

Update on Atopic Dermatitis

A Dermatite Atópica em Revisão



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ABSTRACT

With an increasing prevalence during the past decades, atopic dermatitis has become a global health issue. A literature search following a targeted approach was undertaken to perform this non-systematic review, which intends to provide an overview of the epidemiology, pathophysiology, clinical features, comorbidities, and current therapies for the treatment of atopic dermatitis. In sum, this is a heterogeneous skin disorder associated with variable morphology, distribution, and disease course. Although not completely understood, its pathogenesis is complex and seems to result from a combination of genetic and environmental factors that induce skin barrier dysfunction, cutaneous and systemic immune dysregulation, skin microbiota dysbiosis, and a strong genetic influence. Diagnosis is based on specific criteria that consider patient and family history and clinical manifestations. Overall disease severity must be determined by evaluating both objective signs and subjective symptoms. Therapeutic goals require a multistep approach, focusing on reducing pruritus and establishing disease control. Patients should be advised on basic skin care and avoidance of triggers. Topical anti-inflammatory agents should be considered in disease flares or chronic/recurrent lesions. In case of inadequate response, phototherapy, systemic immunosuppressants and, more recently, dupilumab, should be added. Nevertheless, the treatment of moderate-to-severe atopic dermatitis remains challenging and novel, efficacious, safe and targeted treatments are urgently needed. In conclusion, although the last few years have seen important improvement in the understanding of the disease, future research in atopic dermatitis will continue exploring gene-environment interactions and how it affects pathophysiology, disease severity, and treatment outcomes.

Keywords: Dermatitis, Atopic/complications; Dermatitis, Atopic/diagnosis; Dermatitis, Atopic/epidemiology; Dermatitis, Atopic/etiology; Dermatitis, Atopic/prevention and control; Dermatitis, Atopic/therapy

RESUMO

Com uma prevalência crescente nas últimas décadas, a dermatite atópica tornou-se um problema de saúde global. Foi realizada uma revisão não sistemática com base numa pesquisa bibliográfica direcionada à epidemiologia, fisiopatologia, características clínicas, comorbilidades e tratamento da dermatite atópica. Em resumo, a dermatite atópica é uma patologia cutânea heterogénea associada a morfologia, distribuição e curso da doença variáveis. A sua patogénese é complexa, combinando fatores genéticos e ambientais que condicionam a disfunção da barreira epidérmica, a desregulação imune cutânea e sistémica e a disbiose do microbioma da pele. O diagnóstico baseia-se em critérios clínicos específicos, incluindo história pessoal e familiar de atopia, evolução da doença e manifestações clínicas. A gravidade da doença é determinada através da avaliação dos sinais objetivos e dos sintomas subjetivos. A sua abordagem deve ser progressiva, focada na redução do prurido e no controlo da doença. Os doentes devem ser aconselhados sobre os cuidados básicos a ter e evicção de agressores externos. Em situações de agudização ou lesões crónico-recidivantes, devem ser aplicados anti-inflamatórios tópicos. Na ausência de resposta ou controlo adequado no médio prazo, deve ponderar-se fototerapia, imunossuppressores sistémicos ou, mais recentemente, dupilumab. Contudo, o tratamento da dermatite atópica moderada a grave permanece desafiador, sendo urgente o desenvolvimento de novas terapêuticas, eficazes, seguras e direcionadas. Concluindo, apesar de atualmente haver uma melhor compreensão e um maior conhecimento da doença, as investigações futuras deverão continuar a explorar a interação entre fatores genéticos e ambientais e seus efeitos na fisiopatologia e gravidade da doença, bem como nos resultados do tratamento.

Palavras-chave: Dermatite Atópica/complicações; Dermatite Atópica/diagnóstico; Dermatite Atópica/epidemiologia; Dermatite Atópica/etiologia; Dermatite Atópica/prevenção e controlo; Dermatite Atópica/tratamento

INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a common, chronic and relapsing inflammatory skin disease with an increasing incidence during the past few decades, especially in developed countries.¹⁻⁴ AD has become a global health issue as it causes high health-care costs worldwide and is associated with considerable morbidity and quality of life (QoL) impairment, disease burden

comparable to other chronic conditions like epilepsy, diabetes mellitus and cystic fibrosis.^{1,2,5-8} AD often develops during childhood, and has a wide spectrum of symptoms and signs which contribute towards profound functional disturbances, limits the ability to perform daily life activities and causes psychosocial distress and stigma.^{2,9} The psychosocial and financial implications of AD affect patients, their families, health care providers, and society in general.^{1,5,8}

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The pathophysiological concepts underlying AD have shifted towards an integrated view, in which genetic and environmental factors interact contributing to varying degrees of epidermal barrier disruption, activation of different T cell subsets, and commensal skin microbiota dysbiosis, causing the varying clinical presentations, presumably encompassing a variety of subtypes with distinct and overlapping pathological mechanisms.² Although the underlying mechanisms causing these conditions are largely unknown and the absolute magnitude of the risks has not yet been well defined, AD has been considered more recently as a systemic disorder associated with increased risk of various allergic and non-allergic comorbidities, namely food allergies, respiratory disorders, cutaneous and extra-cutaneous infections, neuropsychiatric conditions, other inflammatory and autoimmune diseases, lymphoma, and cardiovascular disease, with important implications for management and treatment.^{1,2,5,6,9–13}

Therapeutic goals require a multistep approach, focused on reducing pruritus and establishing disease control. Treatment selection is based primarily on disease severity but also on the patient's age, comorbidities, compliance, and costs.² Licensed treatment options for moderate-to-severe AD are limited, but current insights from basic and clinical research are now being translated into clinical trials and approval of new treatments.^{1,2,14,15}

A literature search following a targeted approach was undertaken to perform this non-systematic review, which aims to provide an overview of the epidemiology, pathophysiology, clinical features, associated comorbid health disorders, as well as the current and novel therapies for the treatment of AD.

