most reliable predictors of allergic rhinitis were the family history and early-onset AD[83]. In a Swedish study in the literature, it was shown that AD increases the risk of allergic rhinitis [odds ratio (OR): 2.63 (95% CI: 1.85-3.73)], with this risk being highest in patients with early-onset, persistent, and severe AD[69].

The presence of allergic rhinitis, asthma, and food allergy (atopic disorders) was reported to increase the risk of having moderate to severe AD by 5.88-fold (95% CI: 5.33-6.49, p<0.001) compared to patients without any other atopic disorders[71]. In another study, where 104 patients with AD (50 males, 54 females) with a mean age of 40.1 years (standard deviation SD: 15.9) and a mean SCORing atopic dermatitis (SCORAD) index score of 39 (SD: 13.1) were examined, bronchial asthma or allergic rhinitis developed in 55.8% and 76.0% of patients with moderate (58.7%) and severe (27.9%) AD, respectively[84]. Sensitization to at least one of the tested molecular compounds was observed in 93.3% of the patients.

Food allergy: AD plays a critical role as a step in the development of the allergic march by inducing food allergy and respiratory allergy through epicutaneous allergen sensitization[83,85]. Recent data indicate that epithelial cell-derived cytokines such as TSLP, IL-25, and IL-33, mediate the progression from AD to asthma and food allergy[84,86].

Food allergies occur in 35% of children with AD[11,71]. Similarly, individuals with confirmed food allergies had a 1.83-fold higher risk of having moderate to severe AD (95% CI: 1.36-2.47, p<0.001)[71].

In a recent population-based US study on 8,217 adults, AD was more associated with asthma and food allergy (OR: 2.07 - 95% CI: 1.54-2.77, p<0.01; for all) compared with controls[87,88].

Neuropsychiatric disorders

AD has been linked with several neurological, psychiatric, and psychological conditions. Factors such as AD-related pruritus, sleep disturbance, and the stress of regular skincare in pediatric patients adversely affect the QoL of patients with AD[89]. These adverse effects lead to psychological stress, sleep disturbance, anxiety, and depression in patients[90]. Deterioration in social relations has been reported in 40% of adult patients[44]. Potential anxiety and depression have been reported in 43% of adults with moderate and/or severe AD. Patients with AD may be uncomfortable with their skin appearance. They may avoid taking part in society and engaging in daily activities[91]. One study has found significantly higher hospital-diagnosed depression rates in patients with severe AD compared with the general population[92]. Moreover, it was reported in a study that the female gender constituted a risk factor for depression and suicidality[93]. The results of a 2013 survey conducted in Korea also showed that adolescents with AD had significantly higher suicidal ideation (OR: 1.34; 95% CI: 1.24-1.45) and suicide attempts (OR: 1.51; 95% CI: 1.33-1.72) compared to those without AD[94]. With AD and psoriasis studies, patient-reported incidences of anxiety or depression were found to be similar.

In studies on children with AD, the incidence of attention deficit hyperactivity disorder (ADHD) has been reported to be high[95-98]. Previous studies pointed out that sleep disturbances lead to mental health problems, particularly ADHD, in children with AD[95,99-101]. ADHD and other psychiatric disorders may occur even in pre-school children with AD[102]. Sleep disturbance was also reported to be the second most common problem affecting the QoL in children with AD[103].

Relationship with chronic diseases

It has not yet been revealed whether systemic comorbidities are inherent in the disease, or they occur due to the risk factors caused by AD.

Cardiovascular system and metabolic disorders: The relationship between AD and cardiovascular risk factors is still controversial. A US study could show a positive correlation with cardiovascular diseases[104], but another study on an Asian cohort in Taiwan identified an increase only in the risk of ischemic stroke[105]. Two recent studies did not report any correlations between AD and hypertension or type 2 diabetes[106,107]. In a recent systematic review and meta-analysis study reported by Ascott et al.[108], it was stated that significant correlations with cardiovascular outcomes were more common in cohort studies but no evidence of a relationship between AD and cardiovascular disorders could be obtained in cross-sectional studies. Andersen et al.[109] reported that conflicting cardiometabolic risk findings in adults with AD might also be attributed to the use of AD classification methods heterogeneously across study populations. In a systematic review and meta-analysis, it was stated that adult patients with AD had a high prevalence of having some disease risk factors such as obesity and smoking, but the AD was unlikely to be an independent risk factor for cardiometabolic disease[110]. Likewise, it has been reported that pediatric patients with severe AD

are less active in physical activities, participate less in sports activities, and spend long hours watching television and/or playing computer games every day[111].

In a meta-analysis of 30 observational studies, a correlation was shown between being overweight/obese and having AD in North American and Asian populations[112]. It was also decided that the correlation found in this study was not significant for the European population[110].

Other chronic diseases: Despite low incidences, inflammatory bowel disease has been found in a study to have the highest figures [1.86 (1.01-3.45)] of balanced risk ratios[113,114]. In parallel, a 2020 Delphi study reported that patients with AD had a higher relative risk (43.8%) of having immune-mediated inflammatory diseases such as rheumatoid arthritis and chronic inflammatory bowel disease[115]. In another study examining the relationship between type 2 diabetes and AD, the presence of AD in adults was associated with prediabetes, diabetes, and adult-onset diabetes[104]. More recent studies examining the relationship between AD and type 2 diabetes, hypertension, stroke, and heart attacks have yielded diverse results.

Cancer: Another controversial issue is the relationship between AD and cancer. There is insufficient evidence to advocate cancer-specific screening for patients with AD. However, it may be beneficial to inform and warn patients about restrainable risk factors such as sun exposure and smoking[116-119]. There have been reports in the literature to date about AD-associated diseases, which include lymphomas, pancreatic, esophageal, lung, and brain cancers, cervical high-risk human papillomavirus infections, and non-melanoma skin cancers[118,119].

In a systematic review and meta-analysis in the literature, eight population-based cohort studies (n=5,726,692; participants) and 48 case-control studies (n=114,136; participants) were evaluated[120]. Across the cohort studies, statistically significant correlations of AD were found with keratinocyte carcinoma (five studies; pooled SIR, 1.46; 95% CI: 1.20-1.77) and kidney cancers (two studies; pooled SIR, 1.86; 95% CI: 1.14-3.04), and central nervous system (two studies; pooled SIR, 1.81; 95% CI: 1.22-2.70) and pancreatic cancers (one study; SIR, 1.90; 95% CI: 1.03-3.50). In the analysis of the 48 case-control studies, the risks of central nervous system cancers (15 studies; pooled OR: 0.76; 95% CI: 0.70-0.82) and pancreatic cancer (5 studies; pooled OR: 0.81; 95% CI: 0.66-0.98) were found to be lower in patients with AD. Furthermore, case-control studies demonstrated a lower risk of lung and respiratory tract cancers (4 studies; pooled OR: 0.61; 95% CI: 0.45-0.82). No evidence of a correlation was found between AD and other types of cancer, including melanoma. The authors noted that there might be a moderate-to-severe risk of bias among the included studies.

A cohort study conducted in Taiwan to evaluate the correlation between AD and colorectal cancer (CRC) risk included 46,703 patients with AD (AD cohort) and gender-, age-, and index year-matched 186,812 patients without AD (non-AD cohort)[121]. In that study, AD was associated with an increased risk of CRC (adjusted HR, 1.26; 95% CI: 1.14-1.40) based on the study results. Remarkably, a significant positive correlation between AD and CRC risk was evident in both genders and all age groups.

Musculoskeletal system disorders

Studies in the literature reported osteoporosis and osteopenia in 4.8% of patients and 32.8% of patients with moderate and severe AD, respectively[122]. Congenital malformations in the limbs, hands, and feet; scoliosis, degenerative joint disease, and lower back pain are more common in pediatric patients with AD compared to the normal population[74]. Furthermore, low serum levels vitamin D levels in the blood may impose a musculoskeletal burden on AD[123]. The use of topical corticosteroids (TCS), systemic corticosteroids, and/or cyclosporine was found not to be associated with musculoskeletal disorders[124].

A meta-analysis study included 562,405 adults out of 3,171,268 from three studies, which evaluated fracture risk in AD[125]. AD was associated with an increased risk of fractures in adults (OR: 1.13; 95% CI: 1.05-1.22; p=0.001). Three studies investigating the association between AD and osteoporosis showed that AD was associated with an increased risk of osteoporosis (OR: 1.95; 95% CI: 1.18-3.23; p=0.009). Furthermore, AD was associated with an increased risk of osteopenia (OR: 1.90; 95% CI: 1.51-2.38; p<0.001) and low bone mineral density in the femur and spine.

8. Diagnostic approach in atopic dermatitis

Diagnostic criteria

The diagnosis of AD is made based on clinical characteristics, medical history, and the typical morphological distribution of cutaneous lesions[28,31,40]. Making a diagnosis is usually not a complex process in infants and children but may be challenging in severe cases and adults. The most widely used and internationally accepted diagnostic criteria in AD are the Hanifin and Rajka criteria developed in 1980[28,30,31,115,126-128]. These criteria consist of four major and 23 minor criteria and are still recognized as the gold standard system in making the diagnosis of AD. The diagnosis of AD requires that at least three major and three minor criteria should be met (Table 2)[129]. The limitations of the Hanifin and Rajka Diagnostic Criteria include the requirement of time-consuming processes for evaluating minor criteria, the difficulty of making the diagnosis in patients under 2 years of age, and the inadequacy of diagnostic criteria in adult-onset patients[31,130,131]. Despite all limitations, the sensitivity of the Hanifin and Rajka Diagnostic Criteria is high[131]. In the consensus report published by the American Academy of Dermatology[41] in 2003, the Hanifin and Rajka Diagnostic Criteria were revised to apply to all age groups (Table 3). The strength and differences of the revised criteria compared with the original Hanifin and Rajka Diagnostic Criteria consist of the inclusion of flexural lesions criterion for any age group (provided that the inguinal and axillary regions are not considered among the typical flexural regions for distributing AD lesions) and exclusionary conditions for differential diagnosis[31,40,41,115,127,128,131]. Another leading system is the diagnostic criteria proposed by the UK Working Party[132] in 1994 (Table 4). Because the UK Working Party's diagnostic system consists of the minimum number of criteria required for AD diagnosis and does not require laboratory tests or detailed evaluation methods, these criteria may be used in epidemiological studies and for rapid screening purposes.

Studies have shown that the UK Working Party's criteria are of more value in making the diagnosis of AD with the age of onset under the age of two[131,133,134]. The Hanifin and Rajka and UK Working Party's diagnostic criteria have been used in various studies and populations. Both diagnostic systems have been validated and demonstrated to be applicable. Although the revised Hanifin and Rajka criteria have not been validated, they are appropriate for clinical use[135]. Making the

diagnosis of AD requires the selection of diagnostic criteria suitable for the age of the patient. Current diagnostic criteria are inadequate to diagnose atypical morphological types such as nummular, papular, follicular, and seborrheic dermatitis and prurigo-like manifestations[115,131]. An AD diagnosis should be made based on clinical criteria.

Diagnostic algorithm

When making the diagnosis is difficult, or there is no response to treatment adjusted to the severity of the disease, skin biopsy samples or other tests (such as serum IgE, potassium hydroxide preparation, patch tests, and genetic tests) may be helpful for the differential diagnosis (Figure 1)[28,31,40].

Laboratory

Although serum IgE levels and eosinophil counts are high in AD, a specific biomarker has not been identified for diagnosis and/or severity assessment[28,31,40].

Table 2. The Hanifin and Rajka diagnostic criteria for atopic dermatitis

Major criteria (must have 3 or more from the below):
1. Pruritus (itching)
2. Skin lesions with typical morphology and distribution (flexural involvement in adolescents and adults, extensor and facial involvement in infants and children)
3. Chronic, relapsing dermatitis
4. Personal or family history of atopy
Minor criteria (must have 3 or more)
1. Xerosis (dry skin)
2. Ichthyosis/palmar hyperlinearity/keratosis pilaris
3. Type 1 skin-test reactivity
4. Elevated levels of IgE in the serum
5. Early age of onset
6. Susceptibility to cutaneous infections
7. Non-specific hand and foot eczema
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Infraorbital skin folds (Dennie-Morgan line)
12. Keratoconus
13. Anterior subcapsular cataracts
14. Periorbital darkening (pigmentation)
15. Facial pallor and erythema
16. Pityriasis alba
17. Anterior neck folds
18. Pruritus with sweating
19. Intolerance to lipid solvents and wool
20. Perifollicular accentuation
21. Food intolerance
22. Triggered by environmental and emotional factors
23. White dermographism
IgE: Immunoglobulin E

Total serum IgE/allergen-specific IgE levels: Elevated levels of total and/or allergen-specific serum IgE are the most common laboratory findings[135]. The measured values of these parameters are high in approximately 80% of patients[40]. AD is divided into two categories as "intrinsic" (unrelated to IgE) and "extrinsic" (related to IgE) based on total and/or allergen-specific IgE levels or results of the prick test against allergens. The distinction between these two forms of the disease provides practical benefits for disease management in terms of avoiding specific triggers[115,126]. Total IgE levels tend to be higher in severe diseases. However, such levels do not always correlate with disease severity[40,136]. The measurement of serum allergen-specific IgE (sIgE) levels is preferred in the presence of significant dermographism and eczematous lesions in the test area, when treatment cannot be discontinued but may affect the skin prick test (SPT) results (e.g. antihistamine therapy), and when test compliance and histamine response are predicted to be low [e.g. in early childhood (>2 years of age)][31]. Several methods (RAST, MAST, FAST) are available for specific IgE measurements. Recently introduced ImmunoCAP®, an enzyme/fluorescent diagnostic system, and Immulite®, an enzyme/chemiluminescent diagnostic system, are reliable and the most frequently used ones[137].

Table 3. Revised Hanifin and Rajka criteria for atopic dermatitis

A. Major characteristics (essential characteristics, the presence of two major criteria are sufficient for diagnosis)
1. Itching
2. Eczematous changes
a. Typical morphologies and age-specific distributions
- Facial, neck, and extensor involvement in infants and children
- Flexural lesions on examination or in history (in adulthood or at any age)
- No inguinal or axillary involvement
b. Chronic course or flare-ups
B. Important characteristics (characteristics seen in most cases and adding support to the diagnosis)
1. Early age of onset
2. Atopy
a. Personal and/or family history
b. IgE reactivity
3. Xerosis
C. Associated characteristics (characteristics that suggest a diagnosis of atopic dermatitis but are non-specific to be used for research or epidemiological studies)
1. Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
2. Keratosis pilaris, palmar hyperlinearity, ichthyosis
3. Ocular/periorbital changes
4. Other regional findings such as perioral changes/periauricular lesions
5. Perifollicular accentuation/lichenification/prurigo lesions
D. Exclusionary conditions
Scabies, allergic contact dermatitis, seborrheic dermatitis, psoriasis, ichthyoses, cutaneous lymphomas, immunodeficiency diseases
IgE: Immunoglobulin E

Blood eosinophil count: Eosinophilia is present in most patients. Because the levels may change more rapidly compared to those of IgE, blood eosinophil count may act as an index for assessing disease status[30].

Serum thymus and activation-regulated chemokine (TARC/CCL17) levels: The serum level of TARC, a Th2 chemokine, has been recognized as the most reliable marker among potential biomarkers, including new T-lymphocyte subsets and cytokines/chemokines to assess AD severity[28,30,136].

Other biomarkers: Other suggested potential biomarkers include eosinophilic cationic protein, CD30, cutaneous T-cell-attracting chemokine (CTACK/CCL27), serum sE-selectin, macrophage-derived chemokine, lactate dehydrogenase, and soluble IL-2R, IL-12, IL-6, IL-18, and IL-31[28,30,136].

Histopathology

Skin biopsy and histopathological examination are not routine diagnostic tests in AD. A histopathological examination may be used to distinguish AD from other diseases such as dermatitis herpetiformis, drug reactions, cutaneous lymphoma, and psoriasis. Biopsy findings obtained in the acute and chronic phases of AD differ. Epidermal edema, perivascular lymphocyte and monocyte infiltration, and, to a lesser extent, dermal infiltration of eosinophils, monocytes, and basophils are observed in the acute phase, whereas epidermal hyperkeratosis and monocyte- and macrophage-rich dermal infiltration are observed in the chronic phase[40,138].

Role of skin tests in diagnosis

Today, there is no simple *in vivo/in vitro* test with high sensitivity and specificity to be used for the diagnosis of AD and the identification of triggering factors. The role of food and aeroallergens in the pathogenesis and exacerbation of AD is controversial[139]. Although specific IgE antibodies against foods and/or aeroallergens are shown in daily practice by SPT and serum-specific IgE levels, the low levels of correlation of these allergens with clinical manifestations of AD complicate the process[28,29,31]. In clinical studies, the role of food allergy was detected in approximately 35% of children with moderate-to-severe AD[140]. Generally, the younger the patient and the more severe AD, it is more likely that specific food allergens can exacerbate the disease. This condition often stands out in the clinical history. Contrarily, the role of food allergies in adult AD is very low[141]. Random or screening tests to identify food allergens are not recommended in patients with AD because they will lead to unnecessary and inappropriate dietary restrictions[29]. Skin tests are optimally performed in treatment-resistant cases, in cases with worsening skin symptoms after food intake (in patients with a compatible clinical history), or in the presence of both of these two conditions[142]. SPT, prick-to-prick tests, and the measurement of serum-specific IgE levels are frequently used methods in cases of suspected IgE-mediated food allergy[31]. The diagnostic approach to food allergy in patients with AD consists of the evaluation of the patient's detailed nutritional history (if breastfed, maternal nutritional history needs to be evaluated), allergen susceptibility tests such as SPT and serum food sIgE levels, and the evaluation of the clinical significance of positive test results[28]. The double-blind, placebo-controlled food challenge test is the gold standard for the diagnosis of food allergy[28,31]. Exposure to aeroallergens, such as house dust mites, pet hair, pollens, and mold, may aggravate AD in some patients. In such cases, it may be useful to determine the sensitivity by SPT. If sensitivity is revealed and the history suggests a causal role in the worsening of AD, measures such as removing the allergen from the patient's environment should be considered[29]. There are no standardized provocation tests that may determine the association of the results of SPT and specific IgE levels with clinical manifestations of AD and show the role of aeroallergens[31]. Recently, the atopy patch test (APT) has been introduced for use to evaluate IgE-dependent and IgE-independent late-phase cutaneous reactions in AD[31]. The European Academy of Allergy and Clinical Immunology recommends APT in patients with suspected food allergy and/or symptoms associated with aeroallergens in the absence of

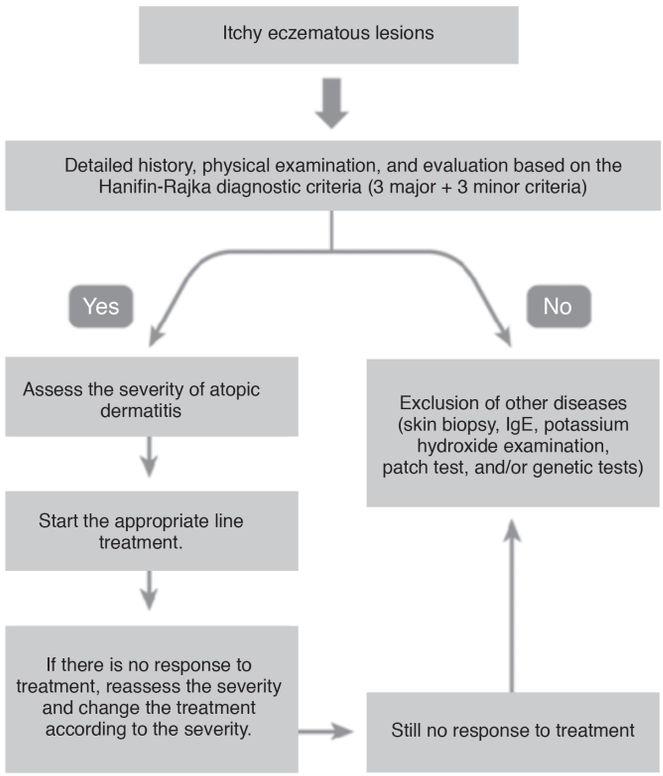


Figure 1. Diagnostic algorithm for atopic dermatitis

Table 4. UK Working Party's diagnostic criteria*

The must-have criterion
The presence of pruritic dermatosis on the skin (or such condition in children should be reported by the parents)
Other criteria
1. Presence of flexural involvement (popliteal fossa, antecubital fossa, neck, frontal faces of ankles; cheek involvement in those under ten years of age)
2. Personal history of asthma or hay fever (history of any atopic disease in a first-degree relative in children under 4 years)
3. A history of widespread dry skin (within the last year)
4. Visible flexural eczema (involvement of the cheeks, forehead, and outer surfaces of the limbs in those younger than 4 years)
5. The onset of the rash before the age of two (this characteristic is not used in children younger than four years of age)
*In addition to the must-have criterion, at least three other criteria must be present for the diagnosis.

positive SPT results or significant serum-specific IgE elevations, in moderate-severe AD with unknown triggers, and in cases of multiple IgE sensitization of no clinical significance[28,31]. The patch test may be useful to exclude the diagnosis of concurrent contact dermatitis[141].

Disease severity instruments in atopic dermatitis

Several different scoring systems have been published recently to determine the clinical severity of AD. These scales are useful in categorizing the disease severity for daily practice and in clinical studies. Despite the availability of several studies, no consensus has been achieved on the reliability and usability of these scoring scales for use in clinical practice. The most well-known tests for determining the severity and prevalence of the disease in adults and children with AD are SCORAD, Patient-Oriented Eczema Measure (POEM), Eczema Area and Severity index (EASI), and Investigators' Global Assessment (IGA)[28]. The SCORAD index and the EASI system have been reported to be the two most reliable and usable methods in clinical practice[143]. EASI, SCORAD, and POEM are adequate scales for use. EASI and SCORAD are considered valuable to objectively assess disease severity. POEM is another valuable scale because it measures disease severity from the patient's perspective[144]. The self-assessment by the patient may help in monitoring the disease status advantageously[145]. Several self-assessment scales have been suggested for use in AD. Among these scales, POEM has been reported to be the only system with adequate validation[31,144,146-151]. Atopic Dermatitis Control Tool (ADCT) and patient global assessment (PtGA) are commonly used in daily clinical practice to establish meaningful grounds of patient-physician communication during the efforts spent to managing AD[150,151]. All the disease severity instruments are summarized in Table 5.

a. SCORing atopic dermatitis

SCORAD is considered to be the gold standard tool. It is an index developed by the European Task Force on Atopic Dermatitis (ETFAD)[152]. It is the most commonly used scoring system for measure the severity of AD. It is a widely used, reliable, and well-adapted test. In the evaluation, objective (A and B data) and subjective (C data) data are evaluated together, and a calculation method is used (Figure 2).

