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Special Article

Severe atopic dermatitis: a practical treatment guide from the Brazilian Association of Allergy and Immunology and the Brazilian Society of Pediatrics

Dermatite atópica grave: guia prático de tratamento da Associação Brasileira de Alergia e Imunologia e Sociedade Brasileira de Pediatria

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ABSTRACT

Atopic dermatitis is a chronic, common, and complex inflammatory skin disease with a multifactorial etiology. It manifests clinically with often disabling pruritus, recurrent eczema-like lesions, and xerosis, and can progress to lichenification. Although understanding of the disease's pathophysiology has been growing in recent years, severe forms are still frequent and represent a challenge for clinicians. A non-systematic review of the literature on severe atopic dermatitis refractory to conventional treatment was conducted to develop the present guide, whose purpose is to help clarify the mechanisms involved in the disease and possible risk factors. The integrity of the skin barrier is fundamental for maintaining skin homeostasis. In addition to general care, patients should avoid triggering and/or irritating agents and moisturizers and seek emotional support, etc.; the use of topical and/or systemic anti-inflammatory/immunosuppressive agents was also reviewed. New agents, immunobiologicals, and small molecules have led to a broader range of therapies for patients with severe forms of the disease, especially cases refractory to conventional treatment.

Keywords: Atopic dermatitis, skin hydration, topical corticosteroids, calcineurin inhibitors, cyclosporine, immunobiologicals, dupilumab, JAK inhibitors.

RESUMO

A dermatite atópica (DA) é uma doença cutânea inflamatória, crônica, comum, complexa e de etiologia multifatorial, que se manifesta clinicamente com prurido muitas vezes incapacitante, lesões recorrentes do tipo eczema, xerose e que pode evoluir para liquenificação. Embora o conhecimento sobre a sua fisiopatologia venham crescendo nos últimos anos, ainda as formas graves são frequentes e representam um desafio para o clínico. Para o presente guia realizou-se revisão não sistemática da literatura relacionada à DA grave refratária aos tratamentos habituais com o objetivo de elaborar um documento prático e que auxilie na compreensão dos mecanismos envolvidos na DA, assim como dos possíveis fatores de risco associados à sua apresentação. A integridade da barreira cutânea é um dos pontos fundamentais para a manutenção da homeostase da pele. Além dos cuidados gerais: evitação dos agentes desencadeantes e/ou irritantes, o uso de hidratantes, suporte emocional, entre outros, o uso de agentes anti-inflamatórios/imunossupressores de uso tópico e/ou sistêmico também foi revisado. A aquisição de novos agentes, os imunobiológicos e as pequenas moléculas, melhorou a terapêutica para os pacientes com formas graves de DA, sobretudo as refratárias aos tratamentos convencionais.

Descritores: Dermatite atópica, hidratação da pele, corticosteroides tópicos, inibidores da calcineurina, ciclosporina, imunobiológicos, dupilumabe, inibidores de JAK.

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Introduction

Atopic dermatitis (AD) is a chronic, common, and complex inflammatory skin disease with a multifactorial etiology. It manifests clinically with often disabling pruritus, recurrent eczema-like lesions, and xerosis, and can progress to lichenification. Distribution and morphology of the skin lesions are variable, onset is generally before 2 years of age, and patients have personal and family history of atopic disease.[1]

In the absence of a conclusive diagnostic laboratory test and because of the great variation in the signs and symptoms observed in different geographic regions and at different ages, diagnosis of AD is based on the presence and distribution pattern of the lesions in combination with clinical findings and the personal and family history of atopic disease. For some time, the Hanifin-Rajka criteria have been the most widely used for diagnosis (Table 1).[2] This diagnostic definition comprises 4 major criteria and 22 minor criteria. Presence of at least three major criteria and three minor criteria identifies an AD patient.[2]

Other diagnostic criteria have been introduced since: the Williams criteria[3] (Table 2) and, more recently, the American Academy of Dermatology criteria, which added a number of exclusionary criteria that must be ruled out to diagnose AD with greater precision (Table 3).[4]

Globally, studies of AD prevalence have predominantly concentrated on the pediatric population and studies in adults are rarer. The heterogeneous nature of the samples studied, the age groups, and the criteria employed all contribute to discrepancies in the results reported.[5,6]

The study of AD prevalence that has covered the largest numbers of countries and research centers is the International Study of Asthma and Allergies in Childhood (ISAAC). It was conducted at 154 different centers in 56 countries including more than 750,000

Table 1
Principal signs, symptoms, and laboratory data used to diagnose atopic dermatitis according to the Hanifin-Rajka criteria[2]

Major criteria (≥ 3)
1. Pruritus
2. Typical morphology and distribution of lesions – Flexural lichenification or linearity in adults – Facial and extensor involvement in children
3. Chronic or chronically relapsing dermatitis
4. Personal or family history of atopic disease (asthma, allergic rhinitis, atopic dermatitis)

Minor criteria	
1. Xerosis	12. Anterior subcapsular cataracts
2. Ichthyosis, palmar hyperlinearity, keratosis pilaris	13. Orbital darkening
3. Positive prick-test	14. Facial pallor or erythema
4. Raised serum IgE	15. Pityriasis alba
5. Tendency to cutaneous infections (*S. aureus*/Herpes)	16. Itch when sweating
6. Tendency to non-specific hand or foot dermatitis	17. Anterior neck folds
7. Nipple eczema	18. Intolerance to wool and lipid solvents
8. Cheilitis	19. Perifollicular accentuation
9. Recurrent conjunctivitis	20. Food intolerance
10. Dennie-Morgan infraorbital fold	21. Course influenced by environmental or emotional factors
11. Keratoconus	22. White dermographism

children in two different age groups (6-7 years and 13-14 years) and administering a standardized instrument at different points in time. The study reported previous 12 months AD prevalence for the 6-7 years age group ranging from 0.9 in India to 22.5% in Ecuador and prevalence in the 13-14 group ranging from 0.2% in China to 24.6% in Colombia. In Brazil, phase III of the ISAAC study reported an 8.2% mean prevalence of eczema for 6-7 year-olds and 5.0% for 13-14 year-olds.[7] The prevalence of severe forms was around 1.5% in both age groups.[7]

Among infants (12 to 15 months), the International study of Wheezing in Infants (EISL) documented elevated rates in children from Europe and Latin America, at 14.2% and 18.2% respectively.[8,9] A recent systematic review assessed 378 studies with sufficient quality for the analysis, of which 352 investigated prevalence and just 26 reported incidence of AD, the majority in children. The overall AD prevalence in children ranged from 1.7% to 32.8%, while the previous year prevalence with a physician diagnosis was from 0.96% to 22.6%. In adults, overall prevalence varied from 1.2% to 9.7% and the previous year prevalence with a physician diagnosis ranged from 1.2% to 17.1%.[10]

Table 2
UK Working Party's atopic dermatitis diagnostic criteria – The Williams Criteria[3]

Skin pruritus during the last 12 months with ≥ 3 of the following criteria:
1. Onset under the age of 2 [a]
2. History of flexural involvement
3. Visible flexural dermatitis (or photo)
4. Personal/family history of asthma and allergic rhinitis [b]
5. History of generalized dry skin

[a] Not used in children < 4 years.
[b] In children < 4 years, family history of atopic diseases.

Table 3
Essential criteria, important findings, and associated features used to diagnose atopic dermatitis by the American Academy of Dermatology[4]

Essential criteria
Pruritus
Eczema (acute, subacute, or chronic) with typical morphology and age-specific patterns and with chronic or relapsing history
Important findings – help with diagnosis in many cases
Early onset
Atopic disease – personal or family, elevated IgE
Xerosis
Associated findings – useful, but nonspecific
Facial pallor, white dermographism, keratosis pilaris, pityriasis alba, ichthyosis, hyperlinear palms, ocular/periocular changes, perioral or auricular changes, lichenification
Conditions that should be ruled out
Scabies
Seborrheic dermatitis
Contact dermatitis (irritant or allergic)
Ichthyosis
Cutaneous T-cell lymphoma
Psoriasis
Photosensitivity dermatosis
Innate errors of immunity
Other causes of erythroderma

Atopic dermatitis has a considerable impact on the quality of life of patients and their families, especially in its moderate and severe forms. It is associated with many atopic comorbidities (allergic rhinitis, asthma, food allergies, and eosinophilic esophagitis) and also with several non-atopic comorbidities, in particular those involving mental health, with frequent associations with depression and anxiety. Over recent years, innovative systemic treatments have become available, including immunobiologicals and small molecules, which act selectively to inhibit cytokines that participate in the AD inflammatory process. These new drug classes offer superior efficacy and safety compared to systemic immunosuppressants and herald a new era in treatment for severe AD. The objective of this guide is to update treatment of severe AD, with a primary focus on the rationale underlying use of biologicals and small molecules.

Clinical features: natural history and phenotypes

In all patients with AD, the characteristic lesion is eczema and pruritus is an obligatory finding.[11] However, the clinical manifestations seen in patients with severe AD are amplified expressions of the clinical presentation of AD and the signs and symptoms are hugely exacerbated. Over the course of life, AD clinical presentation is variable and can be divided into four segments, as described below.

Dermatitis of the infant (0-2 years)

Lesions have onset around 2 months after birth, involving the face (cheeks), scalp, trunk, and extensor surfaces of the limbs. Acute lesions develop vesicles, exudate, scabs, and erythema. Xerosis is common and is observed in around 42% of patients.[12,13]

Dermatitis in the child (pre-pubertal, 2 to 12 years)

The flexor surfaces become more involved, in particular the popliteal fossa and cubital fossa. Hands and wrists may be more involved. The number of subacute, dry, and thickened lesions increases. Chronic lesions with some degree of lichenification may also be observed.[12,13]

Dermatitis in the adult (12-60 years)

Lesions are more widely distributed. In addition to flexural lesions, the head, neck, and hands may be involved. Xerosis is the most common skin complication in patients with AD, and persistence of dry skin can compromise the skin's barrier function and lead to changed microbiota. Lesions are chronic and lichenified, and patients may suffer from acute crises and an increased risk of viral infections.[12,13]

Dermatitis in the elderly adult (over 60 years)

This form is primarily characterized by extensive eczematous lesions and some patients may also have erythroderma with a strong pruriginous component. Lesions can sometimes spare flexural areas. This specific subset undoubtedly merits a more in-depth analysis to define clear clinical criteria for diagnosis. It should be emphasized that as with AD of the infant, differential diagnoses must be considered in the elderly, especially in severe cases.

The natural history of AD has been changing over the years, from lesions restricted to the pediatric age group, to a disease that extends into adulthood, and nowadays there are also reports of dermatitis with onset in the sixth decade of life.

Depending on age at onset of AD lesions, the natural history of AD can progress in the ways described below.

1. *Very early onset (3 months to 2 years)* – there are no Brazilian epidemiological studies, but according to the epidemiological studies that do exist, patients with early onset AD can account for from 60% to 80% of all forms of disease onset. A substantial proportion of patients may have full remission before 2 years of age, but around 40% will continue to exhibit the disease for a long time and may constitute a population at greater risk of allergic march.[14-16]
2. *Early onset (2 to 6 years)* – these patients are also at high risk of having other allergic diseases.[14-16]
3. *Childhood onset (6 to 14 years)* – this is a small group of patients and there are few studies that offer understanding of the risks or benefits of AD with onset at this age.[14,15]
4. *Adolescent onset (14 to 18 years)* – a small group of patients with little data in the literature and little information on progression.
5. *Adult onset (20 to 60 years)* – the third largest group of patients, primarily characterized by female patients, with a very mild clinical phenotype and sensitization spectrum, generally accompanied by normal serum IgE levels.[14,15]

6. *Very late onset (> 60 years)* – this is a recently identified group, which has already been separated into two subsets: those who have had AD in the past, followed by a long remission period, and those who first had the disease very late in life. Observational studies describe patients in this group who have a very severe form of the disease and high total serum IgE levels.[14,15]

Different patterns of progression can also be observed in the clinical course and severity of the disease, which can be subdivided into five underlying types: (1) onset in childhood, progressing to remission; (2) relapsing-remitting disease; (3) persistent chronic disease; (4) long periods of remission followed by recurrence; and (5) onset in adolescence or adulthood. Types 3 and 5 are predominantly moderate and severe forms of the disease.[17]

Phenotypes

As already described, the behavior of AD can vary depending on the age at onset of symptoms, but other factors can also influence the course of the disease and define diverse phenotypes. Classifying AD by severity is another approach to delineating phenotypes, but one that involves challenges. It is important to define severity using validated and widely-adopted severity scores (see assessing severity). Attempts have been made to ensure that the two most widely used scores, SCORAD (Scoring Atopic Dermatitis) and EASI (Eczema Area and Severity Index), can achieve equivalent results, to facilitate standardization and comparability of the population being assessed.