Epidemiology

According to the WHO Global Burden of Diseases initiative's data, it is estimated that AD affects at least 230 million people worldwide, being the leading cause of the non-fatal disease burden within skin conditions.^{2,16} AD is one of the most common chronic diseases worldwide and the most common inflammatory skin disorder in the developed world, affecting men and women of all races, children and adults, often occurring in families with other atopic diseases (bronchial asthma and/or allergic rhinitis).^{2,14,17,18} Originally regarded as an early childhood disease, with an estimated prevalence of 15% – 25% in children, more recent evidence shows that AD is also very prevalent in adults, with rates ranging from 1% to 10%.^{2,6,14,17,19–27} Even though epidemiologic studies report different prevalence estimates throughout the world, even between highly genetically similar populations, the overall prevalence of AD has increased by 2- to 3-fold during the past decades in industrialized countries, especially in the United States (US), Europe, and Japan, with a maximum prevalence of nearly 30% in some populations.^{4,18,23,25,26} The causes of this increase are unknown, although several systematic large-scale studies point to numerous genetic, social and/or environmental factors as potential contributors.^{2,18,23,24,28}

Although AD can manifest at any age in life, the incidence peaks in infancy with approximately 45% of all cases beginning within the first six months of life, 60% during the first year, and 80% – 90% before the fifth year of life.^{1,2,6,18,25} AD is often the first step in the development of other atopic diseases, such as allergic rhinitis, asthma and food allergy, the so-called 'atopic march', characterized by a typical sequence of atopic diseases preceding the development of other allergic disorders later in life.^{4,14,23,25} The number of patients who will develop asthma and/or allergic rhinitis depends on the underlying features of their condition,^{23,24} with evidence suggesting that 50% of those who develop AD before the age of 2 will develop asthma during subsequent years. Furthermore, AD children who develop asthma and allergic rhinitis are more likely to have severe disease.^{23,25}

The course of AD can be continuous for many years but can also show a relapsing-remitting pattern.² Early studies had suggested that the disease clears in > 50% of affected children, with just the more severe cases persisting into adulthood.²³ But more recent cross-sectional studies showed that the proportion of patients with persistent or adult-onset disease or with relapses after long asymptomatic intervals is much higher than previously thought.² One in four adults with AD report adult-onset disease, which appears to be associated with a different disease phenotype compared with childhood-onset AD.²⁹

According to an international, cross-sectional, web-based survey performed in the US, Canada, France, Germany, Italy, Spain, United Kingdom, and Japan, regional variability of adult AD prevalence was observed within countries. Among participants by region, the point prevalence of adult AD in the overall populations was 4.9% in the US, 4.4% in the EU, 3.5% in Canada, and 2.1% in Japan. Severity varied by scale and region. However, the proportion of subjects reporting severe disease was lower than in mild or moderate disease.²²

The first published data regarding AD estimates in the Portuguese population revealed that from approximately 78 300 adult AD patients (0.7% – 1.6% of the Portuguese adult population) seen by a dermatologist in 2017, 40% – 45% had moderate or severe disease,²¹ confirming that severe AD represents a small proportion of the overall AD population regardless of measure or region.²² Most surveyed physicians reported an increase in the number of their patients over the last 3 years; most patients were young adults, 48% under 35 years old,²¹ which also corroborates the international trends. Out of 22 354 Portuguese children under 16, attending dermatology consultation, 3214 (14.4%) had AD.³⁰

Etiology and pathophysiology

The global increasing AD prevalence cannot be attributed to genetics alone as its aetiology is multifactorial involving the interaction between genetics, immune and environmental factors.^{23,31} Environmental exposures may trigger and/or flare disease in predisposed individuals. Exposure to personal care or professional cleansing products, climate, pollution, food and other exogenous factors act in

concert with genetic and acquired skin barrier disruption and immune imbalance to influence disease manifestations.^{23,31} Understanding these complex interacting factors is crucial to develop targeted interventions to prevent or mitigate disease. Moreover, patients require counselling on optimal regimens for avoiding irritants and pruritogens and other harmful exposures.³¹

The strongest known risk factor for AD is a family history of atopic diseases, particularly AD.^{2,23,27} The presence of an atopic disease in one parent is estimated to increase 1.5-fold a child's risk of developing AD, whereas the risk is increased ~3-fold and ~5-fold, respectively, if one or both parents have AD. Other risk factors associated with increased prevalence include living in an urban setting and in regions with low ultraviolet light exposure or dry climatic conditions, diets rich in sugars and polyunsaturated fatty acids (typical of Western countries), repeated exposure to antibiotics before five years of age, smaller family size, higher socioeconomic status and higher level of family education.^{2,23,24}