Table 5. List of scales

SCORAD	Extent of lesions The severity of the lesions via six clinical signs (erythema, edema/papulation, oozing/crusting, excoriation, lichenification, xerosis) and subjective complaints such as itching and insomnia on a visual analog scale.	Mild disease with a score of <25 points, Moderate disease with a score of 25-50 points, Severe disease if a score of more than 50 points. Disease extent, disease severity, and subjective symptoms	Maximum 103 points
Objective SCORAD	Obtained from the "exclusion of subjective symptoms" of the SCORAD index. Obtained by measuring only the extent (A) and the severity (B)	Objective SCORAD=A/5+7B/2 + Additional 10 points (for severe eczema on face and hands)	Maximum 83 points
PO-SCORAD	Patients marked the signs of atopic dermatitis over the last three days on a questionnaire equipped with images as examples. The physician calculated the score according to the SCORAD formula	This questionnaire comprises 7 questions to be scored with respect to the number of days with AD signs and symptoms over the last week (never: 0, 1-2 days: 1, 3-4 days: 2, 5-6 days: 3, every day: 4)	Maximum 28 points
POEM	Simple questions to pediatric and adult patients about the frequency of itching, sleep disturbance, dermal bleeding, oozing, cracking, flaking, and dryness/ roughness.	It is based on patients' perspectives on disease severity. The basic question is the number of days, on which subjective symptoms have affected the patient over the last week.	Maximum 28 points
EASI	Each of the four body areas, head/neck, trunk, and upper and lower limbs, is evaluated individually for erythema, excoriation, lichenification, and induration/ papulation/edema.	Symptoms such as pruritus and findings such as xerosis and squat were excluded by the physical examination of relevant areas. Each finding was assigned a score between 0 and 3 based on severity.	Maximum 72 points
IGA/PGA	It is commonly used in pediatric patients; erythema, infiltration, papulation, oozing, and rough skin are fully evaluated.	On a 6-point scale for each finding, scores range from 0 (clear) to 5 (very severe disease).	Maximum 25 points
PtGA	It is a scale for evaluating disease severity and disease impact from the patient's perspective.	Response options are as follows: 0: clear, 1: almost clear, 2: mild, 3: moderate, 4: severe, and "worst ever" with an optional checkbox. A point of 2 or more indicates a poorly controlled disease.	Maximum 4 points
ADCT	ADCT comprises six short questions, which were considered suitable by patients and clinicians: 1. The overall severity of symptoms, 2. The frequency of intense episodes of itching, 3. The extent of bother, 4. The frequency of sleep impact, 5. Impact on daily activities, and 6. Impact on mood or emotions	Each ADCT question was assigned a score ranging from 0 to 4. The sum of the individual item scores produces the total ADCT score. A point of 7 or more, and 5 points increase from the baseline indicates a poorly controlled disease.	Maximum 24 points

SCORAD: SCORing atopic dermatitis, PO-SCORAD: Patient-oriented SCORAD, POEM: Patient-Oriented Eczema Measure, EASI: Eczema Area and Severity Index, IGA, Investigators' Global Assessment, PGA: Physicians' Global Assessment, PtGA: Patient-Global Assessment, ADCT: Atopic Dermatitis Control Tool

A. Extent: The extent of lesions should be graded based on the rule of nines. After the body is divided into anterior and posterior surfaces, each surface is divided into multiples of 9. Hands and the genital area are given one point each. Thus, the area affected by the lesions in the body may be calculated in percentage.

B. Intensity: Objective findings evaluated by the physician include 1) erythema, 2) edema/papulation, 3) oozing/crusting, 4) excoriation, 5) lichenification, and 6) dryness, respectively. Each marker is graded on a scale of 0-3 (0: none; 1: mild; 2: moderate; 3: severe). Moderate lesions should be selected rather than the worst skin lesions during the assessment. The same area may be evaluated twice or more times.

C. Subjective symptoms: The symptoms subjectively evaluated by the patient are itching and sleep disturbance. Children over the age of 7 rate the severity of their complaints in the previous three days/nights on a scale of 0-10. As a result, all numerical data are summed up to yield a total score by using the formula of A/5+7B/2+C. The maximum total score that can be obtained from the test is 103. A score of <25 is considered an AD of mild severity, a score of ≥25 to ≤50 is considered moderate AD, and a score of more than 50 is considered severe AD.

Objective SCORAD: It was obtained by "excluding the subjective symptoms" from the SCORAD index. The score is obtained by measuring only the extent (A) and the intensity (B) by using the following formula: objective SCORAD=A/5+7B/2. The maximum score is 83 (additional 10 points can be given). The additional 10 points are given in cases of severe eczema on the face and hands[153].

Patient-oriented SCORAD: This is a patient-oriented scoring system, which is based on the principle of marking the signs of AD on a questionnaire form by using visual samples. Markings are performed by the patient, considering the last three days. The score of the completed questionnaire is calculated by the physician using the SCORAD formula (Figure 3). The questionnaire is filled out by the patients in about 5-10 minutes. Results results were compatible with SCORAD scores. The most difficult part of the questionnaire for patients is determining the extent of the disease[154].

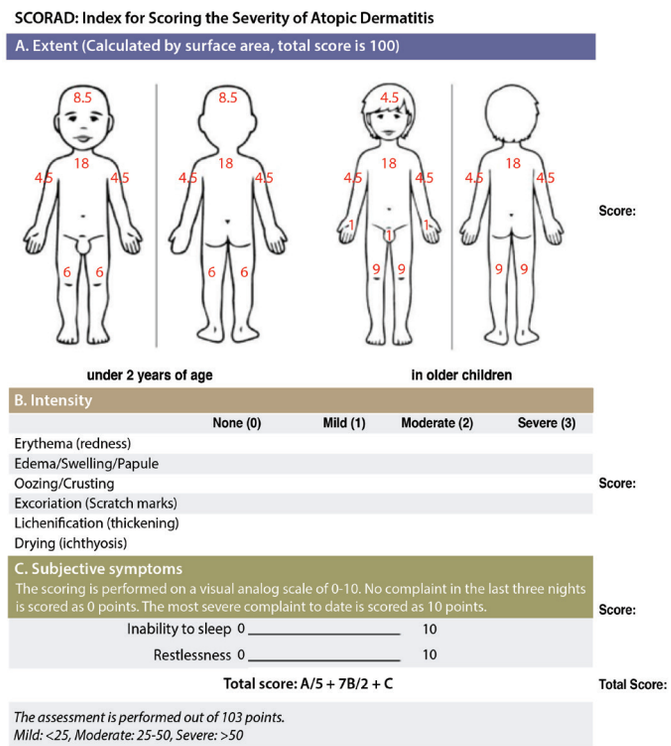


Figure 2. SCORAD index

SCORAD: SCORing atopic dermatitis

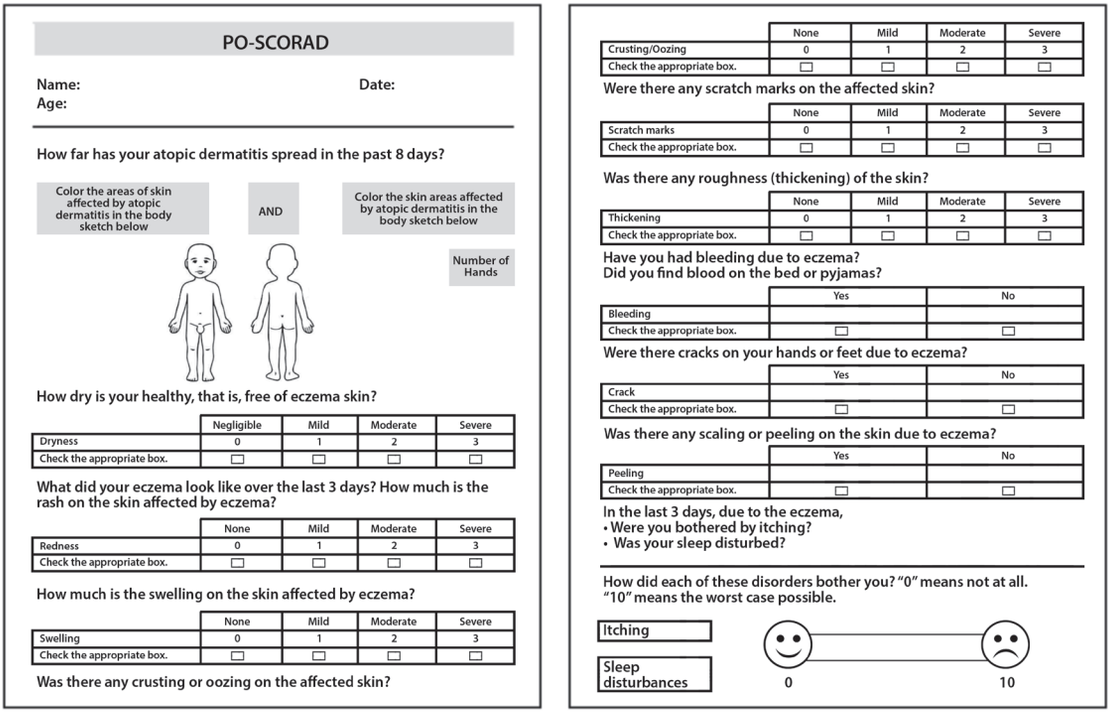
b. Eczema Area and Severity Index

Eczema Area and Severity Index is a commonly used tool. Scores are given to four body regions (Head-neck=h, upper limbs=ul, trunk=t, lower limbs=ll) based on the extent of lesions. Body region scores (A) can be assessed as follows: 1=10%; 2=10-29%, 3=30-49%, 4=50-69%, 5=70-89%, and 6=90-100%). Lesions in four regions are scored between 0 and 3 based on the severity of erythema (E), induration/papule/edema (I), excoriation, and lichenification. Severity and region scores are multiplied by multipliers of each region and summed up. EASI=0.1 (E+I+Ex+L) AH + 0.2 (E+I+Ex+L) Aul + 0.3 (E+I+Ex+L) At + 0.4 (E+I+Ex+L) All. The maximum score was 72. Symptoms such as pruritus and findings such as xerosis and squam were excluded from the assessment regions. This system is used to obtain the baseline standard assessment of eczema and observe changes during follow-up. However, cut-off scores for differentiating mild, moderate, or severe disease have not been established. EASI has been reported as a scoring system with good validity, reliability, and precision. It has been reported that it is well correlated with other severity measures. It is the most comparable scoring method with the SCORAD index[155]. It has been reported that scores obtained using the *EASIdig* method, in which EASI scoring is performed using digital photographs of the patients, are correlated with EASI scores[156].

c. Investigators' Global Assessment/Physicians' Global Assessment

Physicians' Global Assessment is another commonly used scale[157]. It is commonly used for pediatric patients. IGA is a 6-point severity scale: 0 (clear) denotes no inflammatory signs of AD; 1 (almost clear) just perceptible erythema, infiltration, or papulation; 2 (mild disease) mild erythema, infiltration, or papulation; 3 (moderate disease) moderate erythema, infiltration, or papulation; 4 (severe disease) severe erythema, infiltration, or papulation; 5 (very severe disease) severe erythema, infiltration, or papulation with oozing and crusting. It is a static assessment of AD severity and is not compared with any previous assessment[158]. In this simple system, a complete assessment can be performed on a 6-point scale by using the clinical characteristic signs of dermatitis (erythema, infiltration, papulation, oozing, and rough skin). A score of 0 5 was assigned to each finding. Thus, a total score in the range of 0-25 is obtained. The exclusion of subjective symptoms is a limitation[159].

Patient global assessment: It is a scale that evaluates the severity of the disease or the disease impact from the patient's perspective[150]. PtGA may show some variations. PtGA may allow the user to perform a dynamic classification by grading recovery relative to the baseline state/disease severity (for example, how do you rate your current status compared to baseline?) or may allow the user to perform a static classification of the patient's condition at a particular time point (for example, how are you today?). Response options are as follows: 0:



PO-SCORAD

Name: Date:
Age:

How far has your atopic dermatitis spread in the past 8 days?

Color the areas of skin affected by atopic dermatitis in the body sketch below | AND | Color the skin areas affected by atopic dermatitis in the body sketch below

Number of Hands

How dry is your healthy, that is, free of eczema skin?

	Negligible	Mild	Moderate	Severe
Dryness	0	1	2	3
Check the appropriate box.	☐	☐	☐	☐

What did your eczema look like over the last 3 days? How much is the rash on the skin affected by eczema?

	None	Mild	Moderate	Severe
Redness	0	1	2	3
Check the appropriate box.	☐	☐	☐	☐

How much is the swelling on the skin affected by eczema?

	None	Mild	Moderate	Severe
Swelling	0	1	2	3
Check the appropriate box.	☐	☐	☐	☐

Was there any crusting or oozing on the affected skin?

	None	Mild	Moderate	Severe
Crusting/Oozing	0	1	2	3
Check the appropriate box.	☐	☐	☐	☐

Were there any scratch marks on the affected skin?

	None	Mild	Moderate	Severe
Scratch marks	0	1	2	3
Check the appropriate box.	☐	☐	☐	☐

Was there any roughness (thickening) of the skin?

	None	Mild	Moderate	Severe
Thickening	0	1	2	3
Check the appropriate box.	☐	☐	☐	☐

Have you had bleeding due to eczema?
Did you find blood on the bed or pyjamas?

	Yes	No
Bleeding		
Check the appropriate box.	☐	☐

Were there cracks on your hands or feet due to eczema?

	Yes	No
Crack		
Check the appropriate box.	☐	☐

Was there any scaling or peeling on the skin due to eczema?

	Yes	No
Peeling		
Check the appropriate box.	☐	☐

In the last 3 days, due to the eczema,
- Were you bothered by itching?
- Was your sleep disturbed?

How did each of these disorders bother you? "0" means not at all. "10" means the worst case possible.

Itching

Sleep disturbances

0 10

Figure 3. PO-SCORAD index
PO-SCORAD: Patient-qriented SCORAD

clear, 1: almost clear, 2: mild, 3: moderate, 4: severe, and "worst ever" with an optional checkbox[160].

d. Patient-Oriented Eczema Measure

Child and adult patients are asked simple questions about the frequency of itching, sleep disturbances, and bleeding, oozing, cracking, flaking, and dryness/roughness of the skin. It is based on patients' perspectives on disease severity. The basic question is the number of days over the last week, on which subjective symptoms affected the patient. The questionnaire consisted of seven questions. The total score varies in the range of 0-28 as the sum of individual item scores given based on the number of days over the last week, on which symptoms and signs of AD have been present (never: 0, 1-2 days: 1, 3-4 days: 2, 5-6 days: 3, every day: 4). In the clinical setting, it is a well-accepted scoring system because it is a quick and easy-to-apply questionnaire that may be completed by the patient within 1-2 minutes. The limitation of this scoring system (Figure 4) is that it consists of only subjective criteria. Additionally, it may produce false results because low scores are obtained in patients using corticosteroids[148].

e. Atopic Dermatitis Control Tool

The ADCT is a validated, brief, and easy-to-score scale[151]. All aspects of AD are evaluated through six short questions, which were considered suitable by patients and clinicians: 1) The overall severity of AD symptoms, 2) the frequency of intense episodes of itching, 3) the extent of AD-related bother, 4) the frequency of sleep impact, 5) the impact of AD on daily activities, 6) the impact of AD on mood or emotions (Figure 5). While patients may self-administer ADCT, this tool may also be used in routine consultations. ADCT is designed to establish meaningful grounds of patient-physician communication toward the management of AD during daily clinical practice. This tool enables better monitoring of the disease. AD may not be well controlled if the total ADCT score is at least 7 points, or if the total ADCT score has increased by 5 points or more since the last ADCT use[151,161].

Quality of Life Assessment Scales

Various QoL scales are available to assess the impact of AD on the QoL[53] (Table 6). Among these, the most commonly used dermatology-specific scales are the Dermatology Quality of Life Index (DLQI) and the Children's Dermatology Quality of Life Index. Among the infant and family QoL indices specific to AD, the Infants' Dermatitis Quality of Life Index (IDQOL) and the Dermatitis Family Impact are the most commonly used indices.

a. Quality of life assessments for adults: EuroQoL 5-Dimension (EQ-5D), DLQI, and Skindex-29 are the most commonly used scales in adults[28].

EuroQoL 5-Dimension

EQ-5D consists of five dimensions: Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three response options: "no problems", "some problems", and "major problems". The Turkish version was developed in 2009[162].

Dermatology Life Quality Index

It was developed by Finlay and Khan[163] in 1994. It is the most important and most commonly used quality of life index among dermatology-specific tests. The Turkish adaptation of DLQI was performed by Oztürkcan et al.[164] in 2006 (Figure 6). DLQI comprises 10 questions, each offering four possible answers to choose one. The questions are grouped under the following subtitles, including symptoms and the patient's feelings, daily activities, leisure time, school/work life, personal relationships, and treatment. Each question may receive a score from

0 to 3. The total maximum and minimum scores that can be obtained from the test are 30 and 0, respectively. A high score represents a linear relationship an impaired QoL.

Skindex-29

It is a questionnaire composed of 29 questions, particularly designed to assess the health-related QoL in patients with dermatosis[165]. The questionnaire comprises three scales: Symptom, functioning, and mood scales. The Turkish version of Skindex-29 was developed in 2007 by Aksu et al.[166], who reported that it is a comprehensible, practicable, reliable, and valid assessment questionnaire.

b. Quality of life assessments for children:

Infants' (Young Child) Dermatitis Quality of Life index

It was developed for children with AD under the age of four years. It is a short questionnaire consisting of 10 questions that can be completed in two or three minutes by the child's family or the caregiver[167].

Dermatitis Family Index

It was a 10-question questionnaire offering four optional answers to be selected by the family[168]. It is administered to the parents or caregivers of children aged 0 to 4 years.

Scales evaluating itching and sleep disturbance

POEM is used for grading specific symptoms such as itching and sleep. The Visual Analogue Scale (VAS) and the Numeric Rating Scale (NRS) are other scales that are commonly used[169].

In AD, besides the clinical severity scales (SCORAD, EASI, and IGA), which are used to determine the severity of the disease and the selection of treatment, the DLQI needs to be used to evaluate subjective complaints. Additionally, other scales such as VAS and NRS may need to be used to evaluate pruritus and sleep disturbances[127].

Please check one box for each of the seven questions below. Young children should complete the questionnaire with the help of their parents.

Please leave blank any questions yo do not think you can answer.

1. Over the last week, how many days has your or your child's skin been itchy due to eczema?

No days	1-2 days	3-4 days	5-6 days	Every day
☐	☐	☐	☐	☐

2. Over the last week, how many nights has your or your child's sleep been disturbed due to eczema?

No days	1-2 days	3-4 days	5-6 days	Every day
☐	☐	☐	☐	☐

3. Over the last week, how many days has your or your child's skin been bleeding due to eczema?

No days	1-2 days	3-4 days	5-6 days	Every day
☐	☐	☐	☐	☐

4. Over the last week, how many days has your or your child's skin been weeping or oozing clear fluid due to eczema?

No days	1-2 days	3-4 days	5-6 days	Every day
☐	☐	☐	☐	☐

5. Over the last week, how many days has your or your child's skin been cracked due to eczema?

No days	1-2 days	3-4 days	5-6 days	Every day
☐	☐	☐	☐	☐

6. Over the last week, how many days has your or your child's skin been flaking off due to eczema?

No days	1-2 days	3-4 days	5-6 days	Every day
☐	☐	☐	☐	☐

7. Over the last week, how many days has your or your child's skin felt dry or rough due to eczema?

No days	1-2 days	3-4 days	5-6 days	Every day
☐	☐	☐	☐	☐

Figure 4. POEM scale

POEM: Patient-Oriented Eczema Measure

Table 6. Quality of life assessment scales

Scale	Objective	Originality
Dermatology Life Quality Index*	Adults	Dermatology
Skindex-29	Adults	Dermatology
EQ-5D	Adults	Dermatology
Children's Dermatology Life Quality Index*	Children aged 4-16 years:	Dermatology
Family Dermatology Life Quality Index (Basra, 2007)	Family	Dermatology
Quality of Life Index for Atopic Dermatitis (Whalley, 2004)	Adults	Atopic dermatitis
Infants' Dermatitis Quality of Life Index*	Children <4 years old	Atopic dermatitis
Dermatitis Family Impact*	Family	Atopic dermatitis

*These are the most commonly used scales. EQ-5D: EuroQoL 5-Dimension

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9. Differential diagnosis of atopic dermatitis

The diseases that should be considered primarily in the differential diagnosis of AD vary according to the patient's age and the location of the lesions. The disease groups that should be considered in the differential diagnosis, in general, include chronic inflammatory dermatoses such as seborrheic and contact dermatitis; infectious diseases, primarily scabies; primary immunodeficiency syndromes, and autoimmune and metabolic skin diseases[170,171]. (Table 7, 8). Although there are no specific types of tests recommended for routine use in the differential diagnosis, some laboratory tests and histopathological examinations are required for distinguishing AD from primary immunodeficiencies, especially in childhood, and from cutaneous T-cell lymphoma in adults.