Presence of elevated serum IgE also defines an AD phenotype: *extrinsic* dermatitis, which is present in 80% of cases and is defined by elevated total serum IgE levels with mutation of the filaggrin gene in approximately 30%, presence of other atopic diseases, including food allergy, and a possible association with palmar hyperlinearity. In contrast, *intrinsic* AD is more common in adults, primarily women, and there is a possibility of an association with contact dermatitis, particularly when provoked by nickel.[15,16,18]

Definition of clinical phenotypes of AD also raises important issues for discussion. It must be emphasized that, in addition to the classic clinical presentation of AD, other less usual presentations can also constitute atopic stigmata. These include:[16,18]

– *nummular eczema:* coin-shaped lesions that may be atypical presentations of AD, but it is important to remember that not all patients who develop nummular eczema will actually have the same pathophysiologic basis as AD;
– *prurigo nodularis:* hyperkeratotic and extremely itchy papules, which may or may not be related to AD;
– *eczema located on the eyelids, hands and feet, or nipples or angular cheilitis.* If these clinical presentations are associated with other atopic diseases, they may be interpreted as atypical manifestations of AD. Differential diagnosis is essential in these situations,.

Table 4 lists the possible phenotypes of AD, defined on the basis of age group, age of onset, presence or absence of elevated IgE, disease severity, ethnicity, and classical clinical presentation or otherwise.

Immunopathogenesis

There is now a very large body of knowledge about the physiopathogenesis of AD and the most relevant findings appear to be those involving genetic disorders, changes to the cutaneous barrier, immunological dysregulation, and changes to the cutaneous microbioma.

For many years, it was believed that AD was an "inside-out" disease, i.e., that the inflammatory process started in the dermis, leading to damage to the barrier as a consequence. With current knowledge that the inflammation is caused by or starts with changes to the cutaneous barrier, it became recognized as a disease that is predominantly "outside-in".[20]

Cutaneous barrier

Changes to the cutaneous barrier are caused by many factors. One of the first factors known was destruction of corneocytes by excessive protease actions in corneodesmosomes (washing with alkaline soaps, increased skin pH, staphylococcal infection with production and release of enterotoxins) or because of a failure to inhibit these proteases when they exercise their excessive action. The result is a loss of cellular integrity and cohesion or disarrangement of cells. Corneocytes are keratinocytes from the corneum stratum that produce and release antimicrobial peptides, which are one of the elements of innate immune response. They are important in defense

Table 4
Clinical phenotypes of atopic dermatitis (AD), by clinical characteristics, IgE levels, and ethnicity

Differentiating feature	Classification
Clinical presentation	AD in children or AD in adults
Age at disease onset	Early or late
Presence of elevated IgE	Extrinsic or intrinsic
Severity	Mild, moderate, severe
Ethnicity	Euroamerican or Asian subtypes
Clinical presentation	Classic, nummular eczema, eczema of the hands

against microbial aggression and also produce ceramides and cholesterol, which are components of the natural moisturizing factor. We can therefore state that accelerated destruction of corneocytes increases permeability of the defensive barrier, impairing defense, and also reduces the levels of lipids in the skin.[21]

Reduced levels of filaggrin (because of mutations or acquired deficiencies) and other structural skin proteins, such as loricrin and involucrin, also change the cutaneous barrier. Filaggrins are proteins derived from pro-filaggrins that are found in the deeper layers of the skin and which migrate toward the stratum corneum under the action of keratohyalin granules. Enzymatic activity transforms them into fatty acids and they become an important component of the lamellar lipid layer. Some studies have described filaggrin as a substance that behaves as an intercellular cement that increases adhesion between cells.[22]

Junction proteins are members of the physical barrier that are located immediately below the stratum corneum. Claudins, primarily claudin-1, play an important role in these defenses. Mutations of the claudin gene reduce its expression and increase barrier permeability.[23]

All of these mechanisms, like cell disorganization and reduction of proteins such as filaggrin and claudin are important to explain how the skin defends itself from aggressions or how these changes to the level of the cutaneous barrier compromise the skin's integrity, making it possible for allergens and pathogens to penetrate.

A poor cutaneous microbioma, with low microbial diversity (dysbiosis) and deficiencies of antimicrobial peptides, contributes greatly to cutaneous infections, particularly by staphylococcal strains.[24]

Immunological dysregulation

The injured cutaneous barrier causes release of cytokines such as TSLP (thymic stromal lymphopoietin), interleukin (IL)-33, and IL-25, considered alarmins, which provoke immunological dysregulation at the level of the dermis.

TSLP activates a wide range of cell types, such as type 2 innate lymphoid cells (ILC2) and Th2, characterizing what is known as T2 inflammation.

Th1, Th2, Th17, and Th22 cells are the most important in the pathophysiology of AD because they produce and release substances capable of activating other cells or which themselves have proinflammatory primary activities. Th1 cells participate more in progression of the disease to chronicity and release interferon gamma.

Th2, Th17, Th22, and ILC2 are the cells with primary responsibility for initiating the inflammatory process. These cells release many cytokines and have different actions and play important roles in pathogenesis of the disease.[25]

Studies that have investigated participation of the different subpopulations of T lymphocytes in the inflammatory process have identified four principal endotypes – American/European, Asian, Afroamerican, and pediatric, as summarized in

Table 5. It is important to point out that participation of the Th22, Th17, and Th1 subpopulations is variable, whereas the Th2 subpopulation participates in all of the different phenotypes, defining type 2 inflammation as a fundamental element in the pathogenesis of atopic dermatitis.[26]

IL-4 and IL-13 induce formation of IgE. The higher the levels of these cytokines, the lower the expression of filaggrin, and so they also contribute to reduction of the lipid content of the stratum corneum and, indirectly, to tissue damage. IL-5 activates, differentiates, and supports survival of eosinophils. IL-17 is particular important in exacerbation of barrier injury. This cytokine degrades claudin-1, which is a junction protein that plays a barrier role between the stratum corneum and the stratum granulosum.

IL-22 is a cytokine that participates in the cutaneous remodeling phenomenon, activates fibroblasts, and participates in skin hyperkeratosis and hyperpigmentation. IL-25 stimulates ILC2 and Th2 cells and eosinophils and provokes increased release of IL-31. IL-26, which is produced by Th17 cells, induces production and release of Th2 cytokines, amplifying the inflammatory process.

IL-31 is a very important cytokine in the process underlying cutaneous pruritus, because it activates nerve endings, releasing neurotransmitters such as neuropeptides (substance P and calcitonin gene related peptide [CGRP]).[27] IL-33 stimulates mast cells to release histamine and activates eosinophils and ILC2 cells, increasing IL-4 and IL-13 levels, boosting production of IgE and reducing filaggrin levels.[25] The inflammatory process triggered by the activity of these cells and cytokines reduces expression of the IL-10 released by B lymphocytes.

Bacterial infections are another factor that amplifies the inflammatory process. Staphylococcal enterotoxins, such as type B (SEB), act as superantigens and amplify lymphocyte activity, increasing release of proinflammatory cytokines.[27,28]

Trigger factors and aggravating factors

Several different studies concur that the interaction between genetic predisposition, immunological dysfunction, and environmental trigger factors contributes to the pathophysiology of AD.[29]

In addition to adherence to treatment, exposure to environmental factors, including allergens and stimuli in the workplace and at home, factors linked to lifestyle and temperature, and dysregulation of cutaneous physiology are all related to maintenance and exacerbation of AD. Feeling hot, diaphoresis, wool fibers, psychological stress, food, alcohol, and the common cold are considered particularly important factors in induction and exacerbation of pruritus in AD. Details related to factors of initiation and exacerbation and their specific features are discussed below.[30]

Table 5
Participation of T lymphocyte subpopulations in the different endotypes of atopic dermatitis

	American/European	Asian	Afroamerican	Pediatric
Th2	↑↑↑	↑↑↑	↑↑↑	↑↑↑
Th22	↑↑↑↑	↑↑↑↑	↑↑	↑↑↑
Th17	↑	↑↑↑	absent	↑↑↑
Th1	↑↑	↑↔	absent	absent

↑ = slightly elevated, ↑↑ = elevated, ↑↑↑ = very elevated, ↑↑↑↑ = extremely elevated, ↑↔ = normal or slightly elevated.

Climate and temperature

Studies have associated increased prevalence of AD with places with low humidity, low exposure to UV radiation, and low temperature, or use of indoor heating.[31]

Household pollutants

There is still doubt with relation to the role in AD recurrence played by substances released in homes, such as tobacco smoke, combustion products (biomass, stoves, fireplaces), construction materials, biological sources, and cleaning products,[31] and also with relation to mites.[11]

Atmospheric pollutants

Cohort studies have linked exposure to air pollution to greater prevalence of AD, possibly caused by oxidative stress and damage to the cutaneous barrier caused by these external factors. Therefore, changes to climatic factors such as temperature, humidity, radiation, and air pollution can influence AD response and symptoms.[31]

Exposure to pollutants released by burning fossil fuels has been associated with increased risk of preschool children developing AD.[31] Moreover, particulate material in contact with the skin may promote skin itching, scratching and, alloknesis, an abnormal sensory state in which stimuli that would not normally evoke itching do cause it, and thereby exacerbate AD.

Diet/Food antigens

AD and Food allergy (FA) are common conditions that emerge in childhood and can be intimately linked. Approximately 30% of children with moderate to severe AD also have FA. There is evidence that patients with AD should not be put on unjustified elimination diets. Sensitization to a food (with a positive skin prick test and/or specific serum IgE test) does not signify presence of an allergy and unjustified elimination of this specific food may be prejudicial and cause loss of tolerance with a possibility of anaphylactic shock when it is reintroduced. There is strong evidence for a link between early onset of AD and development of other allergic diseases over the course of the patient's lifetime, known as the allergic march, and many preventative interventions have been suggested, such as use of emollients and early introduction of peanuts and eggs for infants at high risk, which have initially shown promising results for prevention of AD and of peanut and egg allergy.[32] A recent systematic review demonstrated that prophylactic administration of emollients started in early infancy can prevent AD, primarily if used continuously in high-risk populations, but did not prevent FA. It is still debatable whether early introduction of foods prevents FA in at-risk children.[33]

A systematic review followed by meta-analysis assessed the disparate points of view of many patients with AD and their carers. Elimination of certain foods from the diet may lead to a discrete and potentially irrelevant improvement in intensity of eczema, pruritus, insomnia, and poor sleep quality in these patients. This conduct should be evaluated in conjunction with the potential risks of indiscriminate food elimination diets for treatment of AD, especially in babies and small children at risk of developing IgE-mediated food allergy and nutritional deficiencies. Treatment focused on elimination diets leads to under-treatment, in the scenario of the growing number of treatment options now available to treat AD.[34]

Food restrictions (elimination of food allergens) should not be recommended for pregnant women or breastfeeding mothers to prevent emergence of AD. There is a possibility that AD can be exacerbated due to transfer of food allergens such as eggs to infants via breastmilk; but these infants should be carefully diagnosed on the basis of the results of tests of food elimination and food challenges via breastmilk.[35]