Effects of maternal and/or postnatal exposure to stress, tobacco, antibiotics or alcohol consumption; long-term exclusive breastfeeding; routine childhood vaccinations; viral or bacterial infections; air pollutants, farm environments and household hair-bearing pets, all remain inconsistent as risk factors for AD.^{2,27,31} In contrast, some maternal exposures may actually lower the risk of AD in childhood, including dietary and probiotics' exposures.^{23,31}

The pathogenesis of AD is complex and combines skin barrier dysfunction, cutaneous and systemic immune dysregulation, the dysbiosis of the skin bacterial microbiome, and genetic factors.^{2,7,11,25} Skin barrier abnormalities appear to be associated with mutations or impaired expression of the filaggrin gene, which encodes a structural protein essential for skin barrier formation.^{2,14,23} Moreover, dysregulation of lipid metabolism with reduction of ceramides are important factors,²⁵ leading to trans-epidermal water loss and increased penetration of irritants, allergens and microbes into the skin.^{7,14,23} Barrier disruption leads to chronic inflammation with epidermal hyperplasia and cellular infiltrates, including dendritic cells, eosinophils, and T-cells.^{7,11} AD is currently considered a biphasic or combined T cell-mediated disease concerning immune dysregulation.²³ A type-2 T-helper cell (Th2) signal rich in IL-4, IL-5, IL-13, IL-25, and IL-31 predominates in the acute phase, whereas a Th2–Th1 switch promotes disease chronicity.²³ Furthermore, IL-22-secreting Th22 cells, and in a smaller degree, IL-17-secreting Th17 cells play a role in the initiation and maintenance of AD.¹¹

The innate immune system provides the first line of defence against microbial pathogens. Defective innate immune responses, with a reduction of antimicrobial peptides, contribute to increased bacterial and viral infections.^{14,23} This interplay of factors leads to T cell responses in the skin with resultant release of chemokines and pro-inflammatory cytokines (namely TSLP and IL-4) that promote immunoglobulin E (IgE) production, skin and systemic

inflammation and high IL-31 leading to severe pruritus.²⁵ Still, although IgE has been considered a hallmark of atopic diseases, including AD, IgE itself is not a key mediator of AD pathogenesis.¹¹ Finally, the skin of patients with AD has substantial microbiotal abnormalities; whether these changes are primary or secondary to epidermal barrier disruption and Th2 cell-skewed immunity is still uncertain. Microbiota diversity decreases in inflamed AD skin in favour of members of the genus *Staphylococcus*. *S. aureus* in particular, colonizes approximately 90% of AD patients²⁵ and expresses numerous virulence factors that have proven roles in the pathogenesis of both superficial and invasive infections, contributing to AD pathogenesis or disease exacerbation through mechanisms acting on keratinocytes and immune cells.^{2,7} During treatment and recovery, the microbiota composition reverts to the pre-flare composition.^{7,32} In addition to the well-characterized role of *S. aureus* in AD, other organisms have substantial roles, including yeasts, as for example, *Malassezia spp.*, which can directly stimulate skin inflammation.²

The relative and temporal influences of all these mechanisms could explain the clinical heterogeneity observed among patients with AD.²

Clinical features and diagnostic

AD is a lifelong disease with highly variable clinical phenotypes, partly related to age, ethnicity and disease severity.^{2,7,29,33,34} AD is characterized by acute flare-ups of eczematous, oozing or weeping pruritic lesions over dry skin. Chronic lesions include red or brownish patches of dry, cracked or scaly skin with lichenification and prurigo nodules. Itchy skin, especially at night, results in sleep disturbance and fatigue, as well as mental health symptoms.^{2,7,9,18,23,29}

There is no specific diagnostic test or pathognomonic laboratory biomarker for AD diagnosis, which is established by characteristic clinical features, pruritus, disease evolution and a personal and/or family history of atopy.^{6,14,25} The most typical feature, the elevation of total or allergen-specific IgE levels in serum, is not present in all individuals, presumably distinguishing two forms of the disease, the non-IgE-associated ('intrinsic') AD and the IgE-associated ('extrinsic') AD.^{6,14,18}

Clinical diagnosis is usually easy except in infants, toddlers and in elderly people, which present more-atypical clinical features. Skin biopsies can help to exclude other common diseases mimicking, coexisting or complicating AD, malignant diseases such as cutaneous T-cell lymphoma or, remarkably in childhood, other rare diseases such as primary immunodeficiencies and nutritional deficiencies. To support diagnosis, several sets of criteria have been proposed over time, but the original Hanifin and Rajka criteria³⁵ remain the most widely used worldwide.¹⁴ The Hanifin and Rajka criteria and the American Academy of Dermatology Consensus Criteria both distinguish the so-called essential, common and associated features of AD and can be useful in the clinical setting.^{2,33,35–37} Accordingly,

the essential features are intense itch; acute, subacute or chronic eczematous lesions; and a chronic or relapsing disease course. AD lesions can occur on any body part, although typically showing an age-related distribution pattern. Infants often show widely distributed and more-acute skin lesions characterized by severe erythema, oedema, excoriations and serous exudate manifesting as oozing and crusting, characteristically located on the face/ cheeks and trunk, with sparing of the diaper area. In childhood, AD becomes more localized and chronic with paler erythema, xerosis and skin thickened from repetitive scratching commonly affecting flexor surfaces. Adolescents and adults can have a diffuse pattern of AD but also localized lesions, most typically affecting hands, eyelids and flexures. Adults can present only with chronic hand AD or the head-and-neck subtype of AD, which involves the upper trunk, shoulders and scalp.^{2,18,23,25,29}