10. Treatment of atopic dermatitis

General treatment principles

Patient/family education

AD is a chronic and recurrent disease. Training of the patient and caregivers on the disease and its management is critical for the proper administration of the treatment and the prevention of relapses. In a randomized and controlled study, adult patients with moderate and severe AD showed significantly superior results, compared to the untrained group, in coping with itching, QoL, and SCORAD scores at their follow-up visits one year after 12-hour training[172]. In another randomized, controlled study conducted on children aged 2-14 years, four courses of group training were provided weekly (long-term treatment, food allergy, skincare and moisturizer use, and family QoL). Compared to the untrained group, a significant difference in the trained

Today's date:

						Write the score for each question in the gray boxes.
1. Over the last week, how would you rate your eczema related symptoms?	(None) 0 points:	(Mild) 1 points:	(Moderate) 2 points:	(Severe) 3 points:	(Very Severe) 4 points:	
2. Over the last week, how many days did you have intense episodes of itching because of your eczema?	(Not at all) 0 points:	(1-2 days) 1 point:	(3-4 days) 2 points:	(5-6 days) 3 points:	(Every day) 4 points:	
3. Over the last week, how bothered have you been by your eczema?	(Not at all) 0 points:	(A little) 1 point:	(Moderately) 2 points:	(Very) 3 points:	(Extremely) 4 points:	
4. Over the last week, how many nights did you trouble falling or staying asleep because of your eczema?	(No nights) 0 points:	(1-2 nights) 1 point:	(3-4 nights) 2 points:	(5-6 nights) 3 points:	(Every nights) 4 points:	
5. Over the last week, how much did your eczema affect your daily activities?	(Not at all) 0 points:	(A little) 1 point:	(Moderately) 2 points:	(Very) 3 points:	(Extremely) 4 points:	
6. Over the last week, how much did your eczema affect your mood or emotions?	(Not at all) 0 points:	(A little) 1 point:	(Moderately) 2 points:	(Very) 3 points:	(Extremely) 4 points:	
					The sum of your scores = your total ADCT score:	

Figure 5. ADCT scales

ADCT: Atopic Dermatitis Control Tool

Table 7. Differential diagnosis of infantile and childhood atopic dermatitis

Disease	Helpful tips for differential diagnosis
Seborrheic dermatitis	Involvement of the glands, large folds, and the scalp and pruritus are milder with earlier onset (<6 weeks) compared to AD, yellowish-adherent scales
Scabies	Papular lesions, tunnels, palmoplantar pustular lesions on interdigital areas, flexor surfaces of wrists, and genital areas, increased itching at night, family history
Viral exanthem	Prodromal symptoms such as fever and malaise, acute onset, pruritus were mostly absent
HyperIgE syndrome	Typical facial features, recurring bacterial and fungal infections, pneumonia
Wiskott-Aldrich syndrome	Recurrent infections and bleeding diathesis
Omenn syndrome	Neonatal infections, lymphadenopathy, alopecia
Netherton syndrome	Neonatal ichthyosis, growth retardation, bamboo hair, ichthyosis linearis circumflexa
Histiocytosis	Involvement of intertriginous and glandular areas, and scalp, itchy papules, and plaques unresponsive to topical corticosteroids
Acrodermatitis enteropathica	Periorificial and acral crusty patches and erosion

AD: Atopic dermatitis

group was found in SCORAD and IDQOL (2-4 years old) scores and the level of knowledge about moisturizer use at month 6[14]. A recent meta-analysis evaluated 13 randomized, controlled trials investigating the impact of patient training programs on pediatric AD[173].

It was concluded in that meta-analysis that, despite the lack of favorable effects of training programs on the QoL, advantageous effects were obtained in SCORAD scores and that such effects were related to session frequency and follow-up time.

- Considering the effects of training programs on disease severity and the QoL, it is recommended to organize training programs, tailored to specific age groups, on the disease course, elimination of triggering factors, effective use of moisturizers and treatments, and possible complications related to the disease and treatments.
- In terms of feasibility and accessibility, it may be recommended to organize programs first for patients with moderate to severe AD.
- Early career counseling, in particular for pediatric patients, is also important in preventing future occupational disease exacerbations and disease-associated loss of workforce.

Avoiding triggers

Avoidance from environmental triggers is central to preventing disease flare-ups. Well-known environmental triggers include irritants such as low ambient humidity, extremely hot environments, sweating, air

1. Over the last week, how itchy, sore, painful or stinging has your skin been?

a. Not at all	**b.** A little	**c.** A lot	**d.** Very much

2. Over the last week, how embarrassed or self conscious have you been about the condition of your skin because of the appearance of your skin?

a. Not at all	**b.** A little	**c.** A lot	**d.** Very much

3. Over the last week, how much has your skin interfered with you going shopping or looking after your garden?

a. Not at all	**b.** A little	**c.** A lot	**d.** Very much

4. Over the last week, how much has your skin influenced the clothes you wear?

a. Not at all	**b.** A little	**c.** A lot	**d.** Very much

5. Over the last week, how much has your skin affected any social or leisure activities?

a. Not at all	**b.** A little	**c.** A lot	**d.** Very much

6. Over the last week, how much has your skin made it difficult for you to do any sport?

a. Not at all	**b.** A little	**c.** A lot	**d.** Very much

7. Over the last week, has your skin prevented you from working or studying?

Yes	No

If "No" (if it didn't prevent you from working or studying), over the last week, how much has your skin been a problem at work or studying?

a. Not at all	**b.** A little	**c.** A lot	**d.** Very much

8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?

a. Not at all	**b.** A little	**c.** A lot	**d.** Very much

9. Over the last week, how much has your skin caused any sexual difficulties?

a. Not at all	**b.** A little	**c.** A lot	**d.** Very much

10. Over the last week, how much of a problem has the treatment for your skin been? For example, by making your home messy, or by taking up time?

a. Not at all	**b.** A little	**c.** A lot	**d.** Very much

Figure 6. Dermatology Quality of Life Index

Table 8. Differential diagnosis of adult atopic dermatitis

Disease	Helpful tips for differential diagnosis
T-cell lymphoma	Mildly indurated patches and plaques with fine squad, histopathological examination
Allergic contact dermatitis	In the contact area after contact with the contact allergens
Scabies	Involvement of interdigital, axillary, and periumbilical areas, penile and scrotal lesions in males, involvement of periareolar and vulvar regions in females
Seborrheic dermatitis	Involvement of eyebrows, nasal edges, back, and mid-chest, no/mild itching

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pollution, active or passive exposure to cigarette smoke, poor hygiene conditions, and woolen textiles[174-176]. Additionally, factors such as emotional stress and increased *S. aureus* colonization may also increase disease severity and exacerbations[177]. In addition to the elimination of triggering factors at home, work, and at school, other methods such as individual psychotherapy and behavioral therapy may be recommended in cases of increased emotional stress[178].

- Tests for food and respiratory allergens are recommended to identify triggers in moderate and severe AD that cannot be controlled despite optimal skincare and treatment[179].
- Patch testing may be recommended, particularly in patients with recurrent/persistent hand-foot, earlobe, or eyelid lesions and suspected allergic contact dermatitis.

Topical treatment approaches

The mainstay of AD management is patient education and therapy. Patient education covers many topics, from the identification of triggers to adopting the principles of proper moisturizing. Here, the patient or his/her family should be informed about the likely extent of the disease, which will depend on the skin barrier dysfunction. They should be well informed to know that it is possible to eliminate this disorder through moisturizing and lubrication. It is possible to provide training on avoidance from triggers and on the timing, areas, and ways of topical treatment administration. The attainability of such training objectives is feasible through adequate management. Furthermore, patient-physician collaboration is essential for this process. It should be explained that AD is a chronic inflammatory disease with intense itching, and recurrent eczematous lesions may occur during the disease course. During infancy, the family should be informed about the characteristics of the skin of infants and about the issues that require the exercise of care in topical treatments. Potential problems associated with the use of treatments lacking high levels of evidence and likely consequences of inadequate treatment and steroid phobia should be explained to patients from all age groups. Note that AD is a pediatric disease that may affect two out of every ten children. Characteristics of adult AD should also be discussed openly with the patient, and if necessary, a discussion about the atopic march must be included[130,180].

Three major features need to be addressed in disease management. These may be summarized as follows:

- Identification of triggering factors and taking measures against them.
- The amelioration of skin barrier disorders with appropriate skincare.
- Pharmacotherapy[30],

Topical agents are the mainstay of treatment for AD. Even in highly severe cases requiring systemic therapy, combinations of protectors against the skin barrier, moisturizers, and topical treatments are often required.

The most commonly used method in topical treatment includes inflammation control with the use of topical steroids and a topical calcineurin inhibitor (TCI) in addition to skincare with moisturizers. Although the mainstay therapy for controlling inflammation in the acute stage consists of topical steroids, the intermittent use of TCIs or topical steroids along with a moisturizer helps prevent flare-ups during remission. This treatment modality is called proactive therapy. This is unlike reactive therapy, where topical therapy is administered only when the rash worsens. Proactive therapy also lowers the cost of treatment[181].

a. Regulation of skin barrier dysfunction and moisturization

Overall skin dryness and epidermal barrier dysfunction comprise the main underlying problem in AD. Although there are no proven primary preventive methods for AD, it has been reported that there may be a 30-50 percent reduction in the incidence of AD diagnosis at month 6 provided that early and safe use of emollients is given to high-risk infants. Therefore, it is primarily necessary to ease the dryness of the skin with moisturizers. Frequent and abundant use of moisturizers should be encouraged[182]. Although there is no consensus on quantities to be used, 150-200 g per week for children and 500 g for adults is recommended by the ETFAD and the European Academy of Dermatology and Venereology[183]. Moisturizers, further, alleviate symptoms and signs such as erythema, itching, fissuring, and lichenification; they have mildly therapeutic properties alone[184-187]. Conventional moisturizers contain emollients, occlusive, and/or humectants as ingredients. While emollients (glycol, glyceryl stearate, soy sterols, etc.) soften the skin, occlusive agents (vaseline, dimethicone, mineral oils, etc.) form a layer and prevent water loss. Humectants such as glycerol, lactic acid, and urea absorb and trap water[187,188]. Ceramides, free fatty acids, and cholesterol found in recently introduced moisturizers are naturally found in the innate structure of the epidermis. Unlike conventional emollients currently prescribed for dry skin to be applied regularly 3-4 times a day, ceramide-containing products provide lasting moisturization for more than 24 h. Nevertheless, adequate data are not available to argue that these moisturizers are superior to others[130,187]. In a study on 39 individuals with mild-to-moderate AD, there were no differences in efficacy between a hydrolipid cream containing glycyrrhetinic acid, a cream containing ceramide, cholesterol, free fatty acids, and an over-the-counter petroleum-based skin protective moisturizer after three weeks of use[189]. Therefore, the choice of moisturizing agent largely depends on individual preferences. The ideal agent should be safe, effective, inexpensive, and free of additives, fragrances, perfumes, and other potentially sensitizing substances[187]. The regular use of products containing sodium lauryl sulfate as a moisturizer is not recommended. The age of the patient is also important in the selection of moisturizer. Urea-containing moisturizers are not appropriate for pediatric patients[130]. Furthermore, the use of moisturizers containing propylene glycol should be avoided in patients under the age of two due to the risk of irritation[190].

Although an exact figure of application frequency has not been established for moisturizer use, it is recommended that moisturizers should be applied at least 2-3 times per day to provide relief from dryness[182]. Transepidermal water loss increases after bathing, therefore, consequent moisturizer use is recommended to improve skin hydration[191]. Moisturizing should be performed within five minutes immediately after the bath and after wiping off excess water with a towel. Moreover, if a topical medication is used along with a moisturizer, the two drugs should not be applied concurrently. This way, the dilution of the topical medication by the moisturizer is prevented[192]. Frequent baths are effective in improving disease symptoms, provided that the moisturizer is applied after every bathing session.

Because it has been reported that thermal spring water and related products have therapeutic effects on the microbial diversity of the skin and immune regulation, they may provide some benefit for patients with mild-to-moderate AD. The most important thing that determines

the efficacy of topical treatment is the patient's compliance with disease management. To promote the patient's adherence to treatment, the most appropriate topical treatment should be selected and the necessity of moisturizers in the treatment should be emphasized by allocating ample time for discussion.

Ideal moisturizer:

- should provide effective moisturization,
- must contain safe ingredients,
- should be inexpensive,
- should be additive-free,
- should not contain fragrance, perfume,
- should not be an allergen,
- should be easily accessible,
- should not contain propylene glycol for use in patients under the age of two,
- should be used in infants only after the urea content is calculated to monitor total urea exposure.

b. Topical corticosteroids

Although different treatment methods have been introduced recently, TCS remain the agents of the first choice in AD treatment for suppressing flare-ups and achieving long-term remission (Table 9). After entering the cell, they bind to steroid receptors in complex with heat shock protein 90 and migrate to the nucleus, where they activate steroid-sensitive genes to exert their anti-inflammatory, anti-allergic, and immunosuppressive effects[193]. Treatment failure is common due to patient non-adherence to TCS therapy, often because of inadequate knowledge and unrealistic fears about corticosteroid use[194]. A survey study, which included 200 patients with AD, reported that 72.5% of the patients were worried about the topical use of TCS on themselves or on their children and 24% admitted non-adherence to therapy because of these concerns[195]. Therefore, physicians should allocate adequate time to explain the disease and its management and to provide a treatment regimen-specific and appropriate for the patient. The most important point to be considered concerning the use of corticosteroids is the selection of the agent with the right potency and suitable carrier according to the characteristics of the lesion, its localization, and the patient's age. In terms of local side effects on considerably sensitive areas such as the face, eyelids, genital area, neck, and intertriginous areas, care should be exercised toward potential local and systemic side effects and the use of highly potent steroids should be avoided in infants and children[30,181-187]. Note that clobetasol propionate 0.05% ointment is 1800 times more potent than hydrocortisone 1% ointment (Table 10). TCSs are applied twice a day. However, studies have shown that there are no differences in efficacy between once-daily and twice-daily administrations, particularly, of highly potent TCSs. Twice-daily application of a potent topical steroid initially and switching to a once-daily application after remission of the lesion is recommended to increase patient compliance and reduce side effects[196]. TCS absorption rates are given in Figure 7. The clinical doses of TCS are given in Table 11.

Factors influencing the potency and side effects of TCS:

- Side chain modifications,
- Condition of the skin barrier,
- Affected skin area,
- Patient's age,
- Use with occlusion,
- The amount of steroid used (using on a large or small area),
- Duration of treatment.

Table 9. Considerations in the use of topical steroids

Cream	Pomade
- They contain oil in water.	- They contain water in the oil.
- Hydrophobic	- Hydrophilic, lipophilic
- Oil-free	- Thick, oily
- Refreshing	- Remains on the skin long
- Anti-inflammatory	- Softens the skin.
- In acute and oozing lesions	- In chronic and dry lesions
- On thin skin and skin of the fold area	- On thick and extensor skin

Side effect = potency X area X time

Requirement for potency = thickness X chronicity / area

The fingertip unit is used as the application amount of the drug. On the adult index finger, the region from the distal interphalangeal joint to the fingertip is called a fingertip unit (See below box). This amount corresponded to approximately 0.5 mg. One topical steroid fingertip unit should be rubbed into a surface area equivalent to

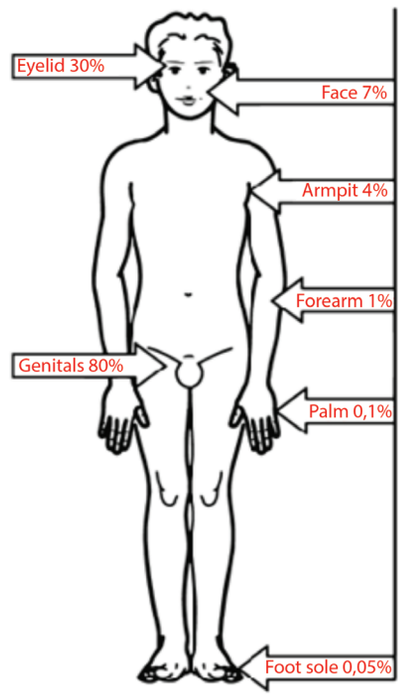

Figure 7. Topical corticosteroid absorption rates

the total surface area of two palms of an adult[187]. The use of TCSs for treating resistant episodes may become more effective and safer with the wet wrap method[187]. Local complications may occur during TCS treatment, including acneiform eruptions, rosacea, skin atrophy, striae, delayed wound healing, hypertrichosis, telangiectasia, purpura, hypopigmentation, gluteal granuloma, contact dermatitis (may be caused by protective ingredients or other base materials), and exacerbation of skin infections[197]. Methods to minimize such side effects may include switching to another medication with lower potency after clinical improvement, intermittent use (2 or 3 days a week), or combination treatment with other non-steroidal drugs.

Fingertip unit use; at each dose for the entire arm and hand.	
- For infants aged 3-6 month	1 fingertip unit
- For 1-2 years of age	1.5 fingertip units
- For 3-5 years of age	2 fingertip units
- For 6-10 years of age	2.5 fingertip units
- For Adults	4 fingertip units

Local side effects of topical steroids:
- Epidermal atrophy,
- Striae,
- Purpura,
- Telangiectasia,
- Hypertrichosis,
- Delay in wound healing,
- Tachyphylaxis,
- Systemic steroid effects,
- Steroid phobia.

c. Topical calcineurin inhibitors

Tacrolimus and pimecrolimus are TCIs that have been used for treating AD for nearly 20 years. They act by inhibiting a cytoplasmic enzyme, calcineurin phosphatase, and by suppressing the synthesis of inflammatory cytokines in T-cells, keratinocytes, and LC[187,198]. An important feature of TCIs is that they are non-steroidal immunomodulators, therefore, they do not have local side effects associated with TCSs[199]. They are particularly useful for treating highly sensitive areas such as the skin folds and the face, where the risk of application of TCSs is at the highest rates of having side effects. Tacrolimus is available in a 0.03% form for patients aged 2-16 years and a 0.1% form for all patients over the age of 16 in moderate to severe AD. Pimecrolimus, on the other hand, is suitable for use in the form of 1% cream in patients aged two years and with mild and moderate AD. Neither agent is approved for use under the age of two[187,200]. Over time, concerns have arisen about the safety of tacrolimus ointment and pimecrolimus cream because some patients have been diagnosed with skin cancer and lymphoma during treatment, although uncommonly. The FDA placed a boxed warning on product labeling in 2006[201]. However, unlike oral calcineurin inhibitors used to prevent graft rejection, systemic absorption of topical tacrolimus and pimecrolimus is negligible even when applied to large body surface areas. Findings from later studies with 10-year follow-up periods did not support the presence of a causal link between malignancy and TCI[202]. TCI therapy is started twice a day, and once the symptoms regress, it may be continued 2-3 times a week in body areas, where lesions recur frequently[187,201]. In order not to increase the risk of carcinogenicity, post-treatment ultraviolet (UV) exposure should be avoided, and TCI therapy should not be combined with phototherapy[30]. It should not be preferred in patients with erythroderma and should not be administered with

Table 10. Potency classification of topical corticosteroids

Group 4 (very potent)		Group 3 (potent)		Group 2 (moderately potent)		Group 1 (weak)	
0.05%	Clobetasol propionate	0.1%	Methylprednisolone aceponate	0.025%	Beclomethasone dipropionate	0.1%	Dexamethasone
0.3%	Diflucortolone valerate	0.1%	Betamethasone valerate	0.1%	Hydrocortisone butyrate	0.1%	Hydrocortisone acetate
0.1%	Halcinonide	0.1%	Diflucortolone valerate	0.05%	Betamethasone dipropionate	0.25%	Methylprednisolone
-	-	0.05%	Fluticasone propionate	0.05%	Clobetasone butyrate	0.5%	Prednisolone
-	-	0.1%	Mometasone furoate	0.02%	Flumethasone pivalate	-	-
-	-	0.025%	Prednicarbate	0.2%	Flucortolone pivalate	-	-

Table 11. Clinical doses of topical corticosteroids

Topical corticosteroids: Following quantities are applied in total over 2 weeks				
Region	**Adult (g)**	**Older child (g)**	**Children (g)**	**Infant (g)**
The arm and hand	60	40	20	15
Back and buttocks	100	70	40	20
The whole body	580	350	190	120
Face or neck	30	30	20	15
Chest and abdomen	15	10	7.5	5
Leg and foot	110	60	30	20

occlusion, which may increase absorption. The most common side effects associated with these agents are mild local side effects such as itching, tingling, and burning sensations. Although such side effects are expected to regress within a few days, the process may be moderated using a moisturizer before treatment or along with a topical steroid for a short period, when the treatment is not tolerated[30]. Importantly, the patient should be informed of this condition.

d. Phosphodiesterase inhibitors

Crisaborole is a small-molecule boron-based benzoxaborole phosphodiesterase 4 (PDE4) inhibitor that modulates multiple immune and inflammatory pathways[202]. Its low molecular weight allows excellent skin penetration. *In vitro* assays have shown that crisaborole can inhibit the synthesis of many cytokines, including interferon gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), IL-2, IL-5, and IL-10[202,203]. When crisaborole enters the systemic circulation, it is rapidly metabolized into inactive metabolites, thus its systemic effect is minimized[204]. Apart from local symptoms such as burning and itching sensations, it has a favorable safety profile for use over 2 years of age, as demonstrated in phase Ib and phase II clinical trials[205,206].

The efficacy trials of other selective PDE4 inhibitors, including E6005 (RVT-501), OPA-15406, DRM02, LEO 29102 (LEO Pharma, Ballerup, Denmark), and OPA-15406 (Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ), for treating AD are ongoing[207].

e. Topical antimicrobials and antiseptics

Atopic individuals are prone to skin infections due to disturbances in AMP synthesis and inadequacy of the physical barrier. *S. aureus* is the most important causative agent of clinical infections in such patients. Because *S. aureus* produces toxins that act as superantigens and because exogenous protease inhibitors increase allergen penetration by damaging the epidermal barrier, just the colonization of this infectious agent even in the absence of clinical infection induces inflammation in patients with AD[187]. In a review of 26 studies, no correlation was found regarding the benefit of adding anti-staphylococcal interventions or topical antimicrobial agents to the treatment in uninfected patients[208]. However, such practices may be beneficial for individuals with superinfection. Therefore, routine use of antimicrobials is not recommended for treating AD to avoid drug resistance[187]. Recently, taking baths has been recommended, in a full tub with water (150 liters), in which half a glass (120 mL) of 6% household bleach was added to achieve a concentration of 0.005%. It is sufficient to stay in the tub for 5-10 minutes twice a week. The face and neck should be protected while taking a bath[209]. The addition of intranasal mupirocin cream along with an anti-inflammatory agent and moisturizer is reported to be an advantageous treatment regimen, particularly in patients with frequent staphylococcal skin infections[210].

f. Topical antihistamines

Topical antihistamines (AH) have been tried for treating AD, but they have been shown to be of little benefit and are not recommended for treatment[187]. Studies investigating topical doxepin have shown a short-term reduction in pruritus in some cases, but no disease control or significant reduction in severity has been observed. It has local side effects such as burning and stinging sensations and it may cause sedation[211,212]. There are no controlled studies on the use of topical diphenhydramine in AD. it may cause allergic or photoallergic contact dermatitis[213]. Widespread application use on damaged skin, and combined use with oral diphenhydramine are not recommended, especially in children, due to the risk of systemic toxicity, which may result in toxic psychosis with hallucinations and delirium[214].

g. Other investigational topical treatments

Janus kinase inhibitors

Janus kinases (JAK) are a group of tyrosine kinases that include JAK1, JAK2, JAK3, and tyrosine kinase 2, which are found mainly in hematopoietic cells. JAKs are required for signaling initiated by several cytokines (IL-4, IL-12, IL-23, TSLP, and interferon proteins) implicated in the pathogenesis of inflammatory skin diseases such as psoriasis and AD. Ruxolitinib is a selective JAK1/JAK2 inhibitor, whereas tofacitinib is a potent JAK3 inhibitor with activity against JAK1 and, to a lesser extent, JAK2[215,216]. Recently, the efficacy and safety of the topical and systemic use of JAK inhibitors in AD have been studied. In a study, it was found that topical tofacitinib for treating AD was superior to placebo in reducing the size of the area of eczema and the severity index. Furthermore, the study demonstrated a significant improvement in itching at week 4 of treatment[217]. Phase II studies on the efficacy of topical application of ruxolitinib in AD are ongoing[207].