Aeroallergens

Aeroallergens can provoke eczematous skin lesions in sensitized patients with AD, which may be because of increased skin permeability caused by inhaled allergens in patients with cutaneous barrier defects. Positive atopic disease contact tests are associated with presence of specific IgE and a positive history of AD flare-up caused by seasonal allergens. Many aeroallergens that provoke AD are derived from *Dermatophagoides pteronyssinus* and *D. farinae* mites. The enzymatic activity of the principal mite allergens destroys the epithelial cell tight junctions in the bronchial mucosa and, therefore, can also worsen skin barrier dysfunction in patients with AD.[36] If these allergens are considered eruption exacerbation factors, they should be carefully assessed, with an in-depth evaluation of medical history, environmental changes, and changes in the characteristics of

eruptions. The evaluation should include the results of elimination tests and challenge tests, if possible, and not be based solely on clinical symptoms or specific IgE assays, or the results of skin prick tests. In common with management of food allergens, elimination of environmental allergens is an adjuvant to pharmacotherapy and skin care.[30]

Many patients report that cutaneous symptoms worsen after contact with animal hair allergens. In the past, it was recommended that patients avoid contact with pets as primary prevention of atopic disease. However, nowadays, only exposure to cat epithelium is considered a risk factor and should therefore be avoided.[29,30] There is no evidence that exposure to dogs increases the risk of AD in children; on the contrary it may even offer protection because of exposure to non-pathogenic microbes.[29,30] Once a patient has become sensitized to a pet and exhibits symptoms after contact, avoidance becomes necessary.[36]

Diaphoresis

Transpiration disorders and excess remnant sweat on the surface of skin exposed to high temperatures and humidity can worsen symptoms of AD. Allergens derived from *Malassezia sp.* found in unevaporated sweat residue can lead to worse symptoms. High temperatures and humidity on the surface of the skin obstruct sweat pores and induce transpiration. To protect against excessive diaphoresis and presence of excessive sweat on the skin, underwear made from breathable and low hygroscopy material is recommended. High temperatures and humidity should be avoided and appropriate measures such as bathing, rinsing with running water, and drying off should be adopted.[37]

Cutaneous infections

Microbiota

The skin is a habitat for a vast collection of microorganisms, including bacteria, virus, fungi, and arthropods. These microorganisms form an ecosystem associated with the favorable habitat, with an abundance of folds, invaginations, and specialized niches. The skin microbiota live in symbiosis with skin immune system factors, performing an essential and complex role in control of skin physiology and immunity.[35]

The role of bacteria

One of the characteristics of AD is that patients have greater bacterial colonization, especially by *Staphylococcus aureus*, which is found on damaged skin in more than 90% of the patients with AD. *S. aureus* plays an important role in pathogenesis of AD, to the extent that treatment to reduce colonization by *S. aureus* reduces disease severity, and this correlates with normalization of pH and transepidermal water loss. The proportion of *S. aureus* in the cutaneous microbioma increases from 35% to 90% during crises, and the severity of AD lesions is associated with the relative density of *S. aureus* colonization of the skin.

In addition to *S. aureus*, the load of other species (*S. epidermidis* and *S. hemolyticus*) is also greatly elevated in the injured skin of patients with AD. In contrast, it has been demonstrated that the inflamed skin of AD patients has notably lower concentrations of *Cutibacterium*, *Streptococcus*, *Acinetobacter*, *Corynebacterium*, and *Prevotella*.

Curiously, the greater concentration of *S. epidermidis* can affect the behavior of *S. aureus* by producing molecules that selectively inhibit colonization by *S. aureus* and increase production of antimicrobial peptides even further.[35]

The role of viruses

Although viral infections of the skin are relatively less common in patients with AD when compared with bacterial infections, diffuse and disseminated viral infections are observed in patients with AD and some of them can be problematic or even fatal. Viral infections that are common in AD include the viruses that cause *eczema herpeticum* (EH), *eczema vaccinatum* (EV), and *eczema molluscatum* (EM). Infection by the *Herpes simplex* virus is common in patients with AD and manifests as a disseminated and distinctly monomorphous eruption of dome-shaped blisters accompanied by fever, indisposition, and lymphadenopathy. Eczema herpeticum can cause serious complications, including keratoconjunctivitis, viremia, meningitis, encephalitis, or secondary bacterial sepsis.[35]

The role of fungi

Fungi also play a role in development and exacerbation of AD. In particular, the role played by *Malassezia* yeasts has been discussed in several studies. *Malassezia sp.* yeasts are part of the

normal cutaneous flora of humans that inhabit the superficial layers of the stratum corneum near to sebaceous glands and in the superior parts of hair follicles. Distribution and isolation of these yeasts vary in density and presence in many skin conditions and sites. It has been reported that *Malassezia* colonization is found both in patients with AD and in healthy individuals, with detection rates of 100% and 78%, respectively.[38] Among patients with AD, the head and neck are more prone to colonization than the limbs and trunk. Several different studies have indicated that *Malassezia sp.* induces production of specific IgE that is exclusively observed in patients with AD and not in patients with allergic rhinitis, urticaria, or allergic contact dermatitis.[39]

Differential diagnosis

The wide clinical spectrum of AD can frequently lead to erroneous diagnoses and treatment. Characteristics of AD including age of onset, distribution, intense pruritus, xerosis, lichenification, and association with atopic disease, can help to distinguish between AD and alternative diagnoses.[40]

Occasionally, patients with a diagnosis of AD may exhibit atypical clinical characteristics, leading physicians to question the diagnosis. In these cases, knowledge of the characteristic clinical findings of AD and recognition of possible alternative diagnoses are both important for patients, considering that management and prognosis are totally different.[41]

There is a long list of differential diagnoses for AD in children and adults, primarily comprising dermatological diseases and conditions that can manifest with cutaneous lesions and can be very similar to AD. These should be considered not only when the patient presents with an eczematous cutaneous eruption for the first time, but also when a patient diagnosed with AD does not respond to the appropriate treatment.[42] The most important diagnoses are listed in Table 6. One of the most important classes of diagnoses are the Inborn Errors of Immunity (IEI), since these are diseases that must be managed by an immunologist-allergist and careful examination is needed to make the correct diagnosis.[43]

Of note among the IEI are the Primary Atopic Disorders (PAD), which comprise a subset that are hereditary monogenic diseases that predominantly cause allergic manifestations. This makes it harder to diagnose them as IEI, because they do not exhibit the recurrent infection phenotypes seen in the majority of these diseases.[45] It is essential that physicians are able to recognize the PADs, considering the individual management of each case and impacting on patient morbidity and lethality. Table 7 lists the clinical warning signs that can facilitate diagnosis of PADs.

The principal differential diagnoses of AD and their specific morphological characteristics are described below.

Allergic contact dermatitis

Diagnosis is based on the pattern of dermatitis, normally following exposure to a specific substance, and on a positive patch test. The pattern is related to the locations of lesions in the region that comes into contact with the allergen (for example, on the face, for reactions to cosmetics). The characteristics of these lesions are very similar to AD and it is sometimes impossible to differentiate them on the bases of clinical findings alone. The most common allergens in children and adolescents are metals, fragrances, preservatives, and colorings.[44]

Seborrheic dermatitis

This is an important differential diagnosis of AD, particularly in its pediatric form, because of the similar distribution of the lesions. Diagnosis is based on clinical history and physical examination, including the distribution of eczema. Pediatric seborrheic dermatitis generally has onset within the first 3 months of life, i.e. earlier than the typical age of onset of AD. It almost always involves the diaper area, face, and scalp. In contrast, the diaper area tends to be spared in AD. Compared with AD, seborrheic dermatitis lesions tend to be less inflamed and scaling is greasier and while it can last several months, it does not last beyond 12 months of age, which also differs from the chronic character of AD. However, both diseases can occur concomitantly.[40]

Psoriasis

Although it is more common in adolescents and adults, psoriasis can occur in people of any age. It is a chronic dermatosis most often characterized by lesions in plaques and cutaneous thickening, clearly demarcated with erythema, and with presence of silver scaling in the region of the elbows, knees,

Table 6
Principal types of dermatitis/eczema and their differential diagnoses[44]

Dermatitis / Eczema	Atopic dermatitis Contact dermatitis Seborrheic dermatitis Nummular dermatitis Asteatotic dermatitis (eczema craquelé)
Other chronic dermatosis	Psoriasis Lichen simplex chronicus
Infections and infestations	Scabies Dermatophytosis Viral infections
Genetic and metabolic diseases	Netherton syndrome Ichthyosis Acrodermatitis enteropathica
Autoimmune diseases	Systemic lupus erythematosus Dermatopolymyositis
Inborn Errors of Immunity	Hyper-IgE syndrome Wiskott-Aldrich syndrome Omenn syndrome
Cancers	Langerhans cell histiocytosis Cutaneous T-cell lymphoma
Others	Drug-induced skin disorders

and scalp. There may also be ungueal and articular involvement (psoriatic arthritis). A cutaneous biopsy may be needed for diagnostic confirmation.[41]

Scabies

Differential diagnosis with AD includes both the pruriginous characteristic of *Sarcoptes scabiei* infestation and the cutaneous lesions caused by itching, with presence of erythematous papules and excoriation, predominating in interdigital areas and the flexural regions of the wrists, feet, and ankles, which could indicate an atypical eczema. Diagnosis is confirmed by observation of the mites with dermatoscopy.[40]

Table 7
Clinical warning signs of primary atopic disorders (PADs)[45]

Elevated IgE and eosinophilia
Atopic manifestations
Malignancy
Autoimmune manifestations
Short stature / growth disorders
Repeated infections
Connective tissue diseases

Ichthyosis vulgaris

This is the most common type of ichthyosis, caused by mutation of the filaggrin gene (FLG). The typical clinical status includes dry skin with fine, white scaling, very often free from erythema. Pruritus and eczematous lesions may be present, making differential diagnosis from AD difficult. It is debatable whether the eczematous lesions in ichthyosis vulgaris are actually AD, since around one third of all patients with AD are heterozygous for mutations of the FLG gene.[41]

Netherton syndrome

An autosomal recessive disease caused by mutation of the SPINK5 gene. At birth, newborns may present with erythrodermal ichthyosis. In older children, the disease is characterized by a distinct dermatitis, ichthyosis linearis circumflexa, in which the cutaneous lesions disseminate in a linear serpiginous or circinate pattern. The lesions are pruriginous and many will progress to eczematous plaques and lichenification of folds. The dermatitis may be difficult to distinguish from AD, since these children generally have elevated serum IgE and food allergies. Examination of the hair may be useful, because microscopy will reveal *trichorrhexis invaginata* (bamboo hair).[46]

Zinc deficiency acrodermatitis enteropathica

May be genetic or acquired (due to insufficient zinc intake) and is characterized by erythematous blemishes and plaques with scabs and erosions, predominantly in periorificial areas. Patients very often have other manifestations, such as diarrhea, alopecia, and growth deficiency. Diagnosis is clinical, combined with serum alkaline phosphatase and zinc assays and, very often, a skin biopsy.[45]

Hyper-IgE syndromes

These are rare inborn errors of immunity (autosomal dominant or recessive forms) and are characterized by severe eczema, recurrent skin infections (*S. aureus*), and very often pneumonia (with formation of pneumatoceles) and very high serum IgE levels (> 2000 UI/mL). Patients have characteristic skeletal features with a characteristic facial appearance (prominent forehead, wide bridge of the nose, bulbous nasal tip, and prognathism). Cutaneous changes are not limited to impetigo, but include boils and abscesses.[47]

Wiskott-Aldrich Syndrome (WAS)

This genetic syndrome is characterized by its association with eczema, although the first cutaneous manifestations are hemorrhagic lesions with petechiae, hematoma, purpura, epistaxis, oral bleeding, or bloody diarrhea. Platelets are characteristically small and autoimmune manifestations and neoplasms are common (primarily B-cell lymphomas).[44]

Omenn syndrome

This is a rare form of severe combined immunodeficiency, with early onset during the first year of life, characterized by erythroderma (similar to eczema) associated with chronic diarrhea, pneumonitis, growth deficiency, lymphadenopathy, and hepatosplenomegaly, characteristics that distinguish it from AD.[43]

Cutaneous T-cell lymphoma (fungoid mycosis)

This is a rare disease that is more frequently observed in adults, with characteristics that are similar to psoriasis or nummular eczema during the initial phases. A cutaneous biopsy should be taken from lesions that are refractory to treatment with topical corticosteroid.[42]

Assessing severity and control: evaluation scores

Assessment of the severity of AD is essential to guide treatment options and gauge the response to treatment. In the absence of a gold standard or specific biomarkers available for clinical use, several instruments have been developed and validated to measure severity and control of AD.[48,49]