Other features that are commonly observed but that are not a prerequisite to establish diagnosis, include early onset (typically during the first year of life), a personal and/or family history of atopic diseases, specific IgE reactivity and the presence of generalized skin dryness.^{2,7} Morphological subtypes of AD include the follicular type, which is characterized by densely aggregated follicular papules and is frequent in dark-skinned individuals and people of Asian origin;²⁵ and the chronic prurigo type, which is characterized by erythematous, often excoriated papules and indurated nodules and is sometimes seen in patients with long-standing disease.²

Disease severity and quality of life

Clinical measures are the basis to define the severity of AD and to assess therapy outcomes. The overall disease severity must be determined by evaluating both objective signs (physician assessments of disease severity) and subjective symptoms (patient-reported symptoms and QoL outcomes). The most commonly used tools for assessing AD severity include Eczema Area and Severity Index (EASI); SCORing Atopic Dermatitis (SCORAD); Physician Global Assessment (PGA); body surface area (BSA); Atopic Dermatitis Severity Index (ADSI); Six Area, Six Sign Atopic Dermatitis (SASSAD); Patient Oriented Eczema Measure (POEM); Dermatology Life Quality Index (DLQI); and pruritus Numerical Rating Scale (NRS).^{2,6,14,38–41}

SCORAD and EASI measure AD signs and the extent of the area affected.² SCORAD attributes around 60% of the total score to the intensity of lesions, 20% to spread and 20% to subjective signs scored by the patient.² A SCORAD > 50 is regarded as severe, while SCORAD scores < 25 are considered mild.¹⁴ The patient-oriented SCORAD (PO-SCORAD) is a physician-independent tool for assessing AD severity.¹⁴ In contrast, EASI is a signs-only score that assesses visible lesions only, giving the same weight to both intensity and extent of the lesions, without evaluating AD subjective symptoms.^{2,14} POEM is a symptoms-only score to measure the subjective symptoms in clinical trials, but not the objective signs.¹⁴ POEM and

PO-SCORAD are the preferred instruments to measure patient-reported symptoms in AD trials.^{2,42} The Investigators Global Assessment (IGA), based on an investigator-only single assessment, is also a frequently used tool.¹⁴ Since both objective and subjective assessments of disease severity are important, clinical characteristics such as disease recurrence or persistence and location of affected areas should be reflected in the overall judgement of disease severity and consideration of therapy choice.^{18,41}

DLQI and the Infants' Dermatology Quality of Life Index (IDQOL) are the QoL instruments most commonly used in AD, taking into account the different disease domains, in particular signs and symptoms; sleep quality; work performance and social and emotional well-being; to quantify the different aspects of the individual burden of AD in a real-world setting.^{43–45}

However, no well-validated instrument that can quantify the physical, social, emotional, cognitive, work-related and disease-related symptoms, as well as the AD economic impact, and perform well in both sexes and across all ages and ethnic groups, has been identified, turning the development and validation of new health-related quality of life (HRQoL) instruments a preeminent need.⁴⁶ There is a similar need to delineate clear, practical definitions and severity measures for AD in the clinical setting.⁶

In general, most AD cases can be regarded as mild, both in children and adults, but 10% – 18% suffer from severe AD. While 67% of children with AD present with mild disease and the remaining present with moderate-to-severe AD,² the percentage of severe cases seems to be higher in the adult AD population.¹⁴

Comorbidities

Patients with AD are at a slightly, but significantly, increased risk of all-cause mortality compared to the general population.⁵ The relation between AD and food allergy, asthma, and allergic rhinitis as part of the 'atopic march' has been extensively documented. AD is also associated with an increased risk of irritant and allergic contact dermatitis, and hand dermatitis.^{2,4,5,12,18}

Remarkably in children, sleep disturbances may be related with growth impairment, lower school performance, attention deficit hyperactivity disorders, and higher accident risks.⁹

Potentially under-recognized AD non-allergic comorbidities include cutaneous and extra-cutaneous infections, other autoimmune- or immune-mediated diseases, neuropsychiatric conditions, and emerging comorbidities, such as obesity, cardiovascular and metabolic diseases, as well as specific cancers.^{2,5–7,9,13,14,18,25,27}

The causative mechanisms underlying these associations are largely unknown, and the absolute magnitude of the risks has not been well defined.⁵ Many of these comorbid conditions are directly related to the underlying severity of AD and inadequate disease control. On the other hand, most of these comorbidities affect children, while others occur during adulthood in patients with long-standing

disease, supporting the systemic nature of AD, and suggesting that measures taken during childhood to reduce disease severity could protect against its development. Therefore, increased surveillance, early detection, and optimizing management are essential to prevent or mitigate the risk for these costly and burdensome comorbidities.^{5,9}