Agents effective on T-cells

Benvitimod is a nonsteroidal anti-inflammatory agent that targets the chemoattractant receptor-homologous molecule expressed on Th2 cells. Benvitimod reduces the synthesis of proinflammatory cytokines and T-cell migration by selectively inhibiting the expression of IFN-γ, IL-2, and TNF-α-like cytokines. Phase II studies showing the efficacy of benvitimod in AD are available. 0.5% and 1% forms applied twice daily were found to be superior to the placebo. The most common side effects associated with benvitimod treatment are reported to be folliculitis, contact dermatitis, and headache. However, it has been reported to be well-tolerated and effective in general in the adult AD population[218].

The algorithm for all topical medications is given in Figure 8.

Phototherapy for the treatment of atopic dermatitis

Phototherapy methods have been used for a long time for treating AD, similar to their use for treating many chronic inflammatory dermatoses. Possible mechanisms of action of phototherapy methods in AD include modification of cytokine expression[219,220], increased T-cell apoptosis, decreased DC numbers[221], inhibition of *S. aureus* proliferation and superantigen production[222], decreased penetration of pathogens and allergens because of increased thickness of SC and decreased epidermal nerve fiber density and nerve growth factor levels[223,224].

Phototherapy modalities used for treating AD include broadband (BB)-UVB, UVA, UVAB, psoralen UVA (PUVA) (topical or systemic), UVA-1 (340-400 nm), and narrowband (NB)-UVB (311-313 nm).

Among the BB phototherapy methods, BB-UVB (280-315 nm) is more effective than placebo[225]. However, UVA caused less irritation despite similar pruritus scores in comparative studies with UVA (315-400 nm)[226]. In a study comparing UVAB (280-400 nm) therapy with cyclosporine, it was found that, although similar changes were obtained in SCORAD scores, the duration of remission was longer in the group receiving cyclosporine[227].

- BB phototherapy methods are not listed among current treatment modalities anymore because of their high erythrogenic potential and

relatively low efficacy. Therefore, they are not preferred for treatment today.

PUVA was used for treating AD in both topical (cream and bathwater PUVA) and systemic (oral PUVA) forms. Excellent response and a mean remission period of 4.6 months were reported in 72% of patients receiving cream PUVA therapy[228]. With bathwater PUVA, itching and lesion severity were reduced by 82% and 74%, respectively[229]. A study comparing bathwater PUVA and NB-UVB reported similar reduction rates (65% vs. 64%) in SCORAD scores[230]. The time to response was shorter with bathwater PUVA treatment. However, patients preferred NB-UVB treatment more because of its ease of application. In a study comparing oral PUVA therapy with UVA-1, it was found that improvement in SCORAD levels was higher and remission periods were longer with PUVA[231].

- Although the systemic toxicity risk and the long-term carcinogenesis potential with oral PUVA therapy limit its use, particularly in children, PUVA may be preferred, especially in patients, who are NB-UVB-resistant or who wish to obtain a rapid response.

UVA-1 therapy is a type of phototherapy that may be used at low (<40 J/cm^2), moderate (40 to 80 J/cm^2), and high doses (80 to 130 J/cm^2). Despite the reported efficacy of high-dose UVA-1 compared with UVAB therapy, especially in acute AD exacerbations, high in-cabin temperatures pose a significant problem in treatment[232]. In studies comparing the efficacy of different doses of UVA-1 therapies, the efficacy of medium-dose UVA-1 phototherapy was found to be comparable to the high dose and superior to the low dose[233,234].

- The use of medium-dose UVA-1 may be recommended both for acute exacerbations of AD and for treating chronic lesions because the side effect profile of UVA-1 phototherapy is better with medium doses than with high doses. However, the use of UVA-1 phototherapy is limited because UVA-1 cabins are available only in a very few centers in our country[235] and their use requires the availability of a large space and an effective ventilation system.

NB-UVB treatment is an effective phototherapy method in both adult and pediatric patients with AD. Studies have reported that the onset of action may occur as early as the fifth session and that rate of complete or nearly complete response are between 40 and 68%[236-240]. Furthermore, the use of NB-UVB reduces the use of potent TCS. The combined use of TCS and moisturizers is recommended during the beginning sessions of NB-UVB therapy to prevent exacerbations and ensure adequate treatment compliance. The initial dose may be determined based on the skin phototype of the patient or 50% of the minimal erythema dose may be administered. Dose increments by 10% of the previous dose are recommended[241].

- It may be preferred as the first-line phototherapy method for treating moderate-to-severe AD in children and adults because of its ease of use, safe side effect profile, and high level of evidence. NB-UVB treatment is recommended to be applied 3 days a week for 6 weeks.

There is a study reported that balneophototherapy (NB-UVB application after 10% Dead Sea salt solution), another less commonly used phototherapy method, is time-consuming but superior to NB-UVB in terms of reduction in severity scores[242]. With the use of Excimer light/laser, one of the targeted phototherapy methods, response rates of up to 67% have been obtained for treating localized lesions[243]. The Goeckerman method (combination of coal tar and UVB) provided a 74% reduction in SCORAD scores in a case series of five patients[244].

- Although there is insufficient evidence to recommend the routine use of these methods, excimer light or laser may be preferred for treating localized lesions in selected patient groups, whereas the Goeckerman method may be used in patients resistant to standard phototherapy methods.

Extracorporeal photopheresis (ECP) is an apheresis method. In ECP, the patient's peripheral blood is collected after oral psoralen treatment, irradiated with UVA, and reinfused into the circulation. Studies reported a relatively small improvement in SCORAD scores but no improvements in the QoL with the use of ECP[245,246].

- Therefore, although ECP is not recommended in routine treatment, it may be reserved to be considered a last resort among others for a limited group of patients, who are unresponsive to standard treatments or cannot tolerate immunosuppressive therapy.

Home phototherapy was used in 24 patients AD in a large study examining various inflammatory diseases. That study reported that

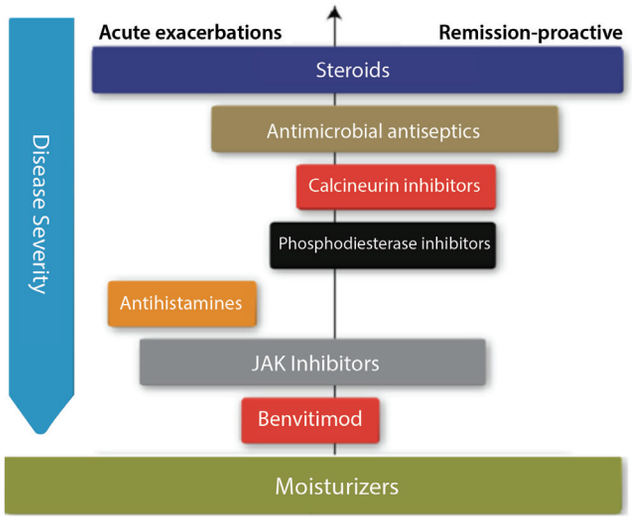

Figure 8. Use of topical medications

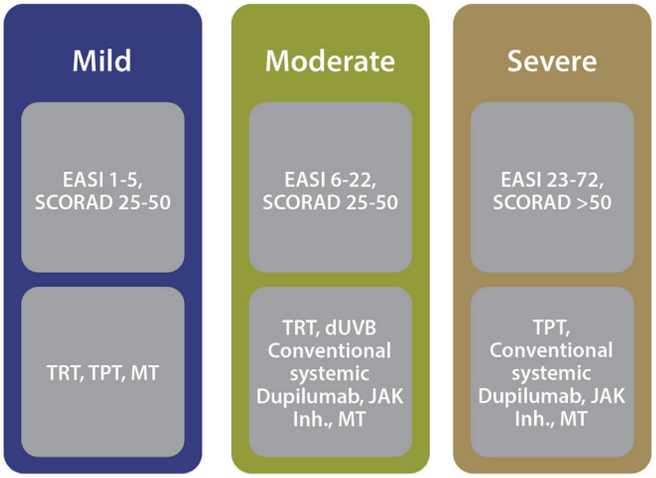

Figure 9. Treatment algorithm by severity

EASI: Eczema Area and Severity Index, SCORAD: SCORing atopic dermatitis

patient satisfaction levels were high with home phototherapy, which was found to be both effective and cost-effective[247].

- Home phototherapy is not available in our country. However, if its use becomes widespread in the future and the level of evidence about its use in AD increases, the use of home phototherapy under the supervision of a dermatologist may be recommended.
- Phototherapy methods should be preferred for treating AD following a course with moderate-severe and extensive lesions before switching to systemic immunosuppressive therapy in pediatric and adult patients.
- NB-UVB should be used first among other phototherapy modalities. However, PUVA and UVA-1 may also be employed in treatment-resistant patients.
- The use of TCS and moisturizers during the beginning phases of treatment is recommended to prevent exacerbations, reduce the cumulative UV dose, and promote treatment compliance until a response occurs.

Systemic treatment approaches

a. Systemic antihistamines

Oral H1-AH are commonly used to alleviate itching for treating AD but evidence-based data are not sufficient to support their use[248]. Generally, AHs are used in the presence of itching that does not respond to standard treatment with topical steroids and moisturizers[249].

Although the optimal dose and duration have not been established, sedative AH (e.g. diphenhydramine, hydroxyzine, and cyproheptadine) is usually preferred in patients with pruritis-related sleep disturbances. However, long-term use of sedative AHs in childhood is not recommended because it may affect sleep quality in children[250].

If there are concomitant-allergic diseases (such as urticaria, allergic rhinitis), nonsedative AH should be preferred. In these cases, they are used at doses recommended for other indications. The dose may be increased up to four times if the patient can tolerate sedation.

A systematic review of 25 randomized trials, with mostly low methodological quality, found no evidence that these agents were effective in improving symptoms of AD[249]. In a study on 795 children (1-2 years of age) with AD, 0.5 mg/kg cetirizine daily for 18 months was found to be not more effective than placebo in reducing severity scores[251]. Another study on 400 adult patients with AD showed that fexofenadine 120 mg daily for one-week reduced itching more than placebo, although the reduction was not clinically significant[252].

Olopatadine, a new generation non-sedating H1-AH, is effective for treating AD by reducing night-time itching without affecting sleep quality[253]. In clinical studies investigating histamine-4 receptor blocking AH (ZPL 3898787), improvement in the inflammatory lesions of AD has been reported[254].

b. Systemic corticosteroids

Systemic corticosteroids are used for treating moderate-to-severe AD in both adult and pediatric patients because of their rapid effects in suppressing acute exacerbations. Their use in long-term maintenance therapy is not recommended due to their high risk/benefit ratio[255,256].

To increase the effectiveness of topical treatment in severe exacerbations or while waiting for the effects of other adjuvant systemic treatment agents to start, systemic steroids may be used for a short time when acute symptom control is necessary and other therapeutic options are contraindicated[257].

However, the dose and duration of "short-term" use of systemic corticosteroids have not been established. It is generally recommended to start 0.5 mg/kg methylprednisolone per day for 1-2 weeks. Then the dose is tapered and discontinued within 2-3 weeks based on the clinical condition[258]. While reducing the dose, patients may be switched to another immunosuppressive agent with a higher safety profile for long-term therapy. Short-term treatment regimens without tapering the dose may lead to increased relapse/rebound rates. However, it should be kept in mind that exacerbations may occur after discontinuation of corticosteroids, even after reduced doses.

c. Cyclosporine

Cyclosporine is approved in our country as the first-line systemic therapy agent for treating widespread and severe AD in pediatric and adult patients. It is one of the fastest-acting agents along with steroids for treating AD and reduces itching within days. Dermatitis usually begins to improve within the first week and completely resolves within eight weeks. Although studies on the long-term safety and efficacy of cyclosporine are few, it is effective with high short-term tolerability for treating severe AD[259]. For treating AD, it is given at a dose of 3-5 mg/kg/day in two divided doses for 4-8 weeks or longer. After the clinical benefit is achieved, the dose is reduced by 0.5-1 mg/kg every two weeks to the minimum effective dose and maintained until stable recovery is achieved. After that, intermittent treatment with 3-5 mg/kg two days a week (for example, on Saturdays and Sundays) may be an option to prevent relapses while minimizing toxicity[260].

The duration of treatment should be tailored individually based on the drug efficacy; this period usually ranges from three months to one year. The relapse may be very rapid after discontinuation of therapy, therefore, switching to an immunosuppressive agent with a better safety profile [e.g., methotrexate (MTX)] or continuing treatment with TCS and emollients should be recommended when discontinuing cyclosporine.

Long-term use of cyclosporine (i.e., more than one year) is limited, especially in old individuals, due to its side effects such as hypertension and nephrotoxicity. Oral cyclosporine is not recommended for infants and children with AD. The use of cyclosporine in older children and adolescents should be reserved for the most severe cases that do not respond to optimal topical therapy and whose QoL is adversely affected. Cyclosporine treatment is better tolerated by pediatric patients compared to adults. In clinical studies, it has been shown that cyclosporine is as effective as systemic glucocorticoids in children with severe AD, reduce erythema intensity and body surface area involved, decrease the need for topical steroids and improve sleep patterns[259,261-263].

In a systematic review of 14 randomized trials, which included 1,653 patients with moderate-to-severe AD, cyclosporine was found to be more effective than placebo in five studies, with an average of 50-95% improvement in different clinical severity scores after short-term treatment (ten days to eight weeks)[263]. In comparative studies, cyclosporine was found to be more effective than prednisolone, intravenous immunoglobulin (IVIg), and UVA/UVB phototherapy. Generally, a faster response was achieved with higher doses (5 mg/kg/day)[263].

Cyclosporine is contraindicated in patients with impaired kidney functions, uncontrolled hypertension, recurrent infections, and

concomitant malignancy. The side effects of cyclosporine are listed in Table 12. Blood pressure and serum creatinine measurement (every two weeks for three months, then monthly) should be monitored in patients receiving cyclosporine. In the event of significant increases in either, the dose should be reduced, or the treatment should be discontinued. Cyclosporine should not be combined with phototherapy because of the increased risk of carcinogenesis. Live vaccine administration is not recommended during the use of cyclosporine. Cyclosporine should be discontinued two weeks before the live vaccine is administered, and treatment should be restarted 4-6 weeks after the vaccine is given.

d. Mycophenolate mofetil

Mycophenolate mofetil (MMF) or mycophenolate sodium (MPS) is an option that may be considered for treating severe AD that is unresponsive to other systemic treatments, especially in adult patients. MMF inhibits T- and B-cell proliferation through the inhibition of inosine monophosphate dehydrogenase, which is involved in *de novo* purine synthesis. The response to MMF and MPS depends on the uridine diphosphate-glucuronosyltransferase1-9 polymorphism, which is involved in drug metabolism. Approximately 85% of individuals with this polymorphism do not respond to this agent[264]. Treatment-responsive patients generally tolerate long-term treatment well, given the relatively favorable toxicity profile of these agents.

Evidence supporting the use of MMF for AD is limited and mainly based on small observational studies[265]. No randomized trials have evaluated the first-line use of MMF and MPS for treating severe AD. In comparative studies with cyclosporine for treating AD in adults, it has been shown that, with MMF, the effect begins later but the remission lasts longer[266]. MMF is reported to be more effective than azathioprine. Studies on MMF for treating AD in children are limited. Its use in children was evaluated in two retrospective case series, where it was found to be effective and tolerable[267,268].

Despite the lack of adequate data about the optimal dose and duration of treatment, doses up to MMF 1-2 g/day, MPS 720-1440 mg/day may be used in adults if cyclosporine is contraindicated or not ineffective. A daily dose of 600-1200 mg/m^2 in children, or doses of 40-50 mg/kg/day in children, and 30-40 mg/kg/day in adolescents are recommended.

Although fatigue, flu-like symptoms, mild gastrointestinal discomfort (nausea, vomiting, abdominal cramps), and hematological disorders may occur during MMF therapy, the safety profile is quite favorable, it is generally well-tolerated, and laboratory abnormalities occur rarely. Nausea is the most common side effect, but occurs less commonly with enteric-coated MPS. At high doses, resting tremors may occur. Because it is teratogenic, women of childbearing potential should be offered effective contraception during treatment.

e. Azathioprine

Azathioprine may be used as an adjuvant therapeutic agent for treating widespread and severe AD in children and adults when cyclosporine is ineffective or contraindicated. Azathioprine is a purine metabolism antagonist that inhibits T-cell proliferation. Its catabolism and concomitant production of active metabolites are regulated by thiopurine methyltransferase (TPMT), which shows variations depending on common allelic polymorphisms across individuals.

Although efficacy has been demonstrated in randomized, controlled trials, long-term efficacy and safety data are limited. Azathioprine is used in short terms in most studies. Its use for up to five years is effective and safe, but the duration of use is usually limited by side effects[269-271].

Evidence supporting the use of azathioprine in children is based on a few observational studies, where it was generally well-tolerated[268,272-274]. The optimal dose range is 1-3 mg/kg/day. Treatment is started with 50 mg/day and the dose is increased within 1-2 weeks. Its effect starts after four weeks and reaches a maximum level at week 8-12.

The risk of myelosuppression is high in individuals with low TPMT activity. The dose may be adjusted according to the enzyme activity. Dose increments can be made after starting treatment with a low dose because the routine use of azathioprine is not common[275].

Side effects include nausea, vomiting, and other gastrointestinal symptoms (bloating, anorexia, diarrhea, hepatitis, and pancreatitis), elevated liver enzyme levels, bone marrow suppression, increased risk of infection, and malignancy (non-melanoma skin cancers and lymphoma). As it interacts with xanthine oxidase inhibitors such as allopurinol, the dose should be reduced to ¼ of the current dose. Azathioprine should not be combined with phototherapy because of the increased risk of carcinogenesis. It may be used with extreme caution and at reduced doses with limited indications during pregnancy

f. Methotrexate

MTX is an alternative treatment option for the long-term control of moderate-to-severe AD in adults and less commonly in children and adolescents. MTX is a folic acid antagonist. It exerts its immunosuppressive effect by inhibiting the purine and pyrimidine synthesis.

It is administered orally or subcutaneously once per week. The recommended dose is 7.5-25 mg in adults and 0.2-0.5 mg/kg in children. This effect starts slowly and reaches a maximum level of efficacy within 8-12 weeks. If no effect has been achieved by this time, the treatment should be stopped. Folic acid supplementation of 1-5 mg is usually recommended once a week to reduce the risk of toxicity. Although a few studies have shown the efficacy of MTX for treating AD in adult and pediatric patients, long-term efficacy and safety data are not adequate[276,277]. In a randomized study comparing MTX and azathioprine for treating moderate-to-severe AD, both agents were found to be equally effective in reducing the AD severity scores[269]. In a randomized trial comparing 15 mg/week oral MTX with 2.5 mg/kg/day cyclosporine in 97 adult patients with moderate-to-severe AD, more patients in the cyclosporine group (42% vs. 8%) achieved a 50% reduction in the SCORAD index at week 8[278].

The most common side effects are nausea, loss of appetite, weakness, alopecia, and stomatitis. Other rare, serious side effects are bone marrow suppression, hepatotoxicity, renal failure, and interstitial pneumonia. Although MTX is well-tolerated, periodic monitoring, including complete blood counts and hepatic and renal function tests, is required to monitor hematological toxicity and hepatotoxicity. As it is teratogenic, effective contraception methods should be offered to men and women of childbearing age during the treatment and for three months after the cessation of treatment[279].

g. Alitretinoin

Alitretinoin has anti-inflammatory and antiproliferative effects. The drug was shown to be effective in a study on 1,032 patients with chronic hand eczema and in a case series of 6 AD patients[280]. The guidelines also recommend the use of alitretinoin in patients with

Table 12. Systemic treatments for atopic dermatitis

	Cyclosporine	Methotrexate	Azathioprine	Mycophenolate mofetil	Oral corticosteroids	Dupilumab
Recommended use	Acute episodes and maintenance	Maintenance	Maintenance	Maintenance	Control of acute episodes	Long-term maintenance
Laboratory tests	Blood pressure monitoring renal functions serum lipids electrolytes	Complete blood count Hepatic and renal functions	Complete blood count Hepatic and renal functions	Blood pressure monitoring Renal functions serum lipids electrolytes	Blood pressure monitoring blood sugar electrolytes hepatic and renal functions	Not recommended
Time to response	1-2 weeks	8-12 weeks	8-12 weeks	4-8 weeks	Day 5	Day 2-4 weeks
Time to relapse	?	?	?	?	Fast	?
Starting dose	3-5 mg/kg/day	7.5-25 mg/week in adults, 0.2-0.5 mg/kg/week in children	If the TPMT level cannot be measured, start at a dose of 50 mg/day and increase the dose within 1-2 weeks.	MMF 1-2 g/day, MPS 720-1440 mg/day. 600-1200 mg/m^2/day in children, 40-50 mg/kg/day in children, and 30-40 mg/kg/day in adolescents	Methylprednisolone (0.5 mg/kg/day is reduced based on the clinical response.	600 mg 400 mg
Maintenance dose	After the benefit is achieved, reduce the dose to 0.5-1 mg/kg every two weeks. Intermittent treatment with 3-5 mg/kg two days a week reduces toxicity	Same as the initial dose	1-3 mg/kg/day	In remission, the dose may be reduced	It is not recommended to be used for maintenance.	For adults and adolescents more than 60 kg: 300 mg every other week; for adolescents less than 60 kg, 200 mg every other week
Use in hepatic and renal failure	Do not use if the creatinine level is high	If your renal or hepatic functions are impaired, avoid using this medication.	-	-	-	No dose adjustment
Major side effects	Nephrotoxicity Hypertension neurotoxicity metabolic disorders (glucose intolerance, hyperlipidemia, hyperuricemia, hyperkalemia, hypomagnesemia) Infections (bacterial, viral, fungal) malignancy (squamous cell carcinoma of the skin, lymphoma, and lymphoproliferative diseases) gastrointestinal side effects (loss of appetite, nausea, vomiting, diarrhea, and abdominal pain) hypertrichosis gingival hyperplasia	Nausea, anorexia, weakness alopecia stomatitis bone marrow suppression hepatotoxicity renal failure Interstitial pneumonia	Nausea, vomiting, and other gastrointestinal symptoms (bloating, anorexia, diarrhea, hepatitis, pancreatitis) liver enzyme elevations, Bone marrow suppression Increased risk of infection Malignancy (non-melanoma skin cancers and lymphoma)	Renal dysfunction high blood pressure sleep disorder high blood sugar numbness and tingling in the hands and feet Hand tremor, headaches	Hypertension hyperglycemia hyperlipidemia water and salt retention osteoporosis truncal obesity Moon face	≥1/10 frequency: Injection site reaction 1/100-1/10 frequency: Cephalalgia Conjunctivitis oral herpes
Use in pregnancy:	Usable	Contraindicated	Usable at low doses depending on the conditions	Contraindicated	Usable	Adequate data unavailable

TPMT: Thiopurine methyltransferase, MMF: Mycophenolate mofetil, MPS: Mycophenolate sodium

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adult atopic hand eczema not responding to topical steroids[28,169,281]. As it is teratogenic, it should be administered together with effective contraception methods for women of childbearing age.

h. Apremilast

PDE4 is the most important enzyme that regulates cyclic 3',5'-adenosine monophosphate metabolism. It is responsible for the inactivation and hydrolysis of cyclic nucleotides. Apremilast is an oral PDE4 inhibitor, used for treating psoriasis. In a 12-week study on 185 adult patients with AD, apremilast (30 and 40 mg twice daily) was shown to improve eczema severity scores by 26-32% compared to placebo in patients with moderate to severe AD[282]. Side effects, including cellulitis, occur more commonly in patients receiving high doses. Consequently, the study was terminated by the Independent Data Safety Monitoring Committee. Large-scale studies are required to support the use of apremilast for treating AD.

i. Intravenous immunoglobulin

IVIg are immunomodulatory agents. IVIg has been used in adult and pediatric patients with severe, treatment-resistant AD. However, high efficacy or rapid onset of action has not been achieved[283,284]. The efficacy of IVIg for treating AD was investigated in three randomized clinical trials, which included 64 patients[283-285]. The duration in these studies ranged from 60 days to 12 weeks. Considering the changes in the SCORAD index in children, IVIg was found to be more effective compared with placebo (mean change of 24% for IVIg and 4% for placebo). In another study, it was concluded that IVIg was not associated with clinically significant improvement in the SCORAD index[284]. Cyclosporine was found to be superior to IVIg in terms of SCORAD index findings (mean change of 70% for cyclosporine and 34% for IVIg)[285].