For measurement of clinical severity by health care professionals, the most widely used and validated scores are Scoring Atopic Dermatitis (SCORAD) and the Eczema Area and Severity Index (EASI).[48,49] It is also recommended that patients assess their own AD severity and the most used instrument for this purpose is the Patient Oriented Eczema Measure (POEM).[49] Beyond these, the validated instrument Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) has been recommended as an instrument specifically for assessing severity in clinical trials.[50]

The SCORAD index is widely used in clinical practice, is scored from 0 to 103 points, and assesses the extent and intensity of lesions

(erythema, edema or papules, exudate or scabs, excoriation, lichenification, and cutaneous xerosis) and of subjective symptoms (itching and impact on sleep). AD is classified as mild when scores are less than 25 points; moderate at 25 to 50 points; and severe when the patient scores over 50 points.[51,52] The mean time for assessment ranges from 7 to 10 minutes. It offers the advantage of considering subjective symptoms, the intensity of xerosis, and of lesions involving the face, eyelids, neck, hands, and feet; and has the disadvantage in comparison to the EASI that it is redundant with regard to inflammatory skin symptoms, gives less weight to the extension of lesions in the final score (maximum of 20% of the value), and only assesses the intensity of the representative lesion for that patient.[48,52]

In turn, the PO-SCORAD (Patient-oriented SCORAD) is a validated score developed from the SCORAD. It has an app with a version in Portuguese that enables the patient to assess the severity of their own AD. Although it is less accurate than the SCORAD for the extent of lesions item, it covers lesions of three types of skin (white, Asian, and black) and it is easy to complete.[53]

The EASI score ranges from 0 to 72 points and covers clinical signs (erythema, edema/papules, excoriation, and lichenification) in each of four areas of the body (head and neck, upper limbs, trunk, and lower limbs) and the extent of disease in each region. It is interpreted as follows: 0 = no lesions; 0.1 to 1.0 = almost free from lesions; 1.1 to 7.0 = mild AD; 7.1 to 21.0 = moderate AD; 21.1 to 50.0 = severe AD; and 50.1 to 72.0 = very severe AD.[48,54,55] The EASI has been preferred over the SCORAD for clinical trials because it assesses all four of the fundamental clinical signs of AD, measures the intensity of lesions in the four body areas, rather than just a representative lesion, and its disease extent score is better distributed compared to the SCORAD. However, it is necessary to combine it with other scores to assess patient symptoms.[48,49]

The POEM uses seven self-administered questions to measure the extent to which patients experience their signs and symptoms over time and has been widely validated.[49] The score ranges from 0 to 28 points, where 0 to 2 points means free from lesions or almost free from lesions; 3 to 7 points, indicates mild AD; 8 to 16 points, moderate AD; 17 to 24 points, severe AD; and 25 to 28 points, very severe AD.[56] It has been translated and linguistically validated for Portuguese (in the Brazilian culture) and is freely available from the University of Nottingham website.[57]

The vIGA-AD considers the overall appearance of AD lesions as scored by an evaluator. Scores vary from 0 to 4 (0 = no lesions, 1 = almost free from lesions, 2 = mild AD, 3 = moderate AD, and 4 = severe AD) and assess the intensity of lesions (erythema, infiltration or papules, lichenification, exudate, or scabs).[3] The instrument is rapid and simple, but does not assess disease extent.[48]

Control of AD and response to treatment can be assessed using the same severity scores sequentially, or other specific instruments can be used.[48,49] For sequential use of a severity score, it is necessary to consider whether the variations exceed a minimal clinically important difference (MCID) or if there is a percentage reduction in the score, for example, the SCORAD 50 or EASI 75, with 50% or 75% reduction compared to a baseline value, respectively.[48]

Two scales were recently developed to monitor control of AD, the Atopic Dermatitis Control Tool (ADCT) and the Recap of atopic eczema (RECAP), both with similar content and validation and especially recommended for clinical trials. There is no preference between them,[49] but to date only the ADCT has been translated and undergone linguistic validation for Brazilian Portuguese.[58]

The ADCT instrument comprises six questions and has proven to be a valid and reliable tool for assessing control of AD in patients over the age of 12 years, with the capacity to detect clinically significant changes in disease control over time. Scores vary from 0 (best disease control) to 24 points (worst disease control) and AD is considered controlled if the score is less than 7 points.[59]

Other instruments for clinical symptoms perceived by the patient and the impact on health related quality of life can also be used in clinical practice and are recommended for research. The most recent update to the global Harmonising Outcome Measures for Eczema (HOME) initiative, which has the objective of standardizing clinical trials of the four principal AD outcome domains, recommends using the EASI to assess signs of severity; POEM and numerical 24-hour peak itching scale for patient-reported symptoms; disease related quality of life for quality of life questionnaires by age group (the Dermatology Life Quality Index– DLQI for adults; the Children's Dermatology Life Quality Index – CDLQI for children 5 to 16 years of age; and the Infants' Dermatitis Quality

of Life Index – IDQoL for under-fives), and the ADCT or RECAP for control of AD activity.[49]

Treatment

Considering the chronic nature of AD and the differing levels of severity, the objectives of AD treatment are as follows: to (a) reduce the extent and severity of lesions; (b) reduce itching and improve sleep quality; (c) maintain normal daily activities; (d) improve quality of life; (e) maximize disease-free periods; (f) prevent infectious complications; and (g) avoid/minimize adverse events related to treatment.

General care

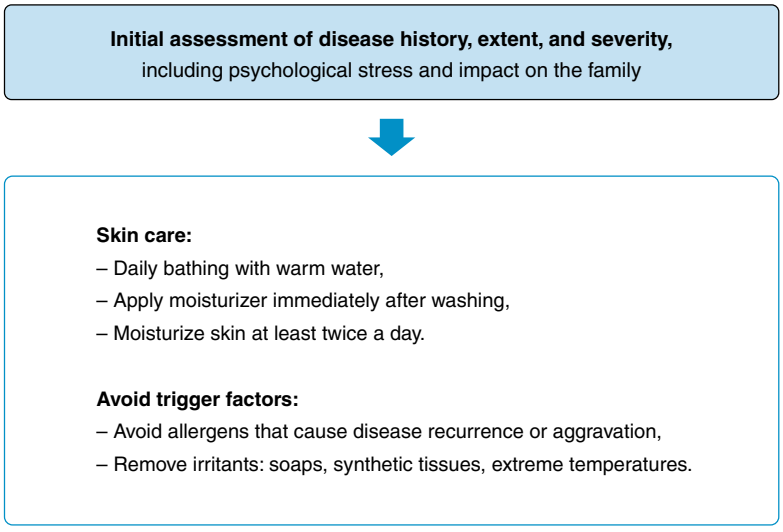
For patients with mild AD, the objectives cited above can be achieved with topical treatments alone, which is not the case of patients with moderate or severe AD, for whom treatment is challenging. The general principals include improving the cutaneous barrier, eliminating trigger factors, education and active participation of patients and family members, and treatment of inflammatory lesions (Figure 1).[1,60]

Improve the cutaneous barrier

Patients with AD have xerotic skin because of deficient barrier function and an unfavorable equilibrium between transepidermal water loss and retention.[61] If applied regularly, moisturizers improve cutaneous barrier function, increase hydration, and reduce xerosis, itching, and inflammation, reducing the need to use anti-inflammatory agents.[1] Randomized clinical studies comparing use or not of moisturizers in participants demonstrated improved SCORAD scores, longer time between crises, and reduced use of topical anti-inflammatories in the group that used moisturizer.[62]

The ideal quantity that should be applied to newborn infants, infants, children, and adolescents/adults ranges from 100 to 150, 200, or 500 grams per week, respectively.[60,63]

The moisturizers available for AD (Table 8) have varying combinations of emollients, occlusive substances, and humectants.[1] Emollients fill the spaces between corneocytes, maintaining moisturization; occlusive substances form a hydrophobic film on the epidermis that reduces evaporation of water and penetration by irritants, such as allergens and toxins;



Adapted from Kulthanan K, et al.[60]

Figure 1
Flow diagram of initial treatment for atopic dermatitis

Table 8
List of some of the moisturizing products available

Moisturizers containing urea
Cetaphil® Pro Urea 10% lotion (Galderma)
Dermovance® S (FQMmelora)
Eucerin® Urearepair 10% lotion (Eucerin)
Nutraplus® cream/lotion (Galderma)
Ureadin® cream/lotion 3%, 5%, 10% (Isdin)
Ureadin® Rx (Isdin)
Uremol® cream/fluid 10% (Stiefel /GSK)
Ureskin® cream/lotion 10% (Genon)
Moisturizers containing ceramides, cholesterol, fatty acids, phospholipids
Atoderm® cream/balm/gel (Bioderma)
CeraVe® cream/lotion (Lóreal)
Cetaphil® Advanced (Galderma)
Cetaphil® cream/lotion/serum (Galderma)
Cetaphil® Restoraderm (Galderma)
Cetaphil® pro AD (Galderma)
Dermovance® (FQMmelora)
Dersani® moisturizing cream (Megalabs)
Epidrat Corpo Intensivo® (Mantecorp)
Eucerin® pH 5 lotion (Eucerin)
Fisiogel® cream/lotion (Megalabs)
Hidrakids® (Biolab)
Hydracell® cream (Germed)
Hydraporin AI® lotion (Mantecorp)
Klaviê® cream/lotion (Theraskin)
Lipikar® lotion (La Roche-Posay)
Nutratopic® cream/lotion (Isdin)
Nutriol® lotion (Darrow)
Saniskin® lotion (Saniplan)
Stelatopia® balm/cream (Mustela)
Xeracalm® AD cream (Avène)
Moisturizers containing glycerin, oatmeal, panthenol, petrolatum
Bepantol Derma® lotion (Bayer)
Neutrogena® body care extra dry skin (Neutrogena)
Norwegian® body moisturizer (Neutrogena)
Nutriol® lotion (Darrow)
Umiditá® lotion (Libbs)
Moisturizers with anti-pruritus activity
Atoderm® SOS spray (Bioderma)
Cetaphil® pro AD fast control (Galderma)
Fisiogel® AI (Megalabs)
Lipikar® AP+M (La Roche-Posay)
Nutratopic® Rx (Isdin)
Umiditá® AI (Libbs)

Adapted from Carvalho VO, et al.[64]

and humectants increase moisturization of the stratum corneum, preserving its structure.[64] They may also contain ceramides and essential fatty acids.[1]

An ideal moisturizer should contain few ingredients, with well-tolerated preservatives, and should be free from fragrances and sensitizers (sodium lauryl sulfate, cetyl alcohol, neomycin, animal lanolin, almond oil, parabens, and methylisothiazolinone) to avoid allergic cutaneous reactions. It can often be necessary to test different products to identify the one that best achieves cutaneous moisturizing, does not sting, and fits the patient's preference for texture, lotion, cream, or balm. Lotions are preferable during the hotter months of the year because they have a more fluid consistency and are easier to spread. In cooler periods, creams and balms with thicker consistency moisturize better.[61,64] Guidelines recommend that moisturizer should be applied two or three times a day, especially with the skin still humid, during the first 3 minutes after bathing, and to areas of skin with and without lesions.[1,65]

A new era of moisturizers includes ingredients such as cannabinoids, bioactive lipids, microbioma modulators (prebiotics and probiotics) and antioxidant enzymes. These substances are intended to exert additional biological effects on the skin: regulate production of lipids, reduce sensorineural transmission of itching signals, revert oxidative stress, reduce inflammatory cell activity, and modulate skin microbiota.[66]

Bathing daily is not associated with clinical deterioration. Bathing reduces irritants, bacteria, and scabs on the skin. Warm water is recommended to avoid drying the skin when washing.[30] Patients can bathe for 5 to 10 minutes using soaps at physiological pH, i.e. slightly acid, or, preferably, using syndets.[60,61] The European guidelines recommend using cleansing oils (Table 9) during the last 2 minutes before finishing washing.[36]

Table 9
List of some cleansing oils available

Lipikar® huile lavante (La Roche-Posay)
Atoderm® cleansing oil (Bioderma)
Eucerin® pH5 body wash (Eucerin)