Prevention

Due to the childhood prevalence of the disease, prevention is focused on the perinatal period. It is recognized that prevention should start as soon as possible, targeting the skin barrier, immune/allergy and environmental aspects.²³ Primary prevention approaches including dietary supplementation, breastfeeding, hypoallergenic milks with hydrolysed formulas, prebiotics and probiotics, have shown inconsistent results and, until now, have failed to show significant effect on decreasing the risk of developing AD.^{7,47–49} Large studies about elimination diets conclude that this approach is not advisable and could even impair oral tolerance. In fact, early exposure to peanut, egg and yogurt could reduce the risk of sensitization.^{7,50–52} As genetic and inflammation-driven changes of epidermal barrier function contribute to AD onset, the daily use of emollients from birth in new-borns at a high risk of developing AD could be an effective prevention strategy.^{2,7,23,25,53,54}

Although influencing the genetic background is not yet feasible, secondary prevention strategies based on trigger avoidance have been implemented in practical guidelines.⁵⁵ Irritants such as air or indoor pollutants can affect patients with sensitive skin and lead to AD exacerbations.³¹ The spectrum of relevant allergens changes with the course of the disease, with food allergens inducing flares in some infants with moderate-to-severe AD, whereas environmental allergens such as house dust mite, pollen or animal fur

seem to be more relevant triggers in older children and adults.^{2,56,57}

Nevertheless, the avoidance of potential allergens is still a matter of debate. The clinical relevance of IgE specific for a suspected allergen can be ascertained by the atopy patch test or by exposure tests in a sealed chamber for aeroallergens. For suspected food allergy the current guidelines propose the suspected food administration in a blinded provocation test. However, these tests remain controversial and avoidance recommendations should only be suggested when there is proven evidence of relevant allergen sensitization. Even in such cases, the impact of avoidance strategies might be marginal.^{2,25,58}

Disease management and therapeutic approaches

Management of AD must consider the individual clinical variability of the disease; therefore, highly standardized treatment rules are not recommended.¹⁴ The aims of therapy goals are reducing pruritus and establishing persistent disease control that is sufficient to enable patients to be fully functional at home, work and school. Hence, a multistep approach with interventions aimed at avoiding relevant triggers, improving the skin barrier, normalizing the skin dysbiosis and reducing inflammation, is mandatory.^{2,7,23,25}

Therapy selection is largely based on disease severity (Table 1), with adjustments based on the patients' age, presence of atopy-related and unrelated comorbidities, treatment response, compliance concerns and cost. Treatment should be paired with a formal patient and caregiver treatment education program in order to achieve the best outcomes.^{2,12,14,15,18,25}

Microbial colonization and superinfection may cause disease exacerbation and require additional treatment. Allergen-specific immunotherapy with aeroallergens may be

Table 1 – Treatment recommendations for adults and children with atopic dermatitis (adapted from the European guidelines for treatment of atopic eczema)^{14,15}

Atopic dermatitis severity	Treatment recommendations	
	Children	Adults
Baseline: Basic therapy	Educational programs, emollients, bath oils, and avoidance of clinically relevant allergens	
Mild: SCORAD < 25 or transient eczema	Reactive therapy with topical glucocorticosteroids class II ⁱ or depending on local cofactors (topical calcineurin inhibitors ⁱ , antiseptics including silver, silver coated textiles)	Reactive therapy with topical glucocorticosteroids class III ⁱ or depending on local cofactors (topical calcineurin inhibitors ⁱ , antiseptics including silver, silver coated textiles)
Moderate: SCORAD 25 – 50 or recurrent eczema	Proactive therapy with topical tacrolimus ⁱ or glucocorticosteroids class II or III ⁱ , wet wrap therapy, UV therapy (UVB 311 nm) ⁱⁱⁱ , psychosomatic counselling, climate therapy	Proactive therapy with topical tacrolimus ⁱ or glucocorticosteroids class III ⁱ , wet wrap therapy, UV therapy (UVB 311 nm, medium dose UVA1), psychosomatic counselling, climate therapy
Severe: SCORAD > 50 or persistent eczema	Hospitalization, systemic immunosuppression: cyclosporine A ⁱⁱ , methotrexate ⁱⁱ , azathioprine ⁱⁱ , mycophenolate mofetil ⁱⁱⁱ	Hospitalization, systemic immunosuppression: cyclosporine A ⁱ , short course of oral glucocorticosteroids ⁱ , dupilumab ⁱⁱⁱ , methotrexate ⁱⁱ , azathioprine ⁱⁱ , mycophenolate mofetil ⁱⁱⁱ , PUVA ⁱⁱⁱ , alitretinoin ⁱⁱⁱ

ⁱ Licensed indication; ⁱⁱ Off-label treatment options; ⁱⁱⁱ Treatment restrictions should be taken cautiously.