As there are very limited data on the use of IVIg therapy in patients with severe AD, its use is not recommended at this stage. It is considered the last treatment option only for severe, treatment-resistant AD in children[28].

j. Immunoadsorption

Immunoadsorption (IA) is based on the principle of non-specific removal of various Igs from the patient's circulation. It is used as an alternative anti-IgE therapy in patients with severe AD and high total serum IgE levels. Clinical evidence shows that IA is an effective treatment option for patients with severe AD with high total serum IgE levels[28,286,287].

k. Interferon-γ

It is an alternative treatment option in the management of extensive and severe AD in patients unresponsive to other systemic treatments. IFN-γ is a Th1 cytokine that acts on the innate and adaptive immune systems by promoting natural killer cell proliferation and macrophage oxidation.

Conflicting results were obtained in two 12-week studies, which included 134 pediatric and adult patients with AD. One study reported no reduction in clinical severity, but another study reported a significant reduction (50/38% for IFN-γ, 8% for placebo)[288,289].

As studies were conducted with different dosage schemes, a conventional dosage scheme recommended for use in treatment has not been established[290-292].

The most common side effects during treatment were headache (60%), myalgia (32%), and pyrexia (39%). It is not a suitable systemic treatment option due to its low efficacy, high cost, and a high number of side effects.

l. Dupilumab

Dupilumab is a human monoclonal antibody that blocks the common alpha chains of the IL-4 and IL-13 receptors. Thus, it prevents Th2 inflammation by inhibiting IL-4 and IL-13 signaling. This resulted in a rapid and significant improvement in the symptoms of patients with AD[293]. It received FDA approval in March 2017 and European approval in September 2017 for treating adults with moderate and severe AD that cannot be adequately controlled with topical treatments.

In adults, the initial dose is 600 mg subcutaneously, followed by 300 mg every other week. In a 36-week study on 422 adults with AD, different dosing regimens were compared by Worm et al.[294] The authors recommended a dose of 300 mg every two weeks and reported that the efficacy decreases with longer intervals. In a meta-analysis study, Siegels et al.[295] emphasized the efficacy and safety in adults for up to one year. In the study (LIBERTY AD OLE), in which the safety and efficacy results of 148-week dupilumab treatment were evaluated in adult patients with moderate and severe AD, Beck et al.[296] reported that continuous and increasing improvements occurred in patients receiving dupilumab treatment and that 97% of the patients achieved EASI-75 by the end of week 148. In the study by Wollenberg et al.[297], laboratory results from a 52-week (LIBERTY AD CHRONOS) and two 16-week (LIBERTY AD SOLO 1 and SOLO 2) randomized and controlled phase III studies were assessed. These studies included 1,376 moderate and severe AD cases. Wollenberg et al.[297] reported that no significant changes were detected compared with baseline values and no follow-up of laboratory test parameters was required with dupilumab therapy. In a phase III study by Simpson et al.[298], on 251 adolescent and adult patients with moderate to severe AD, who were resistant to or could not use topical therapy, improvements in AD symptoms and QoL were observed compared with placebo after 16 weeks of dupilumab treatment. Additionally, dupilumab therapy has been reported to be safe. A randomized, controlled, 16-week phase III study by Paller et al.[299], on 367 children aged 6-11 years with severe AD, reported that dupilumab caused significant improvements in symptoms and the QoL and was well-tolerated. That study reported that the use of 300 mg every four weeks in children <30 kg and the use of 200 mg every two weeks in children ≥30 kg were optimally effective and safe. Conjunctivitis and injection site reactions were observed more commonly in the dupilumab + TCS treatment group compared to the placebo + TCS group.

In the publication, where Silverberg et al.[300] performed a subanalysis of results from randomized phase III studies (SOLO 1, SOLO 2, AD ADOL, and CHRONOS), a significant improvement on a daily pruritus scale was reported with dupilumab treatment compared to placebo in patients with moderate to severe AD. It has been reported that improvements were observed starting from day 2 in adult patients and from day 5 in adolescent patients. Considering the times to response and relapse, specified in Table 12, rapid onset of action is predicted when switching to dupilumab treatment. However, it may be recommended to taper the dose for treatment discontinuation under the guidance of patient-reported outcome measures data because of the possibility that abrupt discontinuation of the previously used systemic treatments may cause exacerbations[301].

The most common side effects of dupilumab are conjunctivitis, herpes infections, and injection site reactions. Pistone et al.[302] reported that they started artificial tears at a dose of one drop twice a day in each eye when they started dupilumab therapy in 30 adult patients with severe AD. They did not observe conjunctivitis or keratitis in none of the patients after six months of therapy. In another study, de Wijs et al.[303] reported paradoxical head and neck erythema at weeks 10-39 after starting dupilumab therapy in seven patients with AD. Pathological examination findings led to the interpretation that the erythema was a drug-induced psoriasiform skin reaction. Jang et al.[304] reported facial erythema following dupilumab therapy in a patient with systemic lupus erythematosus.

Considering the safety profiles of non-FDA-approved conventional systemic therapies used for treating AD and the safe use of dupilumab from the age of six, recent consensus reports suggest that dupilumab may be used as the first-line therapy in adults and/or children with moderate or severe AD when topical therapy is ineffective or cannot be used[29,115,128,305] (Figure 8).

According to the meta-analysis study, where Snast et al.[306] evaluated randomized, controlled, and observational studies; nemolizumab, lebrikizumab, and tralokinumab also appeared to be promising biologics after dupilumab. However, they have not been approved, yet. In that study, it was emphasized that while dupilumab and ustekinumab provided adequate data compared to placebo, there was insufficient efficacy evidence with anti-TSLP receptor, infliximab, and rituximab.

m. Nemolizumab

Nemolizumab is a humanized monoclonal antibody developed against the IL-31 receptor. IL-31 and the IL-31 receptor act as a mediator, which occurs in Th2-inflammation and is involved in the pathophysiology of AD and pruritus. The effect of IL-31 antagonism was investigated in a randomized, controlled phase II study. Different doses (0.1 mg/kg, 0.5 mg/kg, and 2 mg/kg) administered subcutaneously every four weeks for 12 weeks reduce dose-dependently itching. It has been reported that it exerts a very pronounced effect on itching and a lesser effect on disease severity. No systemic side effects have been observed, but peripheral edema has been reported[169,307].

n. Omalizumab

Omalizumab (anti-IgE) is a recombinant humanized IgG1 monoclonal antibody that binds to circulating free IgE at the Ce3 domain of the Fc fragment. It is thought that omalizumab may exert its clinical effect by binding to free IgE. Despite conflicting findings in the literature, high total IgE levels and the use of high doses act on clinical response[306,308-310]. The recommended doses have been reported in the range between 150 and 600 mg/month[309,310]. The efficacy evaluation is not suggested to be performed before three months[311]. It has not been included in recent AD treatment algorithms due to the controversial results.

o. Lebrikizumab

Lebrikizumab is a monoclonal antibody that targets soluble IL-13. In a randomized controlled phase II study investigating the efficacy and safety of lebrikizumab in patients with AD, lebrikizumab was used adjunct to topical steroids at a dose of 125 mg every four weeks in 209 patients[312]. A significant improvement was observed in clinical findings at week 12 and the drug was reported to be well-tolerated.

p. Tralokinumab

Tralokinumab is a monoclonal antibody that blocks IL-13. Its efficacy and safety were observed to be comparable to that of lebrikizumab. Tralokinumab is safe and tolerable in a phase I study[313]. Although tralokinumab is reported as a promising agent in AD, dupilumab is thought to be superior to both these agents[314].

q. Rituximab

Rituximab is an anti-CD20 molecule, with case series reported in AD. Simon et al.[315] reported improvement in symptoms in six disease series. In a study on three patients, rituximab was shown to be ineffective[316]. Rituximab is excluded from the AD treatment algorithms.

r. Ustekinumab

Ustekinumab is an IgG1 monoclonal antibody that blocks the p40 subunit shared by IL-12 and IL-23. In a systematic review investigating the efficacy and safety of ustekinumab in patients with AD, 10 studies were included[317]. Two of those studies were randomized controlled trials. A total of 107 patient outcomes were analyzed. It was reported that improvements were observed in the clinical findings of AD in 58 patients. No significant side effects were observed. Randomized, controlled studies on large patient series appear to be needed to establish the use and treatment regimens of ustekinumab therapy.

s. Janus kinase inhibitors

JAK inhibitors are required for the release of inflammatory cytokines via the JAK-STAT signaling pathway. JAK inhibitors may be effective in allergic diseases by reducing cytokine release. While baricitinib targets multiple JAKs, upadacitinib and abrocitinibs, which are second and new-generation JAK inhibitors, selectively target JAK1[318]. In a phase I study investigating the safety, tolerability, and pharmacokinetics of JTE-052 in healthy volunteers and patients with AD, JTE-052 was reported to reduce the scores of the disease and to be safe in the evaluation after seven days of use[319]. The oral form of tofacitinib was used in six patients with AD. It was reported that 66% improvement was observed in the severity scores of the disease[320]. Baricitinib is a JAK1 and JAK2 inhibitor. In a phase II study on patients with AD, it was reported that EASI 50 was achieved in 61% of the patients and side effects were not different compared with placebo[321]. Simpson et al.[322] published the results of the analysis of two randomized phase III studies (BREEZE-AD1 and BREEZE-AD2) on baricitinib therapy in moderate and severe AD. It was reported that, with baricitinib compared to placebo, significant improvements were found in the signs and symptoms of AD in the 16th week of treatment. In their randomized, controlled study on patients with moderate and severe AD, Reich et al.[323] reported that baricitinib combined with topical steroids provided significant improvements, with the most common side effects being nasopharyngitis, upper respiratory tract infection, and folliculitis. Simpson et al.[324] reported that oral once-daily abrocitinib was effective and well-tolerated as monotherapy in a multicenter, randomized, controlled, phase III study (JADE MONO-1) on adult and adolescent patients with moderate and severe AD. Studies on the use of these drugs in AD are summarized in Table 13.

t. Mepolizumab

Mepolizumab is an antibody that inhibits IL-5, an important cytokine in allergic inflammation. Oldhoff et al.[325] emphasized that mepolizumab

decreased peripheral blood eosinophil levels in AD, but it had no effects on APT or clinical manifestations based on results from randomized, controlled trials[326]. AD is excluded from the treatment algorithms.

u. Anti-tumor necrosis factor agents

Although clinical manifestations were reported to be improved by Jacobi et al.[327] in a study investigating the efficacy of infliximab on nine AD cases, Nakamura et al.[328] reported that anti-TNF treatments used in Th1-mediated inflammatory diseases might cause eczema based on a meta-analysis. These treatments are excluded in the treatment algorithms given in the guidelines.

v. Systemic anti-microbials

Bath-Hextall et al.[208] concluded in their review of randomized, controlled trials that adequate data are not available to support the use of anti-staphylococcal drugs unless AD is infected and that further studies are needed to establish the benefits and harms of antimicrobial therapies in the prevention of disease episodes in the long term. Systemic antibiotic therapy is not recommended by the Japanese guidelines unless there is an infection[329]. In that guideline, it has been emphasized that fungi may play a potential role in AD exacerbations and there are no comprehensive studies on the use of antifungal therapy. Australian guidelines recommend short-term systemic antimicrobial use when there is an infectious condition[128].

Prebiotic and probiotic use

The use of prebiotics and probiotics in the prevention or treatment of AD has been the subject matter in many studies. Recently, many meta-analyses and systematic reviews evaluating those studies have been published.

In a meta-analysis of 16 randomized, controlled studies in which probiotics were used for primary prevention, it was concluded that the use of probiotics containing especially *Lactobacillus* or *Lactobacillus* + *Bifidobacterium* species during the last weeks of pregnancy and the first few months after delivery was protective against the development of AD in both the general population and the allergy-prone population[330]. Different results were obtained in meta-analyses of studies evaluating the use of pre/probiotics for treating AD. Analysis of data from available randomized, controlled studies in these meta-analyses revealed that preparations containing different bacterial species were more effective (*Bifidobacterium* species alone were ineffective, preparations containing *Lactobacillus* were effective), efficacy varied depending on age groups (not effective in infants, effective in children older than 1 year old) and geographical region (ineffective in Europe, effective in Asia), and efficacy was higher in patients with moderate/severe AD. Although no data are available on the side effect profile in many studies, the available data show that the use of pre/probiotics is well-tolerated[331-334].

- There are no adequate data to support the efficacy of prebiotics and probiotics for treating AD and to recommend their routine use. Randomized, controlled studies are needed to determine the optimal content to be used in preparations and to identify patient subgroups, in whom efficacy will be more favorable.

Table 13. Janus kinase inhibitors in atopic dermatitis

Medication	Children (g)	Route of administration
Tofacitinib	JAK1, JAK3	Oral
Abrocitinib	JAK1	Oral
Upadacitinib	JAK1	Oral
Baricitinib	JAK1, JAK2	Oral
Tofacitinib	JAK1, JAK3	Topical
Ruxolitinib	JAK1, JAK2	Topical
Delgocitinib	Pan-JAK	Topical

11. Systemic treatment in special populations

All special conditions are summarized in Table 14.

Pregnancy

AD is a common pathology in pregnant women. Effective treatment before pregnancy is crucial for both the patient and the baby. The first-choice treatment modalities are topical treatments and UVB therapy, as they are the most harmless for the baby. However, it may be necessary to resort to systemic treatments in cases, where the disease cannot be controlled with topical treatments and UVB treatment after conception. The selection of systemic treatment should include considerations about the benefits of treatment for the mother, potential harms on the baby, and treatment costs[335].

In a review written by Heilskov et al.[335] in 2020, the treatment of AD in pregnant patients was discussed. TCS are the first-choice therapy for pregnant women, as well as for all patient groups. TCIs are safe in pregnant women, too, but topical crisaborole is not recommended

Table 14. Use of agents under special conditions for treating atopic dermatitis

	Pregnancy	Breast-feeding	Geriatric patients	Patients with malignancy	Viral hepatitis	COVID-19 pandemic
Topical treatments	+	+	+	+	+	+
Narrowband UVB	+	+	+	+	+	+
Systemic corticosteroids	At the lowest possible doses	At the lowest possible doses	+	+	May lead to activation	X
Cyclosporine	No complications reported	Adequate data unavailable	should be used with caution	X	Suitable for hepatitis C patients	X
Dupilumab	Adequate data unavailable	Adequate data unavailable	+	Adequate data unavailable	Adequate data unavailable	+
Topical treatments	+	+	+	+	+	+

+: Suitable, x: Contraindicated, UVB: Ultraviolet B, COVID-19: Coronavirus disease-2019

in pregnant women. Again, UVB therapy is safe for pregnant women. However, the patient's face should be protected to avoid the development of melasma. As for systemic treatments, systemic corticosteroid therapy is not teratogenic but intrauterine growth retardation may occur at doses of 20 mg/day and higher. Therefore, systemic corticosteroids should be administered at the lowest possible dose. Furthermore, calcium and vitamin D replacements should be given to pregnant patients.

Cyclosporine A can be used in patients when immunosuppression is indicated. Although cyclosporine crosses the placenta by 65%, no pregnancy complications or fetal malformations have been reported in the literature. Prematurity and low birth weight may occur in babies born to pregnant women using cyclosporine. There are inadequate data about the long-term effects of azathioprine, another immunosuppressive, on pregnancy. Other immunosuppressants, MTX and MMF, are contraindicated in pregnant women[335].

Another systemic therapy used for treating adult AD is dupilumab, which acts through the inhibition of IL-4 and IL-13[336]. In most studies on dupilumab, pregnancy was an exclusion criterion; therefore, there is a scarcity of data on the use of dupilumab during pregnancy. Published by the European Medicine Agency, a data report on one phase IIb and three phase III studies shows that 23 patients out of a total of 2,500 became pregnant during the study period[337]. Of these pregnancies, eight resulted in birth (one twin pregnancy), six in spontaneous abortion (two of which had risk factors for miscarriage), and two resulted in induced abortion. Five of these patients are still pregnant, and two patients have been lost to follow-up. Considering this information, no major anomalies or maternal and fetal adverse events associated with dupilumab have been reported. As it is an IgG antibody, dupilumab can cross the placenta, therefore, its effect on the developing fetus is not known dupilumab treatment can be used if the potential maternal benefit outweighs the potential fetal harm[338]. In a case report published in 2020, a 35-year-old female patient became pregnant while using dupilumab therapy for eight months[339]. Pregnancy was noticed in the second week of conception, at which point the drug was discontinued. However, in the third month of pregnancy, the patient started dupilumab on her own because of an episode and continued the treatment while accepting the risks. The patient was followed up by frequent visits, complete remission of skin lesions was achieved with the treatment, and a healthy baby girl was born via spontaneous delivery at week 40. At the time of the report, the patient had been breastfeeding her baby for four months and no problems were reported concerning the patient or the baby.

Breastfeeding

Topical steroids are the safest agents for treatment during breastfeeding. Again, TCIs can be used by nursing mothers. If nursing patients use systemic steroids, 0.1% of the therapeutic dose is reflected in the breastfed infant. The use of systemic steroids at low doses is appropriate for nursing patients. Nursing mothers may use cyclosporine A, but there are inadequate data on the long-term effects of azathioprine on breastfeeding. MTX and MMF is contraindicated in nursing mothers. Adequate data are not available in the literature about the use of dupilumab during breastfeeding[335].

Geriatric patients

The diseases that may accompany AD in geriatric patients are hypertension (58%), cerebrovascular events (26%), cardiovascular diseases (24%), diabetes mellitus (18%), and chronic renal disease (10%) in decreasing order of frequency. The use of systemic corticosteroids and cyclosporine is limited in the geriatric patient population because of comorbidities. As in other patient groups, TCS are the first choice in geriatric patients. TCIs are safe for elderly patients. However, adherence to treatment is low in the geriatric population because these agents may cause irritation[340].

The most commonly used systemic treatment alternatives are corticosteroids prednisolone at a dose of 0.1-0.2 mg/kg/day is effective for treatment. If hepatitis B surface antigen is tested and found to be positive before treatment, antiviral prophylaxis should be administered. Cyclosporine is not as safe as other treatment methods and should be used for no more than 12 weeks. Moreover, care should be exercised to monitor the risk of non-melanoma skin cancers and lymphoma in patients using cyclosporine. The prevalence of these cancers increases with age. Additionally, it should be considered that the risk of cardiovascular toxicity by cyclosporine is increased in elderly patients and that renal function declines with age[340].

NB-UVB is a safe option in the geriatric population, where comorbidities are common. When long-term therapy with three or more sessions per week is required, hospitalization may be needed because it will be difficult for elderly patients to commute to the hospital at such frequent intervals. Dupilumab is a treatment method that may be used in geriatric patients, who are unresponsive to systemic corticosteroids or cyclosporine, or for whom these drugs are contraindicated. As dupilumab is also effective for idiopathic chronic eczema that occurs with aging, the treatment response in AD is quite good. However, injections are painful and injectors suitable for use at home are expensive, reducing treatment adherence in geriatric patients[340].

Patients with malignancy

Long-term safety studies with dupilumab excluded cancer patients. Therefore, data on the use of dupilumab in patients with malignancies are inadequate. Systemic immunosuppressive therapies (azathioprine, MMF, cyclosporine, MTX) used for treating AD are unsafe for use in cancer patients[341]. In a systematic review, it was reported that inhibition of the IL-13 and IL-4 pathways does not increase the risk of malignancy[342]. There is a case report in the literature, where two AD patients with active anal squamous cell cancer and melanoma diagnoses were administered dupilumab therapy[341]. Cancer progression with treatment was not detected in the patient. Considering this information, the use of dupilumab treatment may be considered in patients with malignancy.

Patients with viral hepatitis

Although incidences of Th2-pathway-induced disorders such as atopy, allergy, and asthma are increased in hepatitis B patients, a similar relationship does not exist in hepatitis C patients. Systemic corticosteroid therapy may lead to activation in patients, who are carriers of hepatitis viruses. Therefore, concomitant antiviral prophylaxis is recommended for these patients when systemic steroid therapy is administered. Systemic cyclosporine inhibits viral replication of HCV by preventing the interaction of cyclophilin B, NS5A, and NS5B proteins. Therefore,

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cyclosporine therapy is the most appropriate option for patients with AD and concomitant HCV[343].