Identify trigger factors

a) nonspecific factors

Daily contactants such as saliva, sweat, hair, friction against synthetic clothes, and shampoo, conditioner, and soap residues can exacerbate AD.

b) Contactants

Contact dermatitis should be suspected when treatment fails or eczema location is atypical. The causative agent can be confirmed using patch tests. In general, the most common agents are topical medications, cosmetics, metal, and/or disinfectants.

c) Food allergy

A food should only be eliminated from the diet if its involvement as one of the causes of AD aggravation is proven clinically and using specific tests. Food allergies in AD are more common in children, especially during the first years of life, and are linked to the more severe forms of AD. Studies show that elimination diets (allergenic foods) for pregnant women and breastfeeding mothers do not prevent AD in their babies.

d) Aeroallergens

Domestic dust, pollens, and animal hair are considered factors in clinical deterioration, are more common after the first years of life, and allergies to them can be confirmed with prick tests and/or specific serum IgE assays.

e) Bacteria and fungi

S. aureus can be one of the factors in exacerbation of AD. Administration of antibiotics is not indicated if there is no infection. Some studies have demonstrated clinical improvement with use of topical antifungals on lesions of the head and neck, suggesting that fungi of the genera *Candida* and *Malassezia* are associated with exacerbation of AD lesions.[30,60]

Education of the patient and family members

Since AD is a chronic disease that needs long-term follow-up, patients and their relatives must be educated so that they can understand the course of the disease and how to deal with and prevent crises, improving adherence to treatment and quality of life. Interventions that include patient education reduce the number of medical consultations, facilitate the physician-patient/family partnership, and reestablish family dynamics.[67] Multidisciplinary education programs involving pediatricians, dermatologists, allergists, psychologists, and nurses help to improve the quality of life of patients and their families.[60] In Brazil, there are a number of AD support groups with this mission, which can be consulted on the aada.org.br website. The same site also provides patient-oriented information on atopic dermatitis.

Emotional stress

AD has a significant impact on the quality of life of patients and their families. Stress and emotional factors can exacerbate the disease. Psychosomatic counseling, psychotherapy, behavioral therapy techniques, and/or relaxation techniques can help with patient management.[30,60,67]

Phototherapy

Phototherapy has been used to treat many different inflammatory and immunomediated diseases since the start of the last century, primarily because of the observation that these patients improved during the summer. Treatment employs light in the ultraviolet (UV) spectrum irradiated onto the patient's skin at specific times for controlled durations. The spectra employed are ultraviolet A (UVA), UVA combined with use of psoralens (UVA+P), and ultraviolet B (UVB). The UVB category includes Broad Band UVB (BB-UVB), ranging from 280 to 320 nm, i.e. the entire UVB band, and Narrow Band UVB (NB-UVB), which uses wavelengths from 301 to 311.[36,68,69]

For treatment of AD, both of the modalities employed have similar efficacy: medium-wave UVA (340 to 400 nm, also known as UVA-1) and NB-UVB, although the latter is safer. The different spectra yield different results, and NB-UVB is indicated for chronic cases, while UVA-1 is used for acute presentations.[69]

Phototherapy is effective because it interferes in the cascade of biological events that result in suppression of the immune system linked to the T cells of the skin. Specifically in AD, it provokes suppression of the lymphocytes Th2, Th22, and Th1, improving the cutaneous barrier. It also reduces colonization by *Staphylococcus aureus*, reduces the number of

infections, and provokes reduction of toxin production by *S. aureus*.[68,69]

Phototherapy's role within the arsenal of AD treatments is as an adjuvant when topical treatments fail, before use of systemic immunosuppressant medications. Although it is recommended for adjuvant use, in some patients, SCORAD score reductions after use of phototherapy alone can exceed 50% in the first 12 weeks.[70] Its efficacy has been demonstrated in publications and NB-UVB was recommended in a recent systematic review that analyzed 32 publications that included 1,219 participants (5 to 83 years of age) and all phototherapy modalities. NB-UVB was more effective than placebo, with benefits for improvement of eczema and reduction of pruritus. The lack of uniformity of the studies, small numbers of participants, and even failure to assess patients' quality of life or employ similar severity scores interfered with interpretation of the efficacy results reported.[68,70,71]

The safety and efficacy of NB-UVB phototherapy have been demonstrated in patients up to 3 years of age, but it should be avoided in children who are unable to adhere to the safety protocols. Rates of remission over 1 year of treatment exceeded 50% for complete or near-complete remission, primarily in children with phototypes higher than III. The difficulties with conducting treatment in children, the lack of uniformity of the different publications and, primarily, the small numbers of participants in the pediatric age group are all factors that still need to be addressed.[72-74]

Phototherapy for AD is standardized, but the different types of skin, disease phenotypes, and even tolerance of treatment can all have a direct influence on the results. In cases in which UVA1+P is used for phototypes I to III, it is recommended that treatment initiates at 1 J/cm^2, while for phototypes IV to VI, 2 J/cm^2 can be used initially, with 1 J/cm^2 increments every two or three sessions. It is recommended that sessions be conducted two to three times per week. When using AD NB-UVB, the initial dose is 100 mj/cm^2, and the duration or total dose per session should be as specified in the manufacturer's standard table.[69]

The greatest problems with this treatment method are its cost and, primarily, the availability of equipment and physicians trained to use it. In some regions of Brazil, this method is not a viable option, because the equipment is only found in large urban centers or state capitals and the need for frequent sessions makes it impossible to adhere to treatment for patients who live in places far from these centers. During the COVID-19 pandemic, there were several reports of phototherapy performed at home, increasing coverage of patient care, since patients could be treated at a distance without having to travel, but the cost of the equipment and issues regarding the safety of using it at home are causes for concern. Development of new technologies and, primarily, portable and lower-cost machines are possibilities for future improvements in care of these patients.[68,73,75]

Another concern is the possibility of increased risk of skin cancer linked to exposure to phototherapy, primarily in pediatric patients, and follow-up of patients currently being treated is essential to determine the magnitude of this risk.[73]

Phototherapy offers good clinical results and is apparently safe, but the sizes of the samples of patients studied and also the cost remain factors that limit its routine adoption for the pediatric age group.

Pharmacological treatment

Control of AD requires an approach that is tailored to each phase of the disease. Treatment plans should be developed on the basis of decisions taken in conjunction with patients and their families. The plan should cover control over the short, medium, and long term, with strategies for acute crises and a roadmap for long-term control. The objective is to reduce severity and the number and duration of crises.[76] The plan should ideally be provided in writing, covering the medications to be used and the duration and times of use.[77,78]

Topical

All patients need topical treatment, irrespective of AD intensity. For severe forms of the disease, topical treatment should be combined with systemic medications.[76,77]

Topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) are recommended for basic therapy. Over recent years, new topical substances have been released or studied. Emerging therapies include topical phosphodiesterase-4 inhibitors and topical Janus kinase inhibitors,[76,79] but these are not yet available in Brazil.

Topical corticosteroids

The mechanisms of action of TCS include anti-inflammatory, antiproliferative, and immunosuppressant effects. They suppress inflammatory activity and reduce the number of inflammatory cells and release of cytokines, including neutrophils, monocytes, lymphocytes, Langerhans cells, IL-1α, IL-1β, IL-2, and tumor necrosis factor. Their efficacy has been demonstrated in several vehicles and at varying doses in countless randomized clinical trials.[80]

TCS are the first line treatment for acute AD crises, and efficacy is achieved with correct application, at the strength indicated for each region, and in sufficient quantity. There are seven different strength levels, varying from very weak to very strong (Table 10), and the strength should be adjusted to fit the severity of lesions and the region being treated.[77] Powerful corticosteroids should be avoided in areas with thin skin, such as the face and areas with folds. In children, corticosteroids of medium to low strength should be preferred.[81]

Application should be started as soon as symptoms of itching and erythema appear and the duration of topical treatment with steroids is guided by clinical improvement. However, their use should be restricted to areas with inflammatory lesions and periods of 7 to 14 days, or until the lesions improve.[81] They can be applied once or twice a day with similar efficacy. Proactive use is indicated in severe and difficult to control cases, i.e. after a flare up has subsided, apply 2 days a week to areas that are most resistant to treatment and, ideally, resume reactive use after 3 months.[81,82]

There is no universal standard to quantify TCS for each application. Squeezing the tube enough to cover the fingertip of an adult is sufficient to apply to a lesion the size of two hand breadths.[81]

Corticosteroids have undesirable side effects, which encourages poor compliance with treatment, caused by corticophobia, and results in insufficient clinical response. Cutaneous side effects include atrophy, telangiectasia, stretch marks, hypertrichosis, and acne eruptions.[76] The majority of these effects improve after withdrawal of the medication.[81] Side effects can be avoided if corticosteroids are used correctly and combined with skin moisturizing.[83]

Topical calcineurin inhibitors

TCI inhibit transcription of the genes for proinflammatory cytokines, such as IL-2, which are dependent on nuclear factor of activated T cells. The following have been approved for treatment of AD: tacrolimus cream 0.03% (in children from 2 to 15 years and adults) and ointment 0.1% (in over-15s and adults) for moderate to severe AD; and pimecrolimus cream 1% for mild to moderate AD in children older than 3 months. They are safe and effective for short term (3 weeks) and long term (5 years) treatment of AD.[81]

TCI are indicated for use in sensitive areas with thinner skin, such as areas with folds and the face, applied twice a day to areas with lesions. They do not cause the topical side effects observed with TCS, but there may be local itching and burning at the site of application.[83] Patients should be warned of this symptom to avoid them stopping treatment and if necessary TCS can be used for a few days beforehand and then changed for the immunomodulator, thus reducing burning sensations.[81]

Phosphodiesterase-4 inhibitors

Use of phosphodiesterase-4 inhibitors (PDE4) is founded on the intracellular function of PDE4 in keratinocytes. Circulating leukocytes in patients with AD have PDE4 activity, which is involved in production of inflammatory cytokines such as IL-4, IL-5, IL-10, and IL-13 and prostaglandin E2, by degradation of adenosine monophosphate. PDE4 reduces transcription of countless cytokines involved in acute and chronic inflammation, The PDE4 inhibitor crisaborole has been evaluated in clinical trials.[77]

Crisaborole ointment 2% was approved by the FDA in 2016 for treatment of mild to moderate AD in patients older than 2 years and in March 2020 for infants over 3 months old.[83] Several clinical trials have shown that the product is effective for improving AD lesions and disease severity and for reducing pruritus, with a favorable safety profile,[76] but it can cause burning sensations that limit its use.[83]

Topical JAK/STAT inhibitors

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is used by countless cytokines involving increased Th2 cell response, eosinophil activation, and suppression of regulatory T cells. JAK/STAT inhibitors are classified as small molecules that block intracellular targets.[77] They can prevent Th2 cytokine signaling that induces the inflammatory process in AD. Several pharmaceutical

agents targeting this group of tyrosine kinases (including JAK1, JAK2, JAK3, and TYK2) are being tested in patients with AD, in both systemic and topical treatments.[76]

Sodium hypochlorite

Sodium hypochlorite baths are an antiseptic technique for treatment of moderate to severe AD in patients with recurrent cutaneous bacterial infections. They are active against staphylococci, including methicillin-resistant *S. aureus*. They are indicated for active skin infections and maintenance therapy. The antimicrobial effect is attributed to the capacity to cause irreversible aggregation of bacterial proteins.[84] They also help improve cutaneous barrier function.[81]

The recommendation is to at 100 mL sodium hypochlorite 5% to bathwater in a 100 liter bath. Bathe for 10 minutes, rinse, and apply moisturizers. This should be done 3 days a week for a minimum of 3 months.[81]

A systematic review of sodium hypochlorite baths demonstrated that four out of five studies observed

Table 10
Classification of topical corticosteroids by strength*

Class/strength	Drug	Vehicle	Dose (%)
I - Very high			
	Clobetasol propionate	Cream and ointment	0.05
II - High			
	Betamethasone dipropionate	Cream, ointment, and solution	0.05
	Desoximetasone	Cream and ointment	0.25
	Desoximetasone	Gel	0.05
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream and ointment	0.5
III-IV - Medium			
	Mometasone furoate	Cream	0.1
	Betamethasone valerate	Cream and ointment	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream and ointment	0.025
	Triancinolone acetonide	Cream and ointment	0.1
V - Medium-low			
	Hydrocortisone butyrate	Cream, ointment	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream and ointment	0.2
	Prednicarbate	Cream	0.1
	Methylprednisolone aceponate	Cream	0.1
	Fluticasone propionate	Cream	0.05
VI - Low			
	Desonide	Cream/gel/ foam, and ointment	0.05
	Fluocinolone acetonide	Cream and solution	0.01
VII - Very low			
	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, ointment, lotion, and solution	0.5-2.5
	Hydrocortisone acetate	Cream and ointment	0.5-1
	Methylprednisolone	Cream and ointment	1%

* Adapted from Paller AS, et al. [77]

reduced AD severity.[84] The long-term efficacy and safety of this antiseptic agent is unknown, primarily with regard to continuous use.[84]

Wet Wrap Therapy

Wet wrap therapy (WWT) is an adjuvant for treatment of crises and restoration of the cutaneous barrier in refractory and severe patients who cannot tolerate TCS without bandages.[81] After bathing, moisturizers are applied in generous layers, combined or not with corticosteroids in areas with lesions. A humid bandage is applied over the moisturizer, followed by a dry bandage. WWT can be left in place for 2 to 10 hours and can be applied daily for up to 14 days. It helps to moisturize the skin, reduces pruritus, and constitutes a physical barrier that makes excoriation of the skin less likely.