Additional therapeutic options should be considered for every phase; antiseptics/ antibiotics should be added in case of superinfection; if therapy has insufficient effect compliance and diagnosis should be considered.

considered in selected cases. Psychosomatic counselling is recommended in stress-induced exacerbations.^{15,19} Pruritus is targeted with most of the recommended therapies that target inflammation and skin barrier disruption, but some patients may need additional therapy (cannabinoid receptor agonist, opioid receptor antagonists, memolizumab).^{14,25,59}

The identification of individual trigger factors is crucial to the management of AD, and their avoidance allows longer phases of remission or total clearance of symptoms. Numerous environmental factors can irritate the AD skin and elicit eczema flares, namely mechanical irritants (e.g. wool, irritant fabrics and fibres), chemicals (acids, bleaches, solvents, surfactants in cosmetic and hygiene products), biological (allergens, microbes), and air pollutants, like tobacco smoke, volatile organic compounds, and traffic exhaust. Also, adequate skin care and hygiene procedures in cleansing, bathing and dressing play a relevant role in AD management and should be discussed with the patient and included in the above-mentioned educational intervention.^{6,7,12,14,18}

Basic therapy is also focused on treating disturbed barrier function by hydrating and lubricating topical treatment, the backbone of therapy for patients with mild-to-moderate AD, along with adequate cleansing/bathing practices.^{6,12,14,18,25} When used on a daily basis, moisturizers with non-aqueous emollients, occlusive agents and humectants improve barrier function, reduce AD signs and symptoms, and the need for topical corticosteroids.²

Topical anti-inflammatory treatment based on corticosteroids and calcineurin inhibitors is indicated for flare management and for proactive therapy for long-term control. Topical corticosteroids (TCSs) remain the first line treatment, reducing disease recurrence when used intermittently in patients with established disease.^{2,12,14,18,25} TCSs are grouped into classes according to anti-inflammatory potency, and selection of steroid should be guided by location, extent and acute or chronic nature of skin lesions, patients' age, and disease severity. Low-potency TCSs are indicated for mild disease, flexural and facial skin lesions, young children and pregnant women.^{2,12,18} High potency TCSs are preferred for older patients, lichenified and chronic prurigo-like lesions and palms. Topical calcineurin inhibitors (TCIs), tacrolimus and pimecrolimus, approved for short-term and chronic intermittent use in children aged 2 and older and adults, are preferred in sensitive skin areas, such as face and flexural skin.^{2,12,14,18,25} TCIs inhibit cutaneous T cell activation and proliferation and may also have epidermal barrier repair actions. Their use is limited by reduced efficacy, burning or pruritus commonly observed during the first week of use (especially with tacrolimus), and cost.² Topical phosphodiesterase inhibitors, like crisaborole, a new topical anti-inflammatory class that inhibits the intracellular enzyme cAMP-specific 3',5'-cyclic phosphodiesterase 4 (PDE4), could offer another topical nonsteroidal option for individuals with mild-to-moderate AD or in anatomically sensitive sites.^{2,7,14}

If disease control cannot be achieved with topical measures, short-term phototherapy should be considered as

adjuvant. UV irradiation, preferably with narrow-band ultraviolet B (NB-UVB/UVB 311 nm) and medium-dose ultraviolet A1 (UVA1) light, is the most effective.^{2,6,12,14,18,25}

When topical therapies and phototherapy fail or become unacceptable or impractical, systemic therapy is indicated.^{25,60} Systemic non-biologic therapies include the non-specific immunosuppressants cyclosporine, azathioprine, methotrexate and mycophenolate mofetil, which are the established and widely available options for severe refractory cases.^{2,14,15} Cyclosporine, the only systemic drug licensed for short-term treatment of AD (not more than 1 – 2 years), was the most effective but its use is limited by potential toxicities, particularly nephrotoxicity.^{2,25} Azathioprine and methotrexate are effective and safe off-label treatments for severe AD, even in children. Mycophenolate mofetil, also used off-label for AD, has a more-favourable safety profile, but a more-limited efficacy, and is considered a third line option or a maintenance therapy after disease control with another more-effective systemic treatment. Studies showed azathioprine and mycophenolate mofetil have very similar drug survival profiles, but azathioprine was discontinued mainly because of adverse effects, whereas mycophenolate mofetil was discontinued mainly owing to ineffectiveness.² Although approved for AD treatment, published treatment guidelines suggest that systemic corticosteroids should be used as a last resort to manage acute flares or as a bridge to the use of another systemic, steroid-sparing therapy, and not for long-term management of AD.^{2,6,25,61}

Targeting the Th2 pathway with dupilumab, a fully human monoclonal antibody against IL-4R α that blocks both IL-4 and IL-13 signalling, may be a safe and effective, disease-modifying alternative. It showed significant improvements in disease severity and increased the number of patients achieving a response, particularly when combined with TCSs.^{2,7,12,62} Dupilumab was the first biological drug approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of adults with moderate-to-severe AD and trials are underway to assess its safety as well as its effectiveness in the paediatric population.²

Several therapies are in the late stages of clinical development for AD. Many biologics and small molecule antagonists are actually in phase II and phase III trials targeting different pathways, including Th2 immune response, JAK signalling and itch mediators, among others.^{7,15} Many JAK inhibitors are in development as oral therapies for moderate-to-severe AD or as topical treatments for mild-to-moderate AD. JAK inhibitors block a range of cytokines, growth factors and/or hormone receptor signalling pathways depending on their relative specificity.^{2,6,7,15} Monoclonal antibodies, such as mepolizumab, benralizumab and reslizumab, all three approved to treat asthma, have been developed to neutralize IL-5, which promotes eosinophil recruitment. Thus far, only mepolizumab has been evaluated in AD with unfavourable results, which question the benefit of this anti-eosinophil strategy in adult patients. Ustekinumab, a FDA-approved therapy for psoriasis, which

targets the common p40 subunit of IL-12 and IL-23, failed to show efficacy in adults with moderate-to-severe AD.^{2,7}

Despite these options, the treatment of moderate-to-severe AD remains challenging and novel, efficacious, safe and targeted treatments are urgently needed.