Atopic dermatitis treatment during the COVID-19 pandemic

Various opinions have been put forward on the use of immunosuppressive agents during the coronavirus disease-2019 (COVID-19) pandemic. According to the review by Yim et al.[344], there is no need for treatment discontinuation in a patient using conventional immunosuppressive agents or biological agents during the pandemic. There is no need to stop taking the medication even when the patient has an asymptomatic or mild COVID-19. However, the development of severe infection requires the cessation of treatment. Medication may be restarted, once the patient has fully recovered[344]. According to the review by Ricardo and Lipner[345], systemic corticosteroids and immunosuppressants should not be used for treating AD during the COVID-19 pandemic because they increase the risk of catching the infection. Dupilumab does not increase the risk of developing COVID-19 because it inhibits the IL-4 and IL-13 pathways, which are not associated with viral infections. Therefore, dupilumab treatment during the pandemic is safer than immunosuppressive agents[346]. According to the recommendations of the American Academy of Dermatology, patients with AD, without comorbidities and are at high risk of developing COVID-19, may use dupilumab during the COVID-19 pandemic[347]. According to a study conducted in Milan, only two (0.82%) out of 245 patients using dupilumab were infected with severe acute respiratory syndrome-coronavirus-2 but none of the patients developed severe disease[348]. In summary, dupilumab is the safest treatment for patients with AD during the COVID-19 pandemic.

References

1. Lloyd-Lavery A, Solman L, Grindlay DJC, Rogers NK, Thomas KS, Harman KE: What's new in atopic eczema? An analysis of systematic reviews published in 2016. Part 2: Epidemiology, aetiology and risk factors. Clin Exp Dermatol 2019;44:370-5.
2. Hay RJ, Johns NE, Williams HC, et al.: The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. J Invest Dermatol 2014;134:1527-34.
3. Draaisma E, Garcia-Marcos L, Mallol J, et al.: A multinational study to compare prevalence of atopic dermatitis in the first year of life. Pediatr Allergy Immunol 2015;26:359-66.
4. Broberg A, Svensson A, Borres MP, Berg R: Atopic dermatitis in 5-6-year-old Swedish children: cumulative incidence, point prevalence, and severity scoring. Allergy 2000;55:1025-9.
5. Doğruel D, Bingöl G, Altıntaş DU, et al.: The trend of change of allergic diseases over the years: Three repeated surveys from 1994 to 2014. Int Arch Allergy Immunol 2017;173:178-82.
6. Baççıoğlu A, Söğüt A, Kılıç Ö, Beyhun E: The prevalence of allergic diseases and associated risk factors in school-age children and adults in Erzurum, Turkey. Turk Thorac J 2015;16:68-72.
7. Topal E, Kaplan F, Türker K, Kutlutürk K, Gözükara Baş H: The prevalence of allergic diseases and associated risk factors in the 6-7 age children who are living in Malatya, Turkey. Asthma Allergy Immunol 2017;15:131-6.
8. Cetemen A, Yenigün A: Prevalences of asthma and allergic diseases in primary school children in Aydin. Asthma Allergy Immunol 2012;10:84-92.
9. Akbaş A, Kılınç F, Yakut Hİ, Metin A: Dermatological disorders in children: A prospective analysis of 4025 patients. Turkish Journal of Pediatric Disease 2015;9:6-11.
10. Civelek E, Sahiner UM, Yüksel H, et al.: Prevalence, burden, and risk factors of atopic eczema in schoolchildren aged 10-11 years: A national multicenter study. J Investig Allergol Clin Immunol 2011;21:270-7.
11. Mortz CG, Andersen KE, Dellgren C, Barington T, Bindslev-Jensen C: Atopic dermatitis from adolescence to adulthood in the TOACS cohort: Prevalence, persistence and comorbidities. Allergy 2015;70:836-45.
12. Liang Y, Chang C, Lu Q: The genetics and epigenetics of atopic dermatitis-filaggrin and other polymorphisms. Clin Rev Allergy Immunol 2016;51:315-28.
13. Kim BE, Leung DYM: Significance of Skin barrier dysfunction in atopic dermatitis. Allergy Asthma Immunol Res 2018;10:207-15.
14. Liang Y, Tian J, Shen CP, et al.: Therapeutic patient education in children with moderate to severe atopic dermatitis: A multicenter randomized controlled trial in China. Pediatr Dermatol 2018;35:70-5.
15. Otsuka A, Nomura T, Rerknimitr P, Seidel JA, Honda T, Kabashima K: The interplay between genetic and environmental factors in the pathogenesis of atopic dermatitis. Immunol Rev 2017;278:246-62.
16. Martino D, Kesper DA, Amarasekera M, Harb H, Renz H, Prescott S: Epigenetics in immune development and in allergic and autoimmune diseases. J Reprod Immunol 2014;104-105:43-8.
17. Yang G, Seok JK, Kang HC, Cho YY, Lee HS, Lee JY: Skin barrier abnormalities and immune dysfunction in atopic Dermatitis. Int J Mol Sci 2020;21:2867.
18. Patrick GJ, Archer NK, Miller LS: Which way do we go? Complex interactions in atopic dermatitis pathogenesis. J Invest Dermatol 2021;141:274-84.
19. Nedoszytko B, Reszka E, Gutowska-Owsiak D, et al.: Genetic and epigenetic aspects of atopic dermatitis. Int J Mol Sci 2020;21:6484.
20. Zhu TH, Zhu TR, Tran KA, Sivamani RK, Shi VY: Epithelial barrier dysfunctions in atopic dermatitis: a skin-gut-lung model linking microbiome alteration and immune dysregulation. Br J Dermatol 2018;179:570-81.
21. Kim Y, Lim KM: Skin barrier dysfunction and filaggrin. Arch Pharm Res 2021;44:36-48.
22. Knox S, O'Boyle NM. Skin lipids in health and disease: A review. Chem Phys Lipids 2021;236:105055.
23. Nguyen HLT, Trujillo-Paez JV, Umehara Y, et al.: Role of Antimicrobial peptides in skin barrier repair in individuals with atopic dermatitis. Int J Mol Sci 2020;21:7607.
24. Chieosilapatham P, Kiatsurayanon C, Umehara Y, et al.: Keratinocytes: Innate immune cells in atopic dermatitis. Clin Exp Immunol 2021;204:296-309.
25. Marschall P, Wei R, Segaud J, et al.: Dual function of Langerhans cells in skin TSLP-promoted TFH differentiation in mouse atopic dermatitis. J Allergy Clin Immunol 2021;147:1778-94.
26. Furue M: Regulation of filaggrin, loricrin, and involucrin by IL-4, IL-13, IL-17A, IL-22, AHR, and NRF2: Pathogenic implications in atopic dermatitis. Int J Mol Sci 2020;21:5382.
27. DeVore SB, Gonzalez T, Sherenian MG, Herr AB, Khurana Hershey GK: On the surface: Skin microbial exposure contributes to allergic disease. Ann Allergy Asthma Immunol 2020;125:628-38.
28. Harmancı K, Uysal P, Arga M, et al.: Atopik Dermatit Tanı ve Tedavisine Yaklaşım: Ulusal Rehber 2018 ve Ürtiker Güncel Durum Raporu. Asthma Allergy Immunol 2018;16(Suppl 2):1-95.
29. Kapur S, Watson W, Carr S: Atopic dermatitis. Allergy Asthma Clin Immunol 2018;14(Suppl 2):52.
30. Katayama I, Aihara M, Ohya Y, et al.: Japanese guidelines for atopic dermatitis 2017. Allergol Int 2017;66:230-47.
31. Ertam İ, Su Ö, Alper S, et al.: The Turkish guideline for the diagnosis and management of atopic dermatitis-2018. Turkderm-Arch Turk Dermatol Venereology 2018;52:6-23.
32. Diepgen TL, Fartasch M, Hornstein OP: Kriterien zur Beurteilung der atopischen Hautdiathese. Dermatosen 1991;39:79-83.
33. Bannister MJ, Freeman S: Adult-onset atopic dermatitis. Australas J Dermatol 2000;41:225-8.
34. Ozkaya E: Adult-onset atopic dermatitis. J Am Acad Dermatol 2005;52:579-82.
35. Herzberg J: Little known forms of neurodermitis. Hautarzt 1973;24:47-51.
36. Wüthrich B: Etiology of baker's eczema. Dermatologica 1970;140:395-6.
37. Horakova E, Wozniak KD: Analysis of the occurrence of morphologic changes in atopic dermatitis in childhood. Z Hautkr 1993;68:155-8.

38. Oranje AP, de Waard-van der Spek FB: Atopic dermatitis: Review 2000 to January 2001. Curr Opin Pediatr 2002;14:410-3.
39. Julián-Gónzalez RE, Orozco-Covarrubias L, Durán-McKinster C, Palacios-Lopez C, Ruiz-Maldonado R, Sáez-de-Ocariz M: Less common clinical manifestations of atopic dermatitis: Prevalence by age. Pediatr Dermatol 2012;29:580-3.
40. Engin B, Bülbül Başkan E, Borlu M, et al.: Turkey Atopic Dermatitis Diagnosis and Treatment Guide 2018. Dermatoz 2018;9(Suppl):1-40 (Turkish).
41. Eichenfield LF, Hanifin JM, Luger TA, Stevens SR, Pride HB: Consensus conference on pediatric atopic dermatitis. J Am Acad Dermatol 2003;49:1088-95.
42. Silverberg NB: Typical and atypical clinical appearance of atopic dermatitis. Clin Dermatol 2017;35:354-9.
43. Hanifin JM: Adult-onset atopic dermatitis: Fact or fancy? Dermatol Clin 2017;35:299-302.
44. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA: The burden of atopic dermatitis: summary of a report for the national eczema association. J Invest Dermatol 2017;137:26-30.
45. Dawn A, Papoiu AD, Chan YH, Rapp SR, Rassette N, Yosipovitch G: Itch characteristics in atopic dermatitis: results of a web-based questionnaire. Br J Dermatol 2009;160:642-4.
46. Langenbruch A, Zander N, Augustin M: Itch is a Relevant factor of disease burden in patients with atopic dermatitis in German routine care. Presented at the 29th Congress of the EADV 2020; Virtual meeting; October 29-31, 2020.
47. Anuntaseree W, Sangsupawanich P, Osmond C, Mo-Suwan L, Vasiknanonte P, Choprapawon C: Sleep quality in infants with atopic dermatitis: a community-based, birth cohort study. Asian Pac J Allergy Immunol 2012;30:26-31.
48. Chamlin SL, Mattson CL, Frieden IJ, et al.: The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. Arch Pediatr Adolesc Med 2005;159:745-50.
49. Vakharia PP, Chopra R, Sacotte R, et al.: Burden of skin pain in atopic dermatitis. Ann Allergy Asthma Immunol 2017;119:548-52.e3.
50. Brenninkmeijer EE, Legierse CM, Sillevis Smitt JH, Last BF, Grootenhuis MA, Bos JD: The course of life of patients with childhood atopic dermatitis. Pediatr Dermatol 2009;26:14-22.
51. Silverberg JI: Public health burden and epidemiology of atopic dermatitis. Dermatol Clin 2017;35:283-9.
52. Eckert L, Gupta S, Amand C, Gadkari A, Mahajan P, Gelfand JM: The burden of atopic dermatitis in US adults: Health care resource utilization data from the 2013 National Health and Wellness Survey. J Am Acad Dermatol 2018;78:54-61.e1.
53. Chernyshov PV, Tomas-Aragones L, Manolache L, et al.: Quality of life measurement in atopic dermatitis. Position paper of the European Academy of Dermatology and Venereology (EADV) Task Force on quality of life. J Eur Acad Dermatol Venereol 2017;31:576-93.
54. Koszorú K, Borza J, Gulácsi L, Sárdy M: Quality of life in patients with atopic dermatitis. Cutis 2019;104:174-7.
55. Beattie PE, Lewis-Jones MS: A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. Br J Dermatol 2006;155:145-51.
56. Coutanceau C, Stalder JF: Analysis of correlations between patient-oriented SCORAD (PO-SCORAD) and other assessment scores of atopic dermatitis severity and quality of life. Dermatology 2014;229:248-55.
57. Chrostowska-Plak D, Reich A, Szepietowski JC: Relationship between itch and psychological status of patients with atopic dermatitis. J Eur Acad Dermatol Venereol 2013;27:e239-42.
58. Marciniak J, Reich A, Szepietowski JC: Quality of life of parents of children with atopic dermatitis. Acta Derm Venereol 2017;97:711-4.
59. Boguniewicz M, Beck LA, Sher L, et al.: Dupilumab improves asthma and sinonasal outcomes in adults with moderate to severe atopic dermatitis. J Allergy Clin Immunol Pract 2021;9:1212-23.e6.
60. Bekić S, Martinek V, Talapko J, Majnaric L, Mihaljevic MV, Skrlec I: Atopic dermatitis and comorbidity. Healthcare (Basel) 2020;8:70.
61. Bantz SK, Zhu Z, Zheng T: The Atopic March: Progression from atopic dermatitis to allergic rhinitis and asthma. J Clin Cell Immunol 2014;5:202.
62. van der Hulst AE, Klip H, Brand PL: Risk of developing asthma in young children with atopic eczema: a systematic review. J Allergy Clin Immunol 2007;120:565-9.
63. Rivero Gairaud JI: Dermatitis atópica. Rev Méd Costa Rica Centroamerica 2016;LXXIII:711-6.
64. Gilaberte Y, Pérez-Gilaberte JB, Poblador-Plou B, Bliek-Bueno K, Gimeno-Miguel A, Prados-Torres A: Prevalence and comorbidity of atopic dermatitis in children: A large-scale population study based on real-world data. J Clin Med 2020;9:1632.
65. Ravnborg N, Ambikaibalan D, Agnihotri G, et al.: Prevalence of asthma in patients with atopic dermatitis: A systematic review and meta-analysis. J Am Acad Dermatol 2021;84:471-8.
66. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al.: Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 2006;38:441-6.
67. Rybojad M: La dermatite atopique [Atopic dermatitis]. Archives de pediatrie:organe officiel de la Societe francaise de pediatrie 2012;19:882-5.
68. Kay J, Gawkrodger DJ, Mortimer MJ, Jaron AG: The prevalence of childhood atopic eczema in a general population. J Am Acad Dermatol 1994;30:35-9.
69. von Kobyletzki LB, Bornehag CG, Hasselgren M, Larsson M, Lindström CB, Svensson Å: Eczema in early childhood is strongly associated with the development of asthma and rhinitis in a prospective cohort. BMC Dermatol 2012;12:11.
70. Gustafsson D, Sjöberg O, Foucard T: Development of allergies and asthma in infants and young children with atopic dermatitis–a prospective follow-up to 7 years of age. Allergy 2000;55:240-5.
71. Kok WL, Yew YW, Thng TG: Comorbidities associated with severity of atopic dermatitis in young adult males: A national cohort study. Acta Derm Venereol 2019;99:652-6.
72. Lee E, Lee SH, Kwon JW, et al.: Atopic dermatitis phenotype with early onset and high serum IL-13 is linked to the new development of bronchial hyperresponsiveness in school children. Allergy 2016;71:692-700.
73. Illi S, von Mutius E, Lau S, et al.: The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. J Allergy Clin Immunol 2004;113:925-31.
74. Silverberg JI: Selected comorbidities of atopic dermatitis: Atopy, neuropsychiatric, and musculoskeletal disorders. Clin Dermatol 2017;35:360-6.
75. Rogers AJ, Celedón JC, Lasky-Su JA, Weiss ST, Raby BA: Filaggrin mutations confer susceptibility to atopic dermatitis but not to asthma. J Allergy Clin Immunol 2007;120:1332-7.
76. Kawasaki H, Nagao K, Kubo A, et al.: Altered stratum corneum barrier and enhanced percutaneous immune responses in filaggrin-null mice. J Allergy Clin Immunol 2012;129:1538-46.e6.
77. Hong CH, Sussman G, Turchin I, Wiseman M, Gooderham MJ: Approach to the Assessment and management of adult patients with atopic dermatitis: A consensus document. Section III: Evaluation of atopic dermatitis patients for comorbidities. J Cutan Med Surg 2018;22(Suppl 1):17-20.
78. Elias PM, Steinhoff M: "Outside-to-inside" (and now back to "outside") pathogenic mechanisms in atopic dermatitis. J Invest Dermatol 2008;128:1067-70.
79. Brandt EB, Sivaprasad U: Th2 cytokines and atopic dermatitis. J Clin Cell Immunol 2011;2:110.
80. Langan SM, Irvine AD, Weidinger S: Atopic dermatitis [published correction appears in Lancet 2020;396:758]. Lancet 2020;396:345-60.
81. Leung DY: Our evolving understanding of the functional role of filaggrin in atopic dermatitis. J Allergy Clin Immunol 2009;124:494-5.
82. Ćosićkić A, Skokić F, Selimović A, et al.: Development of respiratory allergies, asthma and allergic rhinitis in children with atopic dermatitis. Acta Clin Croat 2017;56:308-17.
83. Mariño-Sánchez F, Valls-Mateus M, de Los Santos G, Plaza AM, Cobeta I, Mullol J: Multimorbidities of pediatric allergic rhinitis. Curr Allergy Asthma Rep 2019;19:13.
84. Vaňková R, Čelakovská J, Bukač J, Krčmová I, Krejsek J, Andrýs C: Sensitization to molecular components in 104 atopic dermatitis patients in relation to subgroups of patients suffering from bronchial asthma and allergic rhinitis. Acta Medica (Hradec Kralove) 2020;63:164-75.

Turkderm - Turk Arch Dermatol Venereol
2022;56(Suppl 2):86-121

85. Gray CL, Levin ME, Du Toit G: Respiratory comorbidity in South African children with atopic dermatitis. S Afr Med J 2017;107:904-9.
86. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD: The atopic march and atopic multimorbidity: Many trajectories, many pathways. J Allergy Clin Immunol 2019;143:46-55.
87. Silverberg JI, Gelfand JM, Margolis DJ, et al.: Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. Ann Allergy Asthma Immunol 2018;121:604-12.e3.
88. Oliveira C, Torres T: More than skin deep: the systemic nature of atopic dermatitis. Eur J Dermatol 2019;29:250-8.
89. Dalgard FJ, Gieler U, Tomas-Aragones L, et al.: The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol 2015;135:984-91.
90. Billeci L, Tonacci A, Tartarisco G, Ruta L, Pioggia G, Gangemi S: Association between atopic dermatitis and autism spectrum disorders: A systematic review. Am J Clin Dermatol 2015;16:371-88.
91. Zuberbier T, Orlow SJ, Paller AS, et al.: Patient perspectives on the management of atopic dermatitis. J Allergy Clin Immunol 2006;118:226-32.
92. Egeberg A, Andersen YM, Gislason GH, Skov L, Thyssen JP: Prevalence of comorbidity and associated risk factors in adults with atopic dermatitis. Allergy 2017;72:783-91.
93. Nicholas MN, Gooderham MJ: Atopic dermatitis, depression, and suicidality. J Cutan Med Surg 2017;21:237-42.
94. Lee S, Shin A: Association of atopic dermatitis with depressive symptoms and suicidal behaviors among adolescents in Korea: the 2013 Korean Youth Risk Behavior Survey. BMC Psychiatry 2017;17:3.
95. Yaghmaie P, Koudelka CW, Simpson EL: Mental health comorbidity in patients with atopic dermatitis. J Allergy Clin Immunol 2013;131:428-33.
96. Schmitt J, Romanos M, Schmitt NM, Meurer M, Kirch W: Atopic eczema, and attention-deficit/hyperactivity disorder in a population-based sample of children and adolescents. JAMA 2009;301:724-6.
97. Schmitt J, Buske-Kirschbaum A, Roessner V: Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review. Allergy 2010;65:1506-24.
98. Strom MA, Fishbein AB, Paller AS, Silverberg JI: Association between atopic dermatitis and attention deficit hyperactivity disorder in U.S. children and adults. Br J Dermatol 2016;175:920-9.
99. Reuveni H, Chapnick G, Tal A, Tarasiuk A: Sleep fragmentation in children with atopic dermatitis. Arch Pediatr Adolesc Med 1999;153:249-53.
100. Yokomaku A, Misao K, Omoto F, et al.: A study of the association between sleep habits and problematic behaviors in preschool children. Chronobiol Int 2008;25:549-64.
101. Hiscock H, Canterford L, Ukoumunne OC, Wake M: Adverse associations of sleep problems in Australian preschoolers: national population study. Pediatrics 2007;119:86-93.
102. Catal F, Topal E, Soylu N, et al.: Psychiatric disorders, and symptoms severity in preschool children with atopic eczema. Allergol Immunopathol (Madr) 2016;44:120-4.
103. Hon KL, Leung TF, Wong KY, Chow CM, Chuh A, Ng PC: Does age or gender influence quality of life in children with atopic dermatitis?. Clin Exp Dermatol 2008;33:705-9.
104. Silverberg JI, Greenland P: Eczema, and cardiovascular risk factors in 2 US adult population studies. J Allergy Clin Immunol 2015;135:721-8.e6.
105. Su VY, Chen TJ, Yeh CM, et al.: Atopic dermatitis, and risk of ischemic stroke: a nationwide population-based study. Ann Med 2014;46:84-9.
106. Drucker AM, Qureshi AA, Dummer TJB, Parker L, Li WQ: Atopic dermatitis and risk of hypertension, type 2 diabetes, myocardial infarction, and stroke in a cross-sectional analysis from the Canadian Partnership for Tomorrow Project. Br J Dermatol 2017;177:1043-51.
107. Standl M, Tesch F, Baurecht H, et al.: Association of atopic dermatitis with cardiovascular risk factors and diseases. J Invest Dermatol 2017;137:1074-81.
108. Ascott A, Mulick A, Yu AM, et al.: Atopic eczema, and major cardiovascular outcomes: A systematic review and meta-analysis of population-based studies. J Allergy Clin Immunol 2019;143:1821-9.
109. Andersen YMF, Egeberg A, Hamann CR, et al.: Poor agreement in questionnaire-based diagnostic criteria for adult atopic dermatitis is a challenge when examining cardiovascular comorbidity. Allergy 2018;73:923-31.
110. Thyssen JP, Halling-Overgaard AS, Andersen YMF, Gislason G, Skov L, Egeberg A: The association with cardiovascular disease and type 2 diabetes in adults with atopic dermatitis: a systematic review and meta-analysis. Br J Dermatol 2018;178:1272-9.
111. Strom MA, Silverberg JI: Associations of physical activity and sedentary behaviour with atopic disease in United States children. J Pediatr 2016;174:247-53.e3.
112. Zhang A, Silverberg JI: Association of atopic dermatitis with being overweight and obese: a systematic review and meta-analysis. J Am Acad Dermatol 2015;72:606-16.e4.
113. Narla S, Silverberg JI: Association between atopic dermatitis and autoimmune disorders in US adults and children: A cross-sectional study. J Am Acad Dermatol 2019;80:382-9.
114. Kappelman MD, Galanko JA, Porter CQ, Sandler RS: Association of paediatric inflammatory bowel disease with other immune-mediated diseases. Arch Dis Child 2011;96:1042-6.
115. Sastre J, Baldrich ES, Armario Hita JC, et al.: Consensus on the clinical approach to moderate-to-severe atopic dermatitis in Spain: A Delphi survey. Dermatol Res Pract 2020;2020:1524293.
116. Legendre L, Barnetche T, Mazereeuw-Hautier J, Meyer N, Murrell D, Paul C: Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: A systematic review and meta-analysis. J Am Acad Dermatol 2015;72:992-1002.
117. Cheng J, Zens MS, Duell E, Perry AE, Chapman MS, Karagas MR: History of allergy and atopic dermatitis in relation to squamous cell and Basal cell carcinoma of the skin. Cancer Epidemiol Biomarkers Prev 2015;24:749-54.
118. Ruff S, Egeberg A, Andersen YMF, Gislason G, Skov L, Thyssen JP: Prevalence of cancer in adult patients with atopic dermatitis: A Nationwide study. Acta Derm Venereol 2017;97:1127-9.
119. Hagströmer L, Ye W, Nyrén O, Emtestam L: Incidence of cancer among patients with atopic dermatitis. Arch Dermatol 2005;141:1123-7.
120. Wang L, Bierbrier R, Drucker AM, Chan AW: Noncutaneous and cutaneous cancer risk in patients with atopic dermatitis: A systematic review and meta-analysis. JAMA Dermatol 2020;156:158-71.
121. Chou WY, Lai PY, Hu JM, et al.: Association between atopic dermatitis and colorectal cancer risk: A nationwide cohort study. Medicine (Baltimore) 2020;99:e18530.
122. Haeck IM, Hamdy NA, Timmer-de Mik L, et al.: Low bone mineral density in adult patients with moderate to severe atopic dermatitis. Br J Dermatol 2009;161:1248-54.
123. Baïz N, Dargent-Molina P, Wark JD, et al.: EDEN Mother-Child Cohort Study Group. Cord serum 25-hydroxyvitamin D and risk of early childhood transient wheezing and atopic dermatitis. J Allergy Clin Immunol 2014;133:147-53.
124. van Velsen SG, Knol MJ, van Eijk RL, et al.: Bone mineral density in children with moderate to severe atopic dermatitis. J Am Acad Dermatol 2010;63:824-31.
125. Wu D, Wu XD, Zhou X, et al.: Bone mineral density, osteopenia, osteoporosis, and fracture risk in patients with atopic dermatitis: a systematic review and meta-analysis. Ann Transl Med 2021;9:40.
126. Wollenberg A, Barbarot S, Bieber T, et al.: Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I [published correction appears in J Eur Acad Dermatol Venereol 2019 Jul;33(7):1436]. J Eur Acad Dermatol Venereol 2018;32:657-82.
127. Damiani G, Calzavara-Pinton P, Stingeni L, et al.: Italian guidelines for therapy of atopic dermatitis-adapted from consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis). Dermatol Ther 2019;32:e13121.
128. Smith S, Baker C, Gebauer K, et al.: Atopic dermatitis in adults: An Australian management consensus. Australas J Dermatol 2020;61:23-32.
129. Hanifin JM, Rajka G: Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockh) 1980;92(Suppl):44-7.
130. Weidinger S, Novak N: Atopic dermatitis. Lancet 2016;387:1109-22.