In clinical trials, WWT was more effective than moisturizers alone,[85] but caution should be exercised with regard to application of high-strength TCS, because the increased absorption can lead to suppression of the hypothalamus-pituitary-adrenal axis. Low or medium strength TCS are therefore appropriate for use with WWT. It is unclear whether WWT is associated with an increased risk of cutaneous infections.[76]

Systemic

Antibiotic therapy

Patients with AD are more susceptible to cutaneous infections by bacteria, fungi, and viruses because of many reasons, such as inhibition of antimicrobial peptides. *S. aureus* is the bacteria most associated with AD, colonizing up to 90% of patients, even in areas without lesions. Colonization by *S. aureus* intensifies the cutaneous inflammatory process because of release of toxins with superantigenic activity, which accentuate the pruritus. In turn, itching promotes colonization by *S. aureus*, creating a feedback process.[81] Patients with AD may have higher rates of colonization by methicillin resistant *S. aureus* (MRSA). In two Brazilian studies, rates of colonization by *S. aureus* and MRSA were 73.6% and 0% respectively in Porto Alegre, RS, and 82.9% and 22.2% in the city of Rio de Janeiro.[86,87] In Rio de Janeiro, colonization by MRSA was positively associated with greater severity of AD and use of cyclosporine.[87]

Colonization of the skin by *S. aureus* can be reduced with effective anti-inflammatory treatment and topical use of corticosteroids or calcineurin inhibitors.[81] Sodium hypochlorite (0.005%) has antiseptic activity and can be used intermittently in the immersion baths. Presence of yellow crusting, exudate, and blisters is characteristic of bacterial infections and can be treated with topical antibiotics (fucidic acid or mupirocin). Systemic antibiotics should be used in cases with extensive bacterial superinfections, preferably with first generation cephalosporins.[81,88] Wider spectrum antibiotics can be used in cases of MRSA infections.[88] Prophylactic use of antibiotics (whether topical or systemic) for long periods is not recommended.

Immunosuppressants

Systemic immunosuppression is a resource adopted in adults and children with severe AD refractory to usual treatment. Although recent introduction of new and promising treatments such as immunobiologicals and small molecules, such as JAK inhibitors, oral immunosuppressant drugs (OIs) such as corticosteroids, cyclosporine A (CsA), methotrexate (MTX), azathioprine (AZA), and mycophenolate mofetil (MFM) are all treatment options that are established in clinical practice and are widely available for these patients.[89]

To date, cyclosporine is the only OI habitually prescribed for these purposes that is approved in Brazil, for patients over the age of 18. As a result, a significant proportion of patients with moderate/severe AD are given “off-label” prescriptions to control their disease.[90,91]

Before initiating treatment with immunosuppressants, it is necessary to study the indications, contraindications, adverse effects, and drug interactions, to be able to minimize treatment risks. The pediatric age group has a tendency to progressively improve, so it is important to evaluate the risks and benefits of these medications, which can sometimes have serious side effects.

a) Systemic corticosteroids

Systemic corticoid therapy (SCT) is limited for treatment of AD by the known side effects and lack of long-term controlled studies in adults and children. Its should therefore be used with extreme caution, restricted to exceptional cases, and the daily dose should not exceed 0.5 mg/kg body weight of prednisone or prednisolone.[67,89]

Some patients may benefit from a rapid course of SCT during severe acute crises, but clinical improvement is often associated with a high rate of recurrence of symptoms after withdrawal of the medication, resulting in difficult to control cases. Frequent use of oral corticosteroids should prompt use of other immunosuppressant treatments that avoid them.[89]

b) Cyclosporine A

CsA is a lipophilic cyclic polypeptide that inhibits the dependent pathways of calcineurin and reduces the number of activated TCD4+ and TCD8+ cells in the epidermis and, consequently, the levels of several proinflammatory cytokines, such as IL-2 and IFN-γ.[92]

Systematic reviews and meta-analyses recommend CsA as first line treatment for severe AD in adults, children, and adolescents for whom conventional treatment is ineffective or inappropriate.[89,93]

The dose habitually employed is 3-5 mg/kg/day, divided into two doses. Once clinical efficacy is achieved, it is recommended that the dose is reduced by 0.5-1.0 mg/kg/day every 2 weeks, until the maintenance dose of 2.5-3 mg/kg is reached. Treatment duration varies and should be guided by clinical criteria of efficacy and drug tolerance. Both short and long term treatments are effective, but treatment should not exceed 2 years in a continuous regimen.[67]

It is essential to monitor renal function and arterial blood pressure and if abnormal laboratory findings or increased blood pressure occur, CsA should be withdrawn or the dose reduced. Nephrotoxic effects are more likely if the dose exceeds 5 mg/kg body weight, in patients with elevated serum creatinine, the elderly, or with prolonged use of the medication. In general, the effects are reversed by withdrawal of the drug. Combining CsA with ultraviolet radiation is not recommended, because of an increased risk of cutaneous and lymphoproliferative malignancy.[93,94]

Although there are no controlled studies available that have assessed the efficacy of vaccination in children on CsA, it should be considered that attenuated vaccines may not be effective during CsA treatment.[95] Vaccines containing live attenuated microorganisms are contraindicated.

c) Methotrexate

MTX is an analog of folic acid that can competitively and irreversibly inhibit the enzyme dihydrofolate reductase, preventing conversion of dihydrofolate to tetrahydrofolate. It thus interferes in synthesis of DNA and RNA and proliferation of lymphocytes.[92]

Although there is a lack of randomized clinical trials of its use, MTX is widely used “off-label” as an accessible, low-cost treatment option for patients with serious and refractory disease.[96,97]

Studies that have assessed use of MTX in adults, children, and adolescents with severe AD have demonstrated that it is generally well-tolerated and has a good safety profile, in addition to proven clinical efficacy comparable to CsA and azathioprine.[98-100]

Compared to CsA, MTX has a slower onset of activity, but has good efficacy in prolonged treatments.[99]

Initial (5 to 10 mg/week) and maintenance dosages (7.5 to 25 mg/week) vary by age group and according to response to treatment. MTX can be administered as an oral presentation or by intramuscular route, always with weekly folic acid supplementation (5 mg) throughout treatment. The most common side effects include gastrointestinal disorders and elevated hepatic enzymes and are reversed by withdrawal. Severe adverse reactions such as myelosuppression, liver toxicity, and pulmonary fibrosis are very rare.[101,102] Since MTX is a teratogenic medication, men and women of fertile age should use effective contraceptive methods during treatment. Its use is contraindicated during lactation.[67]

d) Azathioprine

AZA is a purine analog that blocks RNA and DNA synthesis, interfering with proliferation of T and B cells, and with functioning of antigen presenting cells.[92]

Clinical trials with adults showed that when compared with placebo, it significantly improved scores for cutaneous lesions, pruritus, sleep disturbances, and interference with daily and employment activities.[103]

It is recommended as a second line treatment option for moderate to severe AD in adults, especially in cases in which CsA is ineffective or contraindicated.[67] Onset of action is slow and the benefits may not become apparent for up to 2 to 3 months after starting treatment.[104]

The most common adverse reactions to AZA are nausea and vomiting, which may occur during the first weeks of treatment and are reversed by withdrawal of the medication. Severe side effects such as leukopenia, liver toxicity, and myelosuppression may also occur. The last of these is dependent on partial or total deficiency of thiopurine methyltransferase (TPMT). Therefore, before initiating treatment, patients should be assessed for activity and/or by genotyping this enzyme to reduce the risk of myelotoxicity and to choose the safest therapeutic dose.[92]

Laboratory monitoring is essential during treatment with AZA and the recommended dose is from 1 to 3 mg/kg/day. A study realized with children with severe AD and normal TPMT levels before starting treatment did not detect myelosuppression using a dosage of 2.5-3.5 mg/kg.[105] Adult patients with moderate/severe AD, in whom the dose of AZA was adapted to TPMT activity (1.0 mg/kg per day) achieved similar clinical improvement to patients with normal TPMT activity given 2.5 mg/kg of AZA.[16] In common with CsA, AZA cannot be combined with UV treatment and effective UV protection should be used.[67]

e) Mycophenolate mofetil (MFM)

MFM is an immunosuppressant that inhibits purine biosynthesis, resulting in reduction of lymphocyte proliferation. Its utility and good safety profile have been documented in uncontrolled clinical trials in adults, children, and adolescents with refractory AD. However, it remains a third line treatment option because of the lack of large scale efficacy studies.[106,107] Adverse gastrointestinal events such as nausea or diarrhea are the most common side effects during treatment with MMF and are more common at the start of treatment. Since it is teratogenic, patients of both sexes of fertile age should use effective contraceptive methods during treatment with MFM.[67]

Table 11 summarizes the principal characteristics of the systemic immunosuppressants most frequently used for treatment of severe AD.

Immunobiologicals

Immunobiologicals are already being used in current clinical practice and have been increasingly adopted for treatment of inflammatory diseases. They constitute a class of pharmacological agents developed with genetic engineering to act on the targets/mediators of allergic inflammation. Advances in knowledge about physiopathogenesis and the arrival of target-specific treatments have triggered a revolution in treatment of immunomediated diseases.[108,109]

Current immunobiologicals are used to modify the Th2 response, blocking IgE and cytokines such as IL-4, IL-13 and IL-22, IL-32, and IL-17/IL-23, which play a fundamental role in pathogenesis of AD.[108] These are safe medications and clinical assessment (patient history/physical examination) is enough to prescribe them to patients with moderate/severe forms of AD that have not been controlled despite adequate treatment and they do not require more intense laboratory assessments, unlike the immunosuppressants.

a) IL-4 and/or IL-13 inhibitors

– Dupilumab

Dupilumab was the first immunobiological to be approved for clinical use by the FDA (US Food and Drug Administration), the EMA (European Medicines Agency) and ANVISA (the Brazilian National Agency for Sanitary Vigilance) for treatment of AD in children over 6 years of age, adolescents, and adults with moderate to severe AD that is not controlled by the usual treatments.[108,109] It is also indicated for allergic asthma and chronic rhinosinusitis with nasal polyps.[110]

Dupilumab is a recombinant human monoclonal antibody of specific IgG4 that binds to the alpha subunit of IL-4 and IL-13 receptors. This causes downregulation of the receptor which signals the JAK/STAT pathway responsible for regulation of the expression of several genes involved in pathogenesis of AD.[109]

By blocking the IL-4 and IL-13 pathway, dupilumab blocks three different relevant mechanisms of disease in AD: impairment of skin barrier function caused by downregulation of the filaggrin protein; IgE class switching caused by Th2 cytokines; and global Th2 differentiation of the inflammatory infiltrate.[109,111,112]