CONCLUSION

AD is one of the most prevalent diseases worldwide and is associated with a very burdensome impact on health-care resources and patients and caregivers' QoL. Moreover, AD is associated with numerous medical and mental health comorbidities, with important implications for its management and treatment. Considering there is also increasing evidence that AD may progress to other allergic phenotypes, a clear need to improve disease prevention arises.

The systemic nature of the disease leads to an urgent need for a more systemic approach to establish safe and effective therapies that target its pathophysiology, which is more complex than previously recognized and not yet fully understood.

The study of AD is a fast-moving field and despite enormous steps forward, a greater understanding of the disease is required. Future research in AD must now focus on exploring gene-environment interactions and its effect on pathophysiology, disease severity, and treatment outcomes.

REFERENCES

- Torres T. Atopic dermatitis: the new therapeutic revolution in dermatology. *Acta Med Port.* 2017;30:669–70.
- Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers.* 2018;4:1.
- Bieber T. How to define atopic dermatitis? *Dermatol Clin.* 2017;35:275–81.
- Milam EC, Jacob SE, Cohen DE. Contact dermatitis in the patient with atopic dermatitis. *J Allergy Clin Immunol Pract.* 2019;7:18–26.
- Paller A, Jaworski JC, Simpson EL, Boguniewicz M, Russell JJ, Block JK, et al. Major comorbidities of atopic dermatitis: beyond allergic disorders. *Am J Clin Dermatol.* 2018;19:821–38.
- Boguniewicz M, Alexis AF, Beck LA, Block J, Eichenfield LF, Fonacier L, et al. Expert perspectives on management of moderate-to-severe atopic dermatitis: a multidisciplinary consensus addressing current and emerging therapies. *J Allergy Clin Immunol Pract.* 2017;5:1519–31.
- Tsakok T, Woolf R, Smith CH, Weidinger S, Flohr C. Atopic dermatitis: the skin barrier and beyond. *Br J Dermatol.* 2019;180:464–74.
- Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Health utility scores of atopic dermatitis in US adults. *J Allergy Clin Immunol Pract.* 2019;7:1246–52.e1.
- Silverberg JI. Associations between atopic dermatitis and other disorders. *F1000Res.* 2018;7:303.
- Brunner PM, Silverberg JI, Guttman-Yassky E, Paller AS, Kabashima K, Amagai M, et al. Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. *J Invest Dermatol.* 2017;137:18–25.
- Malik K, Heitmiller KD, Czarnowicki T. An update on the pathophysiology of atopic dermatitis. *Dermatol Clin.* 2017;35:317–26.
- Brar KK, Nicol NH, Boguniewicz M. Strategies for successful management of severe atopic dermatitis. *J Allergy Clin Immunol Pract.* 2019;7:1–16.
- Ascott A, Mulick A, Yu AM, Prieto-Merino D, Schmidt M, Abuabara K, 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.
- Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol.* 2018;32:657–82.
- Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, 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.
- Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, Margolis DJ, 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.
- Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. *PLoS One.* 2012;7:e39803.
- Waldman AR, Ahluwalia J, Udoff J, Borok JF, Eichenfield LF. Atopic dermatitis. *Pediatr Rev.* 2018;39:180–93.
- Abuabara K, Yu AM, Okhovat JP, Allen E, Langan SM. The prevalence of atopic dermatitis beyond childhood: A systematic review and meta-analysis of longitudinal studies. *Allergy.* 2018;73:696–704.
- Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol.* 2013;132:1132–8.
- Carmo M, Andrade S, Mendes-Bastos P. Patients under atopic dermatitis treatment in Portugal: results from a physicians' survey. *Barcelona: ISPOR Europe; 2018.*
- Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. *Allergy.* 2018;73:1284–93.
- Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab.* 2015;66:S8–16.
- DaVeiga SP. Epidemiology of atopic dermatitis: a review. *Allergy Asthma Proc.* 2012;33:227–34.
- Kapur S, Watson W, Carr S. Atopic dermatitis. *Allergy Asthma Clin Immunol.* 2018;14:S52.
- Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol.* 2009;124:1251–8.e23.
- Davies E, Rogers NK, Lloyd-Lavery A, Grindlay DJ, Thomas KS. What's new in atopic eczema? An analysis of systematic reviews published in 2015. Part 1: epidemiology and methodology. *Clin Exp Dermatol.* 2018;43:375–9.