131. Kavlak Bozkurt P, Özkaya P: Atopic dermatitis diagnostic criteria with beneficial and controversial aspects: review. Türkiye Klinikleri J Dermatol 2012;22:141-8.
132. Williams HC, Burney PG, Pembroke AC, Hay RJ: The U.K. Working Party's diagnostic criteria for atopic dermatitis. III. Independent hospital validation. Br J Dermatol 1994;131:406-16.
133. Yazganoglu KD, Ozkaya E: Non-typical morphology and localization in Turkish atopic dermatitis patients with onset before the age of 18 years. Indian J Dermatol Venereol Leprol 2011;77:23-7.
134. Kulthanan K, Samutrapong P, Jiamton S, Tuchinda P: Adult-onset atopic dermatitis: A cross-sectional study of natural history and clinical manifestation. Asian Pac J Allergy Immunol 2007;25:207-14.
135. Eichenfield LF, Tom WL, Chamlin SL, et al.: Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014;70:338-51.
136. Thijs JL, de Bruin-Weller MS, Hijnen D: Current and future biomarkers in atopic dermatitis. Immunol Allergy Clin North Am 2017;37:51-61.
137. Kartal D, Koç Babayiğit F: Atopik dermatit tanısında in vivo ve in vitro testler. Ed. Su Küçük Ö. Atopik Dermatit 1. Baskı. Ankara: Türkiye Klinikleri; 2020. P17-21.
138. Wallach D, Taïeb A: Atopic dermatitis/atopic eczema. Chem Immunol Allergy 2014;100:81-96.
139. Taşkapan O: The Significance of skin tests in atopic dermatitis. Turk J Dermatol 2013;7,236-41.
140. Kim JS: Pediatric atopic dermatitis: the importance of food allergens. Semin Cutan Med Surg 2008;27:156-60.
141. Akdis CA, Akdis M, Bieber T, et al.: Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma, and Immunology/PRACTALL. J Allergy Clin Immunol 2006;118:152-69.
142. Boyce JA, Assa'ad A, Burks AW, et al.: Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. J Allergy Clin Immunol 2010;126:1105-18.
143. Eichenfield LF: Consensus guidelines in diagnosis and treatment of atopic dermatitis. Allergy 2004;59(Suppl 78):86-92.
144. Schmitt J, Langan S, Williams HC; European Dermato-Epidemiology Network: What are the best outcome measurements for atopic eczema? A systematic review. J Allergy Clin Immunol 2007;120:1389-98.
145. Stalder JF, Barbarot S, Wollenberg A, et al.: Patient-Oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. Allergy 2011;66:1114-21.
146. Housman TS, Patel MJ, Camacho F, Feldman SR, Fleischer AB Jr, Balkrishnan R: Use of the Self-Administered Eczema Area and Severity Index by parent caregivers: results of a validation study. Br J Dermatol 2002;147:1192-8.
147. Lob-Corzilius T, Böer S, Scheewe S, et al.: The 'skin detective questionnaire': a survey tool for self-assessment of patients with atopic dermatitis. first results of its application. Dermatol Psychosom 2004;5:141-6.
148. Charman CR, Venn AJ, Williams HC: The patient-oriented eczema measure: Development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol 2004;140:1513-9.
149. Carel K, Bratton DL, Miyazawa N, et al.: The Atopic Dermatitis Quickscore (ADQ): validation of a new parent-administered atopic dermatitis scoring tool. Ann Allergy Asthma Immunol 2008;101:500-7.
150. Chren MM: The Skindex instruments to measure the effects of skin disease on quality of life. Dermatol Clin 2012;30:231-6, xiii.
151. Pariser DM, Simpson EL, Gadkari A, et al.: Evaluating patient-perceived control of atopic dermatitis: design, validation, and scoring of the Atopic Dermatitis Control Tool (ADCT). Curr Med Res Opin 2020;36:367-76.
152. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology 1993;186:23-31.
153. Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB: Practical issues on interpretation of scoring atopic dermatitis: The SCORAD index, objective SCORAD and the three-item severity score. Br J Dermatol 2007;157:645-8.
154. Vourc'h-Jourdain M, Barbarot S, Taieb A, et al.: Patient-oriented SCORAD: a self-assessment score in atopic dermatitis. A preliminary feasibility study. Dermatology 2009;218:246-51.
155. Hanifin JM, Thurston M, Omoto M, et al.: The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol 2001;10:11-8.
156. Tremp M, Knafla I, Burg G, Wüthrich B, Schmid-Grendelmeier P: "EASIdig"–a digital tool to document disease activity in atopic dermatitis. Dermatology 2011;223:68-73.
157. Charman C, Williams H: Outcome measures of disease severity in atopic eczema. Arch Dermatol 2000;136:763-9.
158. Siegfried E, Korman N, Molina C, Kianifard F, Abrams K: Safety and efficacy of early intervention with pimecrolimus cream 1% combined with corticosteroids for major flares in infants and children with atopic dermatitis [published correction appears in J Dermatolog Treat 2006;17:256]. J Dermatolog Treat 2006;17:143-50.
159. Rehal B, Armstrong AW: Health outcome measures in atopic dermatitis: a systematic review of trends in disease severity and quality-of-life instruments 1985-2010. PLoS One 2011;6:e17520.
160. Perez-Chada L, Taliercio VL, Gottlieb A, et al.: Achieving Consensus on Patient-Reported Outcome Measures in Clinical Practice for Inflammatory Skin Disorders: On Behalf of International Dermatology Outcome Measures and the American Academy of Dermatology. J Am Acad Dermatol 2019:S0190-9622:32745-8.
161. Simpson E, Eckert L, Gadkari A, et al.: Validation of the Atopic Dermatitis Control Tool (ADCT©) using a longitudinal survey of biologic-treated patients with atopic dermatitis. BMC Dermatol 2019;19:15.
162. Kahyaoğlu Süt H, Unsar S: Is EQ-5D a valid quality of life instrument in patients with acute coronary syndrome? Anadolu Kardiyol Derg 2011;11:156-62.
163. Finlay AY, Khan GK: Dermatology Life Quality Index (DLQI)–a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.
164. Oztürkcan S, Ermertcan AT, Eser E, Sahin MT: Cross validation of the Turkish version of dermatology life quality index. Int J Dermatol 2006;45:1300-7.
165. Abeni D, Picardi A, Pasquini P, Melchi CF, Chren MM: Further evidence of the validity and reliability of the Skindex-29: an Italian study on 2,242 dermatological outpatients. Dermatology 2002;204:43-9.
166. Aksu AE, Urer MS, Sabuncu I, Saracoglu ZN, Chren MM: Turkish version of Skindex-29. Int J Dermatol 2007;46:350-5.
167. Lewis-Jones MS, Finlay AY: The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol 1995;132:942-9.
168. Holme SA, Man I, Sharpe JL, Dykes PJ, Lewis-Jones MS, Finlay AY: The Children's Dermatology Life Quality Index: Validation of the cartoon version. Br J Dermatol 2003;148:285-90.
169. Wollenberg A, Barbarot S, Bieber T, et al.: Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. J Eur Acad Dermatol Venereol 2018;32:850-78.
170. Siegfried EC, Hebert AA: Diagnosis of atopic dermatitis: Mimics, overlaps, and complications. J Clin Med 2015;4:884-917.
171. Turner JD, Schwartz RA: Atopic dermatitis. A clinical challenge. Acta Dermatovenerol Alp Pannonica Adriat 2006;15:59-68.
172. Heratizadeh A, Werfel T, Wollenberg A, et al.: Effects of structured patient education in adults with atopic dermatitis: multicenter randomized controlled trial. J Allergy Clin Immunol 2017;140:845-53.
173. Zhao M, Liang Y, Shen C, Wang Y, Ma L, Ma X: Patient education programs in pediatric atopic dermatitis: a systematic review of randomized controlled trials and meta-analysis. Dermatol Ther (Heidelb) 2020;10:449-64.
174. Galli E, Neri I, Ricci G, et al.: Consensus conference on clinical management of pediatric atopic dermatitis. Ital J Pediatr 2016;42:26.
175. Kantor R, Silverberg JI: Environmental risk factors and their role in the management of atopic dermatitis. Expert Rev Clin Immunol 2017;13:15-26.
176. Bonamonte D, Filoni A, Vestita M, et al.: The role of the environmental risk factors in the pathogenesis and clinical outcome of atopic dermatitis. Biomed Res Int 2019;2019:2450605.
177. Geoghegan JA, Irvine AD, Foster TJ: Staphylococcus aureus and atopic dermatitis: a complex and evolving relationship. Trends Microbiol 2018;26:484-97.

178. Lin TK, Zhong L, Santiago JL: Association between stress and the HPA axis in the atopic dermatitis. Int J Mol Sci 2017;18:2131.
179. Caubet JC, Eigenmann PA: Allergic triggers in atopic dermatitis. Immunol Allergy Clin North Am 2010;30:289-307.
180. Borlu M, Öksüm Solak E: Diagnosis and management in adult onset atopic dermatitis. Ed. Su Küçük Ö. Atopik Dermatit 1. Baskı. Ankara: Türkiye Klinikleri: 2020.p71-4.
181. Healy E, Bentley A, Fidler C, Chambers C: Cost-effectiveness of tacrolimus ointment in adults and children with moderate and severe atopic dermatitis: twice-weekly maintenance treatment vs. standard twice-daily reactive treatment of exacerbations from a third party payer (U.K. National Health Service) perspective. Br J Dermatol 2011;16:387-95.
182. Ng JP, Liew HM, Ang SB: Use of emollients in atopic dermatitis. J Eur Acad Dermatol Venereol 2015;29:854-7.
183. Darsow U, Wollenberg A, Simon D, et al.: ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol 2010;24:317-28.
184. Grimalt R, Mengeaud V, Cambazard F: Study investigators' group. The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis: A randomized controlled study. Dermatology 2007;214:61-7.
185. Berth-Jones J, Damstra RJ, Golsch S, et al.: Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. BMJ 2003;326:1367.
186. Lucky AW, Leach AD, Laskarzewski P, Wenck H: Use of an emollient as a steroid-sparing agent in the treatment of mild to moderate atopic dermatitis in children. Pediatr Dermatol 1997;14:321-4.
187. Eichenfield LF, Tom WL, Berger TG, et al.: Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol 2014;71:116-32.
188. Odyakmaz Demirsoy E. Atopik dermatitte topikal tedavi. Ed. Su Küçük Ö. Atopik Dermatit 1. Baskı. Ankara: Türkiye Klinikleri: 2020.p.38-43.
189. Miller DW, Koch SB, Yentzer BA, et al.: An over-the-counter moisturizer is as clinically effective as, and more cost-effective than, prescription barrier creams in the treatment of children with mild-to-moderate atopic dermatitis: a randomized, controlled trial. J Drugs Dermatol 2011;10:531-7.
190. Nowicki R, Trzeciak M, Wilkowska A, et al.: Atopic dermatitis: current treatment guidelines. Statement of the experts of the dermatological section, polish society of allergology, and the allergology section, polish society of dermatology. Postepy Dermatol Alergol 2015;32:239-49.
191. Voegeli D: The effect of washing and drying practices on skin barrier function. J Wound Ostomy Continence Nurs 2008;35:84-90.
192. Simpson EL: Atopic dermatitis: a review of topical treatment options. Curr Med Res Opin 2010;26:633-40.
193. Barnes PJ: Molecular mechanisms and cellular effects of glucocorticosteroids. Immunol Allergy Clin North Am 2005;25:451-68.
194. Aubert-Wastiaux H, Moret L, Le Rhun A, et al.: Topical corticosteroid phobia in atopic dermatitis: a study of its nature, origins, and frequency. Br J Dermatol 2011;165:808-14.
195. Charman CR, Morris AD, Williams HC: Topical corticosteroid phobia in patients with atopic eczema. Br J Dermatol 2000;142:931-6.
196. Williams HC: Established corticosteroid creams should be applied only once daily in patients with atopic eczema. BMJ 2007;334:1272.
197. Drake LA, Dinehart SM, Farmer ER, et al.: Guidelines of care for the use of topical glucocorticosteroids. American Academy of Dermatology. J Am Acad Dermatol 1996;35:615-9.
198. Mayba JN, Gooderham MJ: Review of atopic dermatitis and topical therapies. J Cutan Med Surg 2017;21:227-36.
199. Lebwohl MG, Del Rosso JQ, Abramovits W, et al.: Pathways to managing atopic dermatitis: consensus from the experts. J Clin Aesthet Dermatol 2013;6(7 Suppl):S2-18.
200. Chia BK, Tey HL: Systematic review on the efficacy, safety, and cost-effectiveness of topical calcineurin inhibitors in atopic dermatitis. Dermatitis 2015;26:122-32.
201. Tennis P, Gelfand JM, Rothman KJ: Evaluation of cancer risk related to atopic dermatitis and use of topical calcineurin inhibitors. Br J Dermatol 2011;165:465-73.
202. Zane LT, Chanda S, Jarnagin K, Nelson DB, Spelman L, Gold LS: Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. Immunotherapy 2016;8:853-66.
203. Freund YR, Akama T, Alley MR, et al.: Boron-based phosphodiesterase inhibitors show novel binding of boron to PDE4 bimetal center. FEBS Lett 2012;586:3410-4.
204. Jarnagin K, Chanda S, Coronado D, et al.: Crisaborole topical ointment, 2%: a nonsteroidal, topical, anti-inflammatory phosphodiesterase 4 inhibitor in clinical development for the treatment of atopic dermatitis. J Drugs Dermatol 2016;15:390-6.
205. Zane LT, Kircik L, Call R, et al.: Crisaborole topical ointment, 2% in patients ages 2 to 17 years with atopic dermatitis: a phase 1b, open-label, maximal-use systemic exposure Study. Pediatr Dermatol 2016;33:380-7.
206. Murrell DF, Gebauer K, Spelman L, Zane LT: Crisaborole topical ointment, 2% in adults with atopic dermatitis: a phase 2a, vehicle-controlled, proof-of-concept study. J Drugs Dermatol 2015;14:1108-12.
207. Nygaard U, Deleuran M, Vestergaard C: Emerging treatment options in atopic dermatitis: topical therapies. Dermatology 2017;233:333-43.
208. Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, Williams HC: Interventions to reduce staphylococcus aureus in the management of atopic eczema: an updated cochrane review. Br J Dermatol 2010;163:12-26.
209. Tollefson MM, Bruckner AL: Section on dermatology. Atopic dermatitis: skin-directed management. Pediatrics 2014;134:e1735-44.
210. Ong PY: Recurrent MRSA skin infections in atopic dermatitis. J Allergy Clin Immunol Pract 2014;2:396-9.
211. Drake LA, Fallon JD, Sober A: Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. The Doxepin Study Group. J Am Acad Dermatol 1994;31:613-6.
212. Berberian BJ, Breneman DL, Drake LA, et al.: The addition of topical doxepin to corticosteroid therapy: an improved treatment regimen for atopic dermatitis. Int J Dermatol 1999;38:145-8.
213. Horio T: Allergic and photoallergic dermatitis from diphenhydramine. Arch Dermatol 1976;112:1124-6.
214. Food and Drug Administration, HHS: Labeling of diphenhydramine-containing drug products for over-the-counter human use. Final rule. Fed Regist 2002;67:72555-9.
215. Gooderham M: Small molecules: an overview of emerging therapeutic options in the treatment of psoriasis. Skin Therapy Lett 2013;18:1-4.
216. Fridman JS, Scherle PA, Collins R, et al.: Preclinical evaluation of local JAK1 and JAK2 inhibition in cutaneous inflammation. J Invest Dermatol 2011;131:1838-44.
217. Fukuyama T, Ehling S, Cook E, Bäumer W: Topically administered janus-kinase inhibitors tofacitinib and oclacitinib display impressive antipruritic and anti-inflammatory responses in a model of allergic dermatitis. J Pharmacol Exp Ther 2015;354:394-405.
218. Bissonnette R, Poulin Y, Zhou Y, et al.: Efficacy and safety of topical WBI-1001 in patients with mild to severe atopic dermatitis: results from a 12-week, multicentre, randomized, placebo-controlled double-blind trial. Br J Dermatol 2012;16:853-60.
219. Bogaczewicz J, Malinowska K, Sysa-Jedrzejowska A, Wozniacka A: Medium dose ultraviolet A1 phototherapy and mRNA expression of interleukin 8, interferon , and chemokine receptor 4 in acute skin lesions in atopic dermatitis. Postepy Dermatol Alergol 2016;33:170-5.
220. Gambichler T, Kreuter A, Tomi NS, Othlinghaus N, Altmeyer P, Skrygan M: Gene expression of cytokines in atopic eczema before and after ultraviolet A1 phototherapy. Br J Dermatol 2008;158:1117-20.
221. El Samahy MH, Attia EA, Saad AA, Mahmoud EY: Circulating CD4(+) CD25(high) FoxP3(+) T-regulatory cells in patients with atopic dermatitis after narrowband-ultraviolet B phototherapy. Int J Dermatol 2015;54:e424-9.
222. Yoshimura-Mishima M, Akamatsu H, Namura S, Horio T: Suppressive effect of ultraviolet (UVB and PUVA) radiation on superantigen production by Staphylococcus aureus. J Dermatol Sci 1999;19:31-6.
223. Staniek V, Liebich C, Vocks E, et al.: Modulation of cutaneous SP receptors in atopic dermatitis after UVA irradiation. Acta Derm Venereol 1998;78:92-4.
224. Tominaga M, Tengara S, Kamo A, Ogawa H, Takamori K: Psoralen-ultraviolet A therapy alters epidermal Sema3A and NGF levels and