Investigation of the efficacy of monotherapy with dupilumab (initial dose of 600 mg, followed by 300 mg every 2 weeks, SC) for 16 weeks demonstrated an 82.5% reduction for EASI 50, 60.3% for EASI 75, and 36.5% for EASI 90. Improvement in cutaneous lesions and reduction of itching occurred 2 weeks after starting treatment and were maintained for up to 1 year when combined with TCS.[113]

Table 11
Systemic immunosuppressants for treatment of severe atopic dermatitis

	Cyclosporine	Methotrexate	Azathioprine	Micofenolato
Indication	Severe adults Off-label for children	Off-label for adults and children	Off-label for adults and children	Off-label for adults and children
	Acute intervention Mean duration 1 year	Long term maintenance	Can be used long term	Can be used long term
Onset of action	2 weeks	8-12 weeks	8-12 weeks	8-12 weeks
Relapse	< 2 weeks	> 12 weeks	> 12 weeks	> 12 weeks
Most frequent side effects	Arterial hypertension ↑ Serum creatinine	Hematological ↑ Hepatic enzymes Gastrointestinal	Hematological ↑ Hepatic enzymes Gastrointestinal	Low toxicity Gastrointestinal infections
Adult dosage Initial	3-5 mg/kg/day	5-15 mg/week	50 mg/day	[a] Depending on TPMT 1–2 g/day
Maintenance	2.5-3 mg/kg/day	15 mg/week; may ↑ to max 25 mg/week	2-3 mg/kg/day	15 / week; may ↑ to max 25 mg/week
Child dosage Initial	3-5 mg/kg/day	10-15 mg/m²/week	25-50 mg/day	[a] Depending on TPMT 20–50 mg/kg/day
Maintenance	2.5-3 mg/kg/day	↑ 2.5-5 mg/week, ↓ by 2.5 mg/week to lowest effective dose	2-3 mg/kg/day	↑ total dose by 500 mg every 2-4 weeks up to 30–50 mg/kg/day
Pregnancy	Possible (category C)	Contraindicated (category X)	Contraindicated (category D)	Contraindicated (category X)
Paternity	Possible	Few data Contraindicated	Use possible? Few data	Use possible? Few data
Vaccination [b]	3 months	1 to 3 months	3 months	3 months

[a] TPMT = thiopurine methyltransferase (see text); [b] Minimum interval for attenuated vaccines.
Table based on references 67,89, and 95.

It is recommended that the immunobiological be administered concomitantly with the underlying treatment that the patient is using daily (environmental hygiene, bathing, skin moisturizing, and topical medication, when necessary) (Table 12). Side effects of this medication are minimal, the most common being conjunctivitis (5% to 28%).[114,115]

– Tralokinumab

Not yet available in Brazil, tralokinumab is a humanized antibody that neutralizes IL-13 by inhibiting its interaction with the alpha subunit of the IL-13R receptor.[109] Tralokinumab interferes with downregulation of the filaggrin cutaneous barrier caused by IL-13. IL-13 is elevated both in skin with lesions and in skin without lesions in patients with AD and correlates with disease severity.[108] It has been documented that presence of biomarkers related to increased IL-13 is associated with better response to treatment with this biological.[116]

– Lebrikizumab

This is another specific humanized monoclonal antibody targeting IL-13, but ongoing studies do not yet enable inference of the best dosage regimens or its safety profile.[108]

b) Nemolizumab

This is a specific monoclonal antibody targeting the alpha receptor of IL-31, the principal cytokine involved in pruritus in patients with AD. It is another biological with a high likelihood of future approval for treatment of AD. Inpatients with severe/moderate AD, a double-blind study of nemolizumab *versus* placebo documented better efficacy for the biological for control of pruritus in these patients.[109]

c) Fezakinumab

Fezakinumab is a specific humanized monoclonal antibody targeting IL-22.[108,117] In acute and chronic AD lesions, an increase in IL-22 related to severity was documented. IL-22 is produced by Th22 cells and acts on keratinocytes, impairing cutaneous barrier function. A study of patients with SCORAD ≥ 50 documented significant clinical improvement in the 12th week of treatment with fezakinumab, when compared to placebo.[117] Moreover, there was also progressive improvement in all outcomes assessed up to week 20, even though treatment was ended in week 10, suggesting that the therapeutic effect is sustained after withdrawal.[117]

Immunobiologicals are modern medications and advances in knowledge about the mechanism of the disease should lead to identification of endotypes

Table 12
Dosage recommendations for dupilumab in atopic dermatitis

Body weight	Initial dose	Subsequent doses
15 to less than 30 Kg	600 mg (2 300 mg injections)	300 mg every 28 days
30 to less than 60 Kg	400 mg (2 200 mg injections)	200 mg every 14 days
60 Kg or over	600 mg (2 300 mg injections)	300 mg every 14 days

that will enable the best Candidates for these specific treatments to be chosen, contributing to personalized or precision AD medicine.

d) Small molecules

Small molecules are synthetic drugs with low molecular weight and the capacity for intracellular diffusion that can interfere with intracellular activation pathways. In comparison to the systemic immunosuppressants used for treatment of AD, these drugs have less potential for adverse effects because they enable more selective suppression of immunological pathways.[118] When compared to immunobiologicals, they have greater potential for adverse effects, because they inhibit higher numbers of inflammatory pathways, and they are not licensed for use in children. Table 13 summarizes the principal differences between the biologicals and small molecules.

Table 13
Comparison of the characteristics of biologicals and small molecules

	Biologicals	Small molecules
Molecular weight	Generally >2-5 kDa	Generally <0.5 kDa
General characteristics	Designed monoclonal antibodies	Chemical compound
	May not have a well-defined structure	Well-defined structure
	Generally made using or from live cells and organisms	Synthesized organic molecules
	Very often unstable; generally heat sensitive	Normally stable
	Catabolized into amino acids, sugars, lipids, etc.	Metabolism is by hepatic enzymes such as cytochrome P450
	Limited toxicity	May cause toxicity
	Do not penetrate cells and do not cross the blood-brain barrier	Cross the blood-brain barrier (especially liposoluble)
Route of administration	Parenteral	Oral
Half-life	Long half-life (days to weeks)	Short half-life
	Allow infrequent administration	Need frequent administration
Specificity for target	Highly selective and specific to target	Higher potential for effects beyond the target
Immunogenicity	Possible immunogenicity	Immunogenicity improbable
Cost	High development costs	High cost, but often lower than for a biological

Modified from Ahn J, et al.[118]

JAK inhibitors

JAK enzymes are important mediators of the intracellular activity of many substances, including the inflammatory cytokines (Figure 2). When their receptors are activated, signal transducer and activator of transcription (STAT) proteins undergo phosphorylation and can be transported to the cell nucleus, inducing transcription and regulation of the expression of selected genes. This stimulates expression of many different molecules and cytokines that facilitate mobilization of leukocytes and cell proliferation. The JAK/STAT pathway therefore plays a fundamental role in the function of hematopoietic and immunological cells and recent studies show that this pathway may be more susceptible to activation in patients with asthma, AD, and allergic rhinitis, which are diseases characterized by increased type 2 inflammatory IL.[119,120]

JAK inhibitors are small molecules, i.e. medications with low molecular weight, that can easily cross the cell membrane and reach intracellular targets. They thus act to inhibit signaling mediated by specific cytokines, acting on chains of specific receptors of JAK subtypes: JAK-1, JAK-2, JAK-3, and/or Tyrosine-Kinase 2 (TYK-2).[121,122]

Chronic pruritus is dependent on neuronal JAK-1 signaling, and inhibition of JAK appears to directly block neuronal transmission of itching.[123] Chronic pruritus is dependent on neuronal signaling by IL-4Ra and JAK-1 and patients for whom other immunosuppressant treatments have failed have achieved accentuated improvements when treated with JAK inhibitors. Blocking JAK/STAT can also affect eosinophil activation, B cell maturation, epidermal chemokines, and many other pathways involved in AD pathophysiology.[124]

The first JAK inhibiting drug was granted approval for clinical practice in 2011, for an autoimmune disease.[125] Their clinical applications are wide-ranging, from oncology to viral diseases, and they have great potential for allergic diseases and immune response type 2. The future prospects for JAK inhibitors in AD are increasingly being studied and they have recently been regulated in several countries, both for topical and systemic use.

Table 14 summarizes phase III studies with JAK inhibitors for AD and their efficacy and safety.

Upadacitinib is a selective JAK-1 inhibitor that blocks activity of the principal proinflammatory cytokines. It had already been authorized for use in rheumatoid arthritis in several countries. With

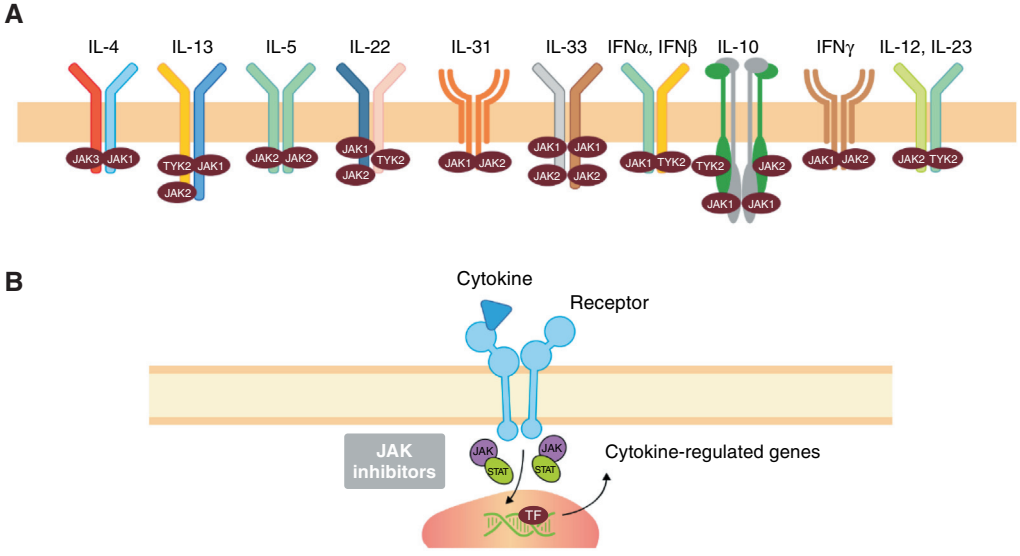


Figure 2

A) JAK signaling with cytokines involved in immune response and immunomediated diseases.

B) JAK/STAT pathway

Adapted from Ahn J, et al. [123]

Table 14
Phase 3 studies with JAK inhibitors in atopic dermatitis [a]

Drug	Target	Phase 3 study	Inclusion criteria	Population	Time of assessment	EASI-75	IgA 0/1 (Improvement ≥ 2 points)	Most common adverse effects
Upadacitinib [127-132] (Up.) Oral route	JAK-1	MEASURE UP 1 (NCT03569293)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	847 (12 - 75 years)	16 weeks	Up. 15 mg: 69.6% Up. 30 mg: 79.7% Placebo: 16.3%	Up. 15 mg: 48.1% Up. 30 mg: 62.0% Placebo: 8.4%	Acne, URTI, nasopharyngitis, headache, increased CPK
		MEASURE UP 2 (NCT03607422)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	836 (12 - 75 years)	16 weeks	Up. 15 mg: 60.1% Up. 30 mg: 72.9% Placebo: 13.3%	Up. 15 mg: 38.8% Up. 30 mg: 52.0% Placebo: 4.7%	Acne, URTI, nasopharyngitis, headache, increased CPK
		AD UP (NCT03568318)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	901 (12 - 75 years)	16 weeks	Up. 15 mg: 64.6% Up. 30 mg: 77.1% Placebo: 26.4%	Up. 15 mg: 39.6% Up. 30 mg: 58.6% Placebo: 10.9%	Acne, nasopharyngitis, URTI, herpes oral, increased CPK, headache
		HEADS UP (NCT03738397)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4	692 (18 - 75 years)	16 weeks	Up. 30 mg: 71.0% Dup. 300 mg: 61.1%	Not reported	Acne, URTI, increased CPK, nasopharyngitis
Abrocitinib [133-140] (Ab.) Oral route	JAK-1	JADE MONO-1 (NCT03349060)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	387 (12 - 75 years)	12 weeks	Ab. 100 mg: 39.7% Ab. 200 mg: 62.7% Placebo: 11.8%	Ab. 100 mg: 23.7% Ab. 200 mg: 43.8% Placebo: 7.9%	Nausea, nasopharyngitis, headache, URTI
		JADE MONO-2 (NCT03575871)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	391 (12 - 75 years)	12 weeks	Ab. 100 mg: 44.5% Ab. 200 mg: 61.0% Placebo: 10.4%	Ab. 100 mg: 38.1% Ab. 200 mg: 28.4% Placebo: 9.1%	URTI, nasopharyngitis, headache, nausea, vomiting, acne
		JADE COMPARE (NCT03720470)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	837 (≥ 18 years)	12 weeks	Ab. 100 mg: 58.7% Ab. 200 mg: 70.3% Dup. 300 mg: 58.1% Placebo: 27.1%	Ab. 100 mg: 36.6% Ab. 200 mg: 48.4% Dup. 300 mg: 36.5%	Similar to the previous studies
		JADE TEEN (NCT03796676)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	285 (12 - 17 years)	12 weeks	Ab. 100 mg: 68.5% Ab. 200 mg: 72.0% Dup. 300 mg: 41.5%	Placebo: 14.0% Ab. 100 mg: 41.6% Ab. 200 mg: 46.2%	URTI, headache, nasopharyngitis, dizziness, acne, vomiting

* Adapted from Nogueira LB, et al.[126] URTI = upper respiratory tract infection, CPK = creatine phosphokinase.