CONFLICTS OF INTEREST

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28. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol.* 2011;131:67–73.
29. Silverberg JI. Adult-onset atopic dermatitis. *J Allergy Clin Immunol Pract.* 2019;7:28–33.
30. Ferreira EO. Análise da estatística nosológica nacional 2009–2013. Grupo Português de Dermatologia Pediátrica. *Rev Soc Port Dermatol Venereol.* 2016;74:169–73.
31. Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. *Expert Rev Clin Immunol.* 2017;13:15–26.
32. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res.* 2012;22:850–9.
33. Torreló A. Atopic dermatitis in different skin types. What is to know? *J Eur Acad Dermatol Venereol.* 2014;28:S2–4.
34. Weidinger S, Novak N. Atopic dermatitis. *Lancet.* 2016;387:1109–22.
35. Hanifin J, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol.* 1980;92:S44–7.
36. Silverberg NB. Typical and atypical clinical appearance of atopic dermatitis. *Clin Dermatol.* 2017;35:354–9.
37. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, 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.
38. Chopra R, Vakharia PP, Sacotte R, Patel N, Immaneni S, White T, et al. Severity strata for Eczema Area and Severity Index (EASI), modified EASI, Scoring Atopic Dermatitis (SCORAD), objective SCORAD, Atopic Dermatitis Severity Index and body surface area in adolescents and adults with atopic dermatitis. *Br J Dermatol.* 2017;177:1316–21.
39. Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *Br J Dermatol.* 2015;172:1353–7.
40. 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.
41. Gooderham MJ, Bissonnette R, Grewal P, Lansang P, Papp KA, Hong CH. Approach to the assessment and management of adult patients with atopic dermatitis: a consensus document. Section II: tools for assessing the severity of Atopic dermatitis. *J Cutan Med Surg.* 2018;22:10S–6.
42. Spuls PI, Gerbens LA, Apfelbacher CJ, Wall D, Arents BW, Barbarot S, et al. The International TREATment of ATopic Eczema (TREAT) Registry Taskforce: an initiative to harmonize data collection across national atopic eczema photo- and systemic therapy registries. *J Invest Dermatol.* 2017;137:2014–16.
43. Hill MK, Kheirandish Pishkenari A, Braunberger TL, Armstrong AW, Dunnick CA. Recent trends in disease severity and quality of life instruments for patients with atopic dermatitis: a systematic review. *J Am Acad Dermatol.* 2016;75:906–17.
44. Finlay AY, Basra MK, Piguat V, Salek MS. Dermatology life quality index (DLQI): a paradigm shift to patient-centered outcomes. *J Invest Dermatol.* 2012;132:2464–5.
45. Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *Br J Dermatol.* 2008;159:997–1035.
46. Heintz D, Prinsen CA, Sach T, Drucker AM, Ofenloch R, Flohr C, et al. Measurement properties of quality-of-life measurement instruments for infants, children and adolescents with eczema: a systematic review. *Br J Dermatol.* 2017;176:878–89.
47. Bath-Hextall FJ, Jenkinson C, Humphreys R, Williams HC. Dietary supplements for established atopic eczema. *Cochrane Database Syst Rev.* 2012;15:CD005205.
48. Høst A, Halken S, Muraro A, Dreborg S, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. *Pediatr Allergy Immunol.* 2008;19:1–4.
49. Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach JF, et al. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. *Epidemiology.* 2012;23:402–14.
50. Van Bever HP, Nagarajan S, Shek LP, Lee BW. OPINION: Primary prevention of allergy — Will it soon become a reality? *Pediatr Allergy Immunol.* 2016;27:6–12.
51. Feeney M, Du Toit G, Roberts G, Sayre PH, Lawson K, Bahnson HT, et al. Impact of peanut consumption in the LEAP Study: Feasibility, growth, and nutrition. *J Allergy Clin Immunol.* 2016;138:1108–18.
52. Roduit C, Frei R, Loss G, Büchele G, Weber J, Depner M, et al. Development of atopic dermatitis according to age of onset and association with early-life exposures. *J Allergy Clin Immunol.* 2012;130:130–6.e5.
53. Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol.* 2014;134:818–23.
54. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol.* 2014;134:824–830.e6.
55. Mohan GC, Lio PA. Comparison of dermatology and allergy guidelines for atopic dermatitis management. *JAMA Dermatol.* 2015;151:1009–13.
56. Roerdink EM, Flokstra-de Blok BM, Blok JL, Schuttelaar ML, Niggemann B, Werfel T, et al. Association of food allergy and atopic dermatitis exacerbations. *Ann Allergy Asthma Immunol.* 2016;116:334–8.
57. Werfel T, Heratizadeh A, Niebuhr M, Kapp A, Roesner LM, Karch A, et al. Exacerbation of atopic dermatitis on grass pollen exposure in an environmental challenge chamber. *J Allergy Clin Immunol.* 2015;136:96–103.e9.
58. Wollenberg A, Oranje A, Deleuran M, Simon D, Szalai Z, Kunz B, 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.
59. Pereira MP, Mittal A, Ständer S. Current treatment strategies in refractory chronic pruritus. *Curr Opin Pharmacol.* 2018;46:1–6.
60. Simpson EL, Bruin-Weller M, Flohr C, Ardern-Jones MR, Barbarot S, Deleuran M, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol.* 2017;77:623–33.
61. Drucker AM, Eyerich K, de Bruin-Weller MS, Thyssen JP, Spuls PI, Irvine AD, et al. Use of systemic corticosteroids for atopic dermatitis: International Eczema Council consensus statement. *Br J Dermatol.* 2018;178:768–75.
62. Thomson J, Wernham AG, Williams HC. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a critical appraisal. *Br J Dermatol.* 2018;178:897–902.