modulates epidermal innervation in atopic dermatitis. J Dermatol Sci 2009;55:40-6.
225. Jekler J, Larkö O: UVB phototherapy of atopic dermatitis. Br J Dermatol 1988;119:697-705.
226. Jekler J, Larkö O: UVA solarium versus UVB phototherapy of atopic dermatitis: a paired-comparison study. Br J Dermatol 1991;125:569-72.
227. Granlund H, Erkko P, Remitz A, et al.: Comparison of cyclosporin and UVAB phototherapy for intermittent one-year treatment of atopic dermatitis. Acta Derm Venereol 2001;81:22-7.
228. Yoshiike T, Aikawa Y, Sindhvananda J, Ogawa H: A proposed guideline for psoralen photochemotherapy (PUVA) with atopic dermatitis: successful therapeutic effect on severe and intractable cases. J Dermatol Sci 1993;5:50-3.
229. de Kort WJ, van Weelden H: Bath psoralen-ultraviolet a therapy in atopic eczema. J Eur Acad Dermatol Venereol 2000;14:172-4.
230. Der-Petrossian M, Seeber A, Hönigsmann H, Tanew A: Half-side comparison study on the efficacy of 8-methoxypsoralen bath-PUVA versus narrow-band ultraviolet B phototherapy in patients with severe chronic atopic dermatitis. Br J Dermatol 2000;142:39-43.
231. Tzaneva S, Kittler H, Holzer G, et al.: 5-Methoxypsoralen plus ultraviolet (UV) A is superior to medium-dose UVA1 in the treatment of severe atopic dermatitis: a randomized crossover trial. Br J Dermatol 2010;162:655-60.
232. Krutmann J, Czech W, Diepgen T, Niedner R, Kapp A, Schöpf E: High-dose UVA1 therapy in the treatment of patients with atopic dermatitis. J Am Acad Dermatol 1992;26:225-30.
233. Kowalzick L, Kleinheinz A, Weichenthal M, et al.: Low dose versus medium dose UV-A1 treatment in severe atopic eczema. Acta Derm Venereol 1995;75:43-5.
234. Abeck D, Schmidt T, Fesq H, et al.: Long-term efficacy of medium-dose UVA1 phototherapy in atopic dermatitis. J Am Acad Dermatol 2000;42:254-7.
235. Seçkin D, Fototerapi Çalışma Grubu, Yılmaz E: Results of Photo(chemo) therapy applications survey in TurkeyTURKDERM-Arch Turkish Dermatology Venerol 2010;44:131-7.
236. George SA, Bilsland DJ, Johnson BE, Ferguson J: Narrow-band (TL-01) UVB air-conditioned phototherapy for chronic severe adult atopic dermatitis. Br J Dermatol 1993;128:49-56.
237. Reynolds NJ, Franklin V, Gray JC, et al.: Narrow-band ultraviolet B and broad-band ultraviolet a phototherapy in adult atopic eczema: a randomised controlled trial. Lancet 2001;357:2012-6.
238. Clayton TH, Clark SM, Turner D, Goulden V: The treatment of severe atopic dermatitis in childhood with narrowband ultraviolet B phototherapy. Clin Exp Dermatol 2007;32:28-33.
239. Clowry J, Molloy K, Nestor L, et al.: Narrow-band ultraviolet B phototherapy outcomes in atopic dermatitis-A single-centre retrospective review. Photodermatol Photoimmunol Photomed 2018;34:217-9.
240. Darné S, Leech SN, Taylor AE: Narrowband ultraviolet B phototherapy in children with moderate-to-severe eczema: a comparative cohort study. Br J Dermatol 2014;170:150-6.
241. Sidbury R, Davis DM, Cohen DE, et al.: Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol 2014;71:327-49.
242. Heinlin J, Schiffner-Rohe J, Schiffner R, et al.: A first prospective randomized controlled trial on the efficacy and safety of synchronous balneophototherapy vs. narrow-band UVB monotherapy for atopic dermatitis. J Eur Acad Dermatol Venereol 2011;25:765-73.
243. Nisticò SP, Saraceno R, Capriotti E, Felice CD, Chimenti S: Efficacy of monochromatic excimer light (308 nm) in the treatment of atopic dermatitis in adults and children. Photomed Laser Surg 2008;26:14-8.
244. Farahnik B, Beroukhim K, Danesh M, et al.: Successful use of a modified goeckerman regimen in the treatment of chronic severe atopic dermatitis: A prospective pilot study. J Am Acad Dermatol 2016;75:1068-71.
245. Wolf P, Georgas D, Tomi NS, Schempp CM, Hoffmann K: Extracorporeal photochemotherapy as systemic monotherapy of severe, refractory atopic dermatitis: results from a prospective trial. Photochem Photobiol Sci 2013;12:174-81.
246. Rubegni P, Poggiali S, Cevenini G, et al.: Long term follow-up results on severe recalcitrant atopic dermatitis treated with extracorporeal photochemotherapy. J Eur Acad Dermatol Venereol 2013;27:523-6.
247. Cameron H, Yule S, Dawe RS, Ibbotson SH, Moseley H, Ferguson J: Review of an established UK home phototherapy service 1998-2011: improving access to a cost-effective treatment for chronic skin disease. Public Health 2014;128:317-24.
248. He A, Feldman SR, Fleischer AB Jr: An assessment of the use of antihistamines in the management of atopic dermatitis. J Am Acad Dermatol 2018;79:92-6.
249. Matterne U, Böhmer MM, Weisshaar E, Jupiter A, Carter B, Apfelbacher CJ: Oral H1 antihistamines as 'add-on' therapy to topical treatment for eczema. Cochrane Database Syst Rev 2019;1:CD012167.
250. Schmitt J, Buske-Kirschbaum A, Tesch F, et al.: Increased attention-deficit/hyperactivity symptoms in atopic dermatitis are associated with history of antihistamine use. Allergy 2018;73:615-26.
251. Diepgen TL; Early Treatment of the Atopic Child Study Group: Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. Pediatr Allergy Immunol 2002;13:278-86.
252. Kawashima M, Tango T, Noguchi T, Inagi M, Nakagawa H, Harada S: Addition of fexofenadine to a topical corticosteroid reduces the pruritus associated with atopic dermatitis in a 1-week randomized, multicentre, double-blind, placebo-controlled, parallel-group study. Br J Dermatol 2003;148:1212-21.
253. Yamanaka K, Motomura E, Noro Y, et al.: Olopatadine, a non-sedating H1 antihistamine, decreases the nocturnal scratching without affecting sleep quality in atopic dermatitis. Exp Dermatol 2015;24:227-9.
254. Werfel T, Layton G, Yeadon M, et al.: Efficacy and safety of the histamine H4 receptor antagonist ZPL-3893787 in patients with atopic dermatitis. J Allergy Clin Immunol 2019;143:1830-17.e4.
255. Wollenberg A, Christen-Zäch S, Taieb A, et al.: ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. J Eur Acad Dermatol Venereol 2020;34:2717-44.
256. Ring J, Alomar A, Bieber T, et al.: Guidelines for treatment of atopic eczema (atopic dermatitis) part I. J Eur Acad Dermatol Venereol 2012;26:1045-60.
257. Drucker AM, Eyerich K, de Bruin-Weller MS, et al.: Use of systemic corticosteroids for atopic dermatitis: International Eczema Council consensus statement. Br J Dermatol 2018;178:768-75.
258. Wollenberg A, Oranje A, Deleuran M, et al.: ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. J Eur Acad Dermatol Venereol 2016;30:729-47.
259. Schmitt J, Schmitt N, Meurer M: Cyclosporin in the treatment of patients with atopic eczema - a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2007;21:606-19.
260. Garrido Colmenero C, Blasco Morente G, Tercedor Sánchez J: Oral cyclosporine weekend therapy: a new maintenance therapeutic option in patients with severe atopic dermatitis. Pediatr Dermatol 2015;32:551-2.
261. Schmitt J, Schäkel K, Fölster-Holst R, et al.: Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. Br J Dermatol 2010;162:661-8.
262. Gooderham M, Lynde CW, Papp K, et al.: Review of systemic treatment options for adult atopic dermatitis. J Cutan Med Surg 2017;21:31-9.
263. Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J: Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. J Allergy Clin Immunol 2014;133:429-38.
264. Thijs JL, Van Der Geest BAM, Van Der Schaft J, et al.: Predicting therapy response to mycophenolic acid using UGT1A9 genotyping: towards personalized medicine in atopic dermatitis. J Dermatolog Treat 2017;28:242-5.
265. Phan K, Smith SD: Mycophenolate mofetil and atopic dermatitis: Systematic review and meta-analysis. J Dermatolog Treat 2020;31:810-4.
266. Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA: Enteric-coated mycophenolate sodium versus cyclosporin a as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. J Am Acad Dermatol 2011;64:1074-84.
267. Heller M, Shin HT, Orlow SJ, Schaffer JV: Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. Br J Dermatol 2007;157:127-32.

268. Waxweiler WT, Agans R, Morrell DS: Systemic treatment of pediatric atopic dermatitis with azathioprine and mycophenolate mofetil. Pediatr Dermatol 2011;28:689-94.
269. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI: A randomized trial of methotrexate versus azathioprine for severe atopic eczema. J Allergy Clin Immunol 2011;128:353-9.
270. Berth-Jones J, Takwale A, Tan E, et al.: Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. Br J Dermatol 2002;147:324-30.
271. Meggitt SJ, Gray JC, Reynolds NJ: Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. Lancet 2006;367:839-46.
272. Caufield M, Tom WL: Oral azathioprine for recalcitrant pediatric atopic dermatitis: clinical response and thiopurine monitoring. J Am Acad Dermatol 2013;68:29-35.
273. Hon KL, Ching GK, Leung TF, Chow CM, Lee KK, Ng PC: Efficacy and tolerability at 3 and 6 months following use of azathioprine for recalcitrant atopic dermatitis in children and young adults. J Dermatolog Treat 2009;20:141-5.
274. Fuggle NR, Bragoli W, Mahto A, Glover M, Martinez AE, Kinsler VA: The adverse effect profile of oral azathioprine in pediatric atopic dermatitis, and recommendations for monitoring. J Am Acad Dermatol 2015;72:108-14.
275. Flohr C, Irvine AD: Systemic therapies for severe atopic dermatitis in children and adults. J Allergy Clin Immunol 2013;132:774-e6.
276. Dvorakova V, O'Regan GM, Irvine AD: Methotrexate for Severe childhood atopic dermatitis: clinical experience in a tertiary center. Pediatr Dermatol 2017;34:528-34.
277. Gerbens LAA, Hamann SAS, Brouwer MWD, Roekevisch E, Leeflang MMG, Spuls PI: Methotrexate and azathioprine for severe atopic dermatitis: a 5-year follow-up study of a randomized controlled trial. Br J Dermatol 2018;178:1288-96.
278. Goujon C, Viguier M, Staumont-Sallé D, et al.: Methotrexate versus cyclosporine in adults with moderate-to-severe atopic dermatitis: a phase iii randomized noninferiority Trial. J Allergy Clin Immunol Pract 2018;6:562-9.e3.
279. Vestergaard C, Wollenberg A, Barbarot S, et al.: European task force on atopic dermatitis position paper: treatment of parental atopic dermatitis during preconception, pregnancy, and lactation period. J Eur Acad Dermatol Venereol 2019;33:1644-59.
280. Ruzicka T, Lynde CW, Jemec GB, et al.: Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. Br J Dermatol 2008;158:808-17.
281. Grahovac M, Molin S, Prinz JC, Ruzicka T, Wollenberg A: Treatment of atopic eczema with oral alitretinoin. Br J Dermatol 2010;162:217-8.
282. Samrao A, Berry TM, Goreshi R, Simpson EL: A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. Arch Dermatol 2012;148:890-7.
283. Jee SJ, Kim JH, Baek HS, Lee HB, Oh JW: Long-term efficacy of intravenous immunoglobulin therapy for moderate to severe childhood atopic dermatitis. Allergy Asthma Immunol Res 2011;3:89-95.
284. Paul C, Lahfa M, Bachelez H, Chevret S, Dubertret L: A randomized controlled evaluator-blinded trial of intravenous immunoglobulin in adults with severe atopic dermatitis. Br J Dermatol 2002;147:518-22.
285. Bemanian MH, Movahedi M, Farhoudi A, et al.: High doses intravenous immunoglobulin versus oral cyclosporine in the treatment of severe atopic dermatitis. Iran J Allergy Asthma Immunol 2005;4:139-43.
286. Meyersburg D, Schmidt E, Kasperkiewicz M, Zillikens D: Immunoadsorption in dermatology. Ther Apher Dial 2012;16:311-20.
287. Kasperkiewicz M, Mook SC, Knuth-Rehr D, et al.: IgE-selective immunoadsorption for severe atopic dermatitis. Front Med (Lausanne) 2018;5:27.
288. Hanifin JM, Schneider LC, Leung DY, et al.: Recombinant interferon gamma therapy for atopic dermatitis. J Am Acad Dermatol 1993;28:189-97.
289. Jang IG, Yang JK, Lee HJ, et al.: Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. J Am Acad Dermatol 2000;42:1033-40.
290. Reinhold U, Kukel S, Brzoska J, Kreysel HW: Systemic interferon gamma treatment in severe atopic dermatitis. J Am Acad Dermatol 1993;29:58-63.
291. Panahi Y, Davoudi SM, Madanchi N, Abolhasani E: Recombinant human interferon gamma (gamma immunex) in treatment of atopic dermatitis. Clin Exp Med 2012;12:241-5.
292. Noh G, Lee KY: Successful interferon alpha therapy in atopic dermatitis of Besnier's prurigo pattern with normal serum IgE and blood eosinophil fraction: randomized case-controlled study. Cytokine 2001;13:124-8.
293. Beck LA, Thaçi D, Hamilton JD, et al.: Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014;371:130-9.
294. Worm M, Simpson EL, Thaçi D, et al.: Efficacy and safety of multiple dupilumab dose regimens after initial successful treatment in patients with atopic dermatitis: a randomized clinical trial. JAMA Dermatol 2020;156:131-43.
295. Siegels D, Heratizadeh A, Abraham S, et al.: Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis. Allergy 2021;76:1053-76.
296. Beck LA, Thaçi D, Deleuran M, et al.: Dupilumab provides favorable safety and sustained efficacy for up to 3 years in an open-label study of adults with moderate-to-severe atopic dermatitis. Am J Clin Dermatol 2020;21:567-77.
297. Wollenberg A, Beck LA, Blauvelt A, et al.: Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). Br J Dermatol 2020;182:1120-35.
298. Simpson EL, Paller AS, Siegfried EC, et al.: Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. JAMA Dermatol 2020;156:44-56.
299. Paller AS, Siegfried EC, Thaçi D, et al.: Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol 2020;83:1282-93.
300. Silverberg JI, Yosipovitch G, Simpson EL, et al.: Dupilumab treatment results in early and sustained improvements in itch in adolescents and adults with moderate to severe atopic dermatitis: Analysis of the randomized phase 3 studies SOLO 1 and SOLO 2, AD ADOL, and CHRONOS. J Am Acad Dermatol 2020;82:1328-36.
301. de Wijs LEM, Bosma AL, Erler NS, et al.: Effectiveness of dupilumab treatment in 95 patients with atopic dermatitis: daily practice data. Br J Dermatol 2020;182:418-26.
302. Pistone G, Tilotta G, Gurreri R, Castelli E, Curiale S, Bongiorno MR: Ocular surface disease during dupilumab treatment in patients with atopic dermatitis, is it possible to prevent it?. J Eur Acad Dermatol Venereol 2020;34:e255-6.
303. de Wijs LEM, Nguyen NT, Kunkeler ACM, Nijsten T, Damman J, Hijnen DJ: Clinical and histopathological characterization of paradoxical head and neck erythema in patients with atopic dermatitis treated with dupilumab: a case series. Br J Dermatol 2020;183:745-9.
304. Jang DH, Lee JI, Bae JY, Jung HJ, Park MY, Ahn J: Facial erythema after the treatment of dupilumab in SLE patient. Allergy Asthma Clin Immunol 2020;16:60.
305. Chan TC, Wu NL, Wong LS, et al.: Taiwanese dermatological association consensus for the management of atopic dermatitis: A 2020 update. J Formos Med Assoc 2021;120:429-42.
306. Snast I, Reiter O, Hodak E, Friedland R, Mimouni D, Leshem YA: Are biologics efficacious in atopic dermatitis? A systematic review and meta-analysis. Am J Clin Dermatol 2018;19:145-65.
307. Ruzicka T, Hanifin JM, Furue M, et al.: Anti-interleukin-31 receptor A antibody for atopic dermatitis. N Engl J Med 2017;376:826-35.
308. Belloni B, Ziai M, Lim A, et al.: Low-dose anti-IgE therapy in patients with atopic eczema with high serum IgE levels. J Allergy Clin Immunol 2007;120:1223-5.
309. Wang HH, Li YC, Huang YC: Efficacy of omalizumab in patients with atopic dermatitis: A systematic review and meta-analysis. J Allergy Clin Immunol 2016;138:1719-22.e1.
310. Amrol D: Anti-immunoglobulin e in the treatment of refractory atopic dermatitis. South Med J 2010;103:554-8.

311. Kim DH, Park KY, Kim BJ, Kim MN, Mun SK: Anti-immunoglobulin E in the treatment of refractory atopic dermatitis. Clin Exp Dermatol 2013;38:496-500.
312. Simpson EL, Flohr C, Eichenfield LF, et al.: Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE). J Am Acad Dermatol 2018;78:863-71.e11.
313. Baverel P, She D, Piper E, et al.: A randomized, placebo-controlled, single ascending-dose study to assess the safety, tolerability, pharmacokinetics, and immunogenicity of subcutaneous tralokinumab in Japanese healthy volunteers. Drug Metab Pharmacokinet 2018;33:150-8.
314. Hajar T, Gontijo JRV, Hanifin JM: New and developing therapies for atopic dermatitis. An Bras Dermatol 2018;93:104-7.
315. Simon D, Hösli S, Kostylina G, Yawalkar N, Simon HU: Anti-CD20 (rituximab) treatment improves atopic eczema. J Allergy Clin Immunol 2008;121:122-8.
316. McDonald BS, Jones J, Rustin M: Rituximab as a treatment for severe atopic eczema: failure to improve in three consecutive patients. Clin Exp Dermatol 2016;41:45-7.
317. Pan Y, Xu L, Qiao J, Fang H: A systematic review of ustekinumab in the treatment of atopic dermatitis. J Dermatolog Treat 2018;29:539-41.
318. Katoh N: Emerging treatments for atopic dermatitis. J Dermatol 2021;48:152-7.
319. Nakagawa H, Nemoto O, Yamada H, Nagata T, Ninomiya N: Phase 1 studies to assess the safety, tolerability, and pharmacokinetics of JTE-052 (a novel Janus kinase inhibitor) ointment in Japanese healthy volunteers and patients with atopic dermatitis. J Dermatol 2018;45:701-9.
320. Levy LL, Urban J, King BA: Treatment of recalcitrant atopic dermatitis with the oral janus kinase inhibitor tofacitinib citrate. J Am Acad Dermatol 2015;73:395-9.
321. Guttman-Yassky E, Silverberg JI, Nemoto O, et al.: Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. J Am Acad Dermatol 2019;80:913-21.e9.
322. Simpson EL, Lacour JP, Spelman L, et al.: Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol 2020;183:242-55.
323. Rreich k, kabashima k, peris k, et al.: Efficacy and safety of baricitinib combined with topical corticosteroids for treatment of moderate to severe atopic dermatitis: a randomized clinical trial. JAMA Dermatol 2020;156:1333-43.
324. Simpson EL, Sinclair R, Forman S, et al.: Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020;396:255-66.
325. Oldhoff JM, Darsow U, Werfel T, et al.: Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. Allergy 2005;60:693-6.
326. Oldhoff JM, Darsow U, Werfel T, et al.: No effect of anti-interleukin-5 therapy (mepolizumab) on the atopy patch test in atopic dermatitis patients. Int Arch Allergy Immunol 2006;141:290-4.
327. Jacobi A, Antoni C, Manger B, Schuler G, Hertl M: Infliximab in the treatment of moderate to severe atopic dermatitis. J Am Acad Dermatol 2005;52:522-6.
328. Nakamura M, Lee K, Singh R, et al.: Eczema as an adverse effect of anti-TNFα therapy in psoriasis and other Th1-mediated diseases: a review. J Dermatolog Treat 2017;28:237-41.
329. Katoh N, Ohya Y, Ikeda M, et al.: Japanese guidelines for atopic dermatitis 2020. Allergol Int 2020;69:356-69.
330. Panduru M, Panduru NM, Sălăvăstru CM, Tiplica GS: Probiotics and primary prevention of atopic dermatitis: a meta-analysis of randomized controlled studies. J Eur Acad Dermatol Venereol 2015;29:232-42.
331. Kim SO, Ah YM, Yu YM, Choi KH, Shin WG, Lee JY: Effects of probiotics for the treatment of atopic dermatitis: a meta-analysis of randomized controlled trials. Ann Allergy Asthma Immunol 2014;113:217-26.
332. Chang YS, Trivedi MK, Jha A, Lin YF, Dimaano L, García-Romero MT: Synbiotics for prevention and treatment of atopic dermatitis: a meta-analysis of randomized clinical trialsJAMA Pediatr 2016;170:236-42.
333. Huang R, Ning H, Shen M, Li J, Zhang J, Chen X: Probiotics for the treatment of atopic dermatitis in children: a systematic review and meta-analysis of randomized controlled trials. Front Cell Infect Microbiol 2017;7:392.
334. Zhao M, Shen C, Ma L: Treatment efficacy of probiotics on atopic dermatitis, zooming in on infants: a systematic review and meta-analysis. Int J Dermatol 2018;57:635-41.
335. Heilskov S, Deleuran MS, Vestergaard C: Immunosuppressive and immunomodulating therapy for atopic dermatitis in pregnancy: an appraisal of the literature. Dermatol Ther (Heidelb) 2020;10:1215-28.
336. Rodrigues MA, Nogueira M, Torres T: Dupilumab for atopic dermatitis: evidence to date. G Ital Dermatol Venereol 2019;154:696-713.
337. Dupixent (dupilumab) product information. https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf. (date of access: 19.04.2021).
338. Napolitano M, Ruggiero A, Fontanella G, Fabbrocini G, Patruno C: New emergent therapies for atopic dermatitis: A review of safety profile with respect to female fertility, pregnancy, and breastfeeding. Dermatol Ther 2021;34:e14475.
339. Kage P, Simon JC, Treudler R: A case of atopic eczema treated safely with dupilumab during pregnancy and lactation. J Eur Acad Dermatol Venereol 2020;34:e256-7.
340. Tanei R: Atopic dermatitis in older adults: a review of treatment options. Drugs Aging 2020;37:149-60.
341. Fowler E, Rosen J, Lev-Tov H, Yosipovitch G: Two cancer patients receiving dupilumab for treatment of atopic dermatitis. Acta Derm Venereol 2019;99:899-900.
342. Braddock M, Hanania NA, Sharafkhaneh A, Colice G, Carlsson M: Potential risks related to modulating interleukin-13 and interleukin-4 signalling: a systematic review. Drug Saf 2018;41:489-509.
343. Gnarra M, De Simone C, Garcovich M, Garcovich S: Low-dose cyclosporine a in the treatment of severe atopic dermatitis complicated by chronic hepatitis C virus infection. Pediatr Dermatol 2017;34:374-6.
344. Yim RM, Singh I, Armstrong AW: Updates on treatment guidelines for psoriasis, atopic dermatitis (eczema), hidradenitis suppurativa, and acne/rosacea during the COVID-19 pandemic. Dermatol Online J 2020;26:13030/qt0j5150df.
345. Ricardo JW, Lipner SR: Considerations for safety in the use of systemic medications for psoriasis and atopic dermatitis during the COVID-19 pandemic. Dermatol Ther 2020;3:e13687.
346. Ordóñez-Rubiano MF, Campo I, Casas M: Dupilumab in atopic dermatitis, a protocol for SARS-COV-2-infected patients. Dermatol Ther 2020;33:e14172.
347. Kearns DG, Uppal S, Chat VS, Wu JJ: Assessing the risk of dupilumab use for atopic dermatitis during the COVID-19 pandemic. J Am Acad Dermatol 2020;83:e251-2.
348. Ferrucci S, Romagnuolo M, Angileri L, Berti E, Tavecchio S: Safety of dupilumab in severe atopic dermatitis and infection of Covid-19: two case reports. J Eur Acad Dermatol Venereol 2020;34:e303-4.