Table 14 *(continuation)*
Phase 3 studies with JAK inhibitors in atopic dermatitis [a]

Drug	Target	Phase 3 study	Inclusion criteria	Population	Time of assessment	EASI-75	IgA 0/1 (Improvement ≥ 2 points)	Most common adverse effects
Baricitinib [141-146] (Bar.) Oral route	JAK-1 JAK-2	BREEZE 1 (NCT03334396)	EASI ≥ 16 IGA ≥ 3	624 (≥ 18 years)	16 weeks	Bar. 1 mg: 17.3% Bar. 2 mg: 18.7% Bar. 4 mg: 24.8% Placebo: 8.8%	Bar. 1 mg: 11.8% Bar. 2 mg: 11.4% Bar. 4 mg: 16.8% Placebo: 4.8%	Nasopharyngitis, URTI, diarreia, headache
		BREEZE 2 (NCT03334422)	EASI ≥ 16 IGA ≥ 3	615 (≥ 18 years)	16 weeks	Bar. 1 mg: 12.8% Bar. 2 mg: 17.9% Bar. 4 mg: 21.1% Placebo: 6.1%	Bar. 1 mg: 8.8% Bar. 2 mg: 10.6% Bar. 4 mg: 13.8% Placebo: 4.5%	Herpes simplex, nasopharyngitis, increased CPK, headache
		BREEZE 4 (NCT03428100)	EASI ≥ 16 IGA ≥ 3 BSA ≥ 10% Contraindication to ciclosporin	463 (≥ 18 years)	16 weeks	Bar. 1 mg: 22.6% Bar. 2 mg: 27.6% Bar. 4 mg: 31.5% Placebo: 17.2%	Bar. 1 mg: 12.9% Bar. 2 mg: 15.1% Bar. 4 mg: 21.7% Placebo: 9.7%	Nasopharyngitis, herpes simplex, influenza, headache, back and abdominal pain, diarrhea, conjunctivitis
		BREEZE 5 (NCT03435081)	EASI ≥ 16 IGA ≥ 3 BSA ≥ 10%	440 (≥ 18 years)	16 weeks	Bar. 1 mg: 12.9% Bar. 2 mg: 29.5% Placebo: 8.2%	Bar. 1 mg: 12.9% Bar. 2 mg: 24.0% Placebo: 5.4%	Nasopharyngitis, URTI
		BREEZE 7 (NCT03733301)	EASI ≥ 16 IGA ≥ 3 BSA ≥ 10%	329 (≥ 18 years)	16 weeks	Bar. 2 mg: 43.1% Bar. 4 mg: 47.7% Placebo: 22.9%	Bar. 2 mg: 23.9% Bar. 4 mg: 30.6% Placebo: 14.7%	Folliculitis, URTI, nasopharyngitis
Ruxolitinibe [147] (Rux.) Topic	JAK-1 JAK-2	TRuE-AD 1 (NCT03745638)	IGA 2/3 BSA 3-20% (except for scalp)	631 (≥ 12 years)	8 weeks	Rux. 0.75%: 56.0% Rux. 1.5%: 62.1% Vehicle: 24.6%	Rux. 0.75%: 50.0% Rux. 1.5%: 53.8% Vehicle: 15.1%	Nasopharyngitis, URTI, headache
		TRuE-AD 2 (NCT03745651)	IGA 2/3 BSA 3-20% (except for scalp)	618 (≥ 12 years)	8 weeks	Rux. 0.75%: 51.5% Rux. 1.5%: 61.8% Vehicle: 14.4%	Rux. 0.75%: 39.0% Rux. 1.5%: 51.3% Vehicle: 7.6%	URTI, nasopharyngitis
Delgocitinib [148,149] (Del.) Topic	pan-JAK	QBA 4-1 (JapicCTI-173554)	EASI ≥ 10 BSA 10-30%	158 (≥ 16 years)	4 weeks	Del. 0.5%: 26.4% Vehicle: 5.8%	Del. 0.5%: 10.4% Vehicle: 3.8% FACE: Del. 0.5%: 22.8% Vehicle: 4.0%	Contact dermatitis
		(JapicCTI-184064)	EASI ≥ 5 IGA 2-4 BSA 5-30%	137 (2 - 15 years)	4 weeks	Del. 0.25%: 37.7% Vehicle: 4.4%	Not reported	Nasopharyngitis, folliculitis

* Adapted from Nogueira LB, et al.[126] URTI = upper respiratory tract infection, CPK = creatine phosphokinase.

publication of promising results, upadacitinib was approved for treatment of AD in patients over the age of 12 years by the European Union in August 2021,[150] by the FDA in January 2022,[151] and by ANVISA in May of the same year, for use at initial doses of 15 mg/day.[152]

Abrocitinib is a selective JAK-1 inhibitor with systemic action that is administered orally. This drug has also been approved by the FDA for use in patients with AD over the age of 18 in the United States, since January 2022.[153] This drug is still going through the regulatory process in Brazil.

Baricitinib is a JAK-1 and JAK-2 inhibitor that has been studied for use in AD since 2016, when phase 2 studies began. Although it has less efficacy than the other two oral JAK inhibitors that have had phase 3 studies for AD, baricitinib was the first JAK inhibitor approved in Europe for treatment of eczema, in September 2020,[154] and it is available in Brazil.

Ruxolitinib is a topical JAK-1 and JAK-2 inhibitor. It was developed to optimize the drug action directly on affected areas and reduce the risks of adverse systemic effects. In September 2021, ruxolitinib was approved for use with AD by the FDA and was the first JAK inhibitor approved for use in the United States, at a concentration of 1.5%, in patients over the age of 12 years.[147]

Delgocitinib is a topical pan-JAK inhibitor, i.e. it inhibits JAK-1, JAK-2, JAK-3, and TYK-2. Delgocitinib was approved for topical use with AD in Japan at concentrations of 0.25% and 0.5% for adults and for children over 2 years old in March 2021.[155]

Considering the potential for adverse events observed in pivotal clinical trials of JAK inhibitors for AD, it is necessary to conduct clinical and laboratory assessments before starting treatment to evaluate contraindications and also to monitor clinical events and laboratory findings throughout treatment. Clinical assessment must include patient history and risk factors for infectious diseases (tuberculosis, Herpes zoster, viral hepatitis, and HIV infection) and assess risk factors for thromboembolism and history of malignant cancers. The initial laboratory assessment should include full blood test, hepatic function, renal function, lipid profile, markers of viral hepatitis (B and C), and anti-HIV serology. Basic laboratory toxicity monitoring includes full blood tests, hepatic function, renal function, and lipid profile, which should be done every 3 months, and additional tests should be ordered depending on the clinical context. Investigation of active and latent tuberculosis should be conducted with PPD, chest X-ray, and interferon gamma release assay (IGRA) before treatment and over the course of treatment, if there are clinical indications. It is also recommended that immunization is up to date as scheduled before starting treatment.[156]

General recommendations for systemic treatments

According to the recommendations of national and international guidelines, systemic treatments should only be used for severe AD, i.e., for patients for whom adequate control of the disease cannot be achieved with optimized topical treatment and phototherapy. Severity should be assessed using widely used standardized and validated instruments, such as SCORAD and EASI. It is also important to assess the impact on patients' quality of life using the DLQI and the CDLQI. Patients who have moderate forms of AD, but with a major impact on their quality of life, are also Candidates for systemic treatment.[64,156,157]

Before initiating systemic treatment, it is important to revisit differential diagnosis, ruling out severe conditions that mimic AD, such as T cell lymphoma and inborn errors of immunity and evaluate adherence to treatment; investigate participation of trigger factors and aggravating factors, such as exposure to allergens (inhaled agents, foods, contactants), irritants, and psychological aspects. The choice of systemic treatment should be personalized and participatory, taking into account age group, comorbidities, adverse event profile, need for laboratory monitoring, patient preference (oral *versus* injectable medications), and the local scenario of access to the different medications. Table 15 summarizes the principal characteristics of medications for systemic treatment of AD licensed in Brazil, including those used off-label.[157]

Final comments

AD is a disease that is very prevalent in childhood and that tends to remission over time in the majority of cases. Changes to the cutaneous barrier creating the possibility of penetration by allergens and pathogens and consequent immunological dysregulation are the primary causes that explain the inflammatory process established at the level of the skin.[158]

Once epithelial damage has occurred, many different cells and cellular products are involved in the

process. We now know that Th2, Th17, Th22, and ILC-2 cells participate most actively in physiopathogenesis of AD. Several studies have shown the importance of release of many different cytokines by these cells, the direct or indirect actions of which cause greater epidermal differentiation and more severe cutaneous barrier dysfunction. It should be emphasized that many of these cytokines also function to activate cells that release products that initiate, aggravate or perpetuate the inflammatory process.[25]

Many medications have been used with the objective of inhibiting the inflammation that establishes in the dermis. Topical corticosteroids and calcineurin inhibitors are still the drugs most used as anti-inflammatory agents during the initial stages of treatment.

Table 15
General recommendations for systemic treatment of patients with atopic dermatitis [a]

	Conventional systemic treatment			Biological	JAK inhibitors		Rescue treatments
	Cyclosporine	**Methotrexate**	**Azathioprine**	**Dupilumab**	**Baricitinib**	**Upadacitinib**	**Systemic corticosteroids**
Recommendation	↑↑	↑	↑	↑↑	↑↑	↑↑	↑
Age group	≥ 16 years	Off-label	Off-label	≥ 6 years	≥ 18 years	≥ 12 years	Licensed for all age groups
Time to respond (weeks)	1-2	8-12	8-12	4-6	1-2	1-2	1-2
Basic monitoring (may be expanded depending on the context)	Complete blood count, hepatic and renal function, blood pressure	Complete blood count, hepatic and renal function, screening for chronic infections	Complete blood count, hepatic and renal function, screening for chronic infections	Unnecessary	Complete blood count, hepatic function, and lipid profile	Complete blood count, hepatic function, and lipid profile	Unnecessary for short term use Consider glycemia and adrenal suppression test with prolonged use
Most relevant adverse events	↑ Creatinine, ↑ Blood pressure	Nausea, fatigue, ↑ hepatic enzymes and myelotoxicity	Gastro-intestinal disorders, hyper-sensitivity reactions, liver toxicity, myelotoxicity	Conjunctivitis, upper airway infections	UAI, ↑ LDL-cholesterol, trombocytosis, nausea and abdominal pains, herpes, acne	UAI, acne, anemia and neutropenia, ↑ CPK, ↑ LDL-cholesterol, nausea and abdominal pains, herpes	Cutaneous atrophy, weight gain, sleep disorders, mood changes, hyperglycemia, diabetes, gastritis/peptic ulcer, osteoporosis

[a] Adapted from Wollenberg A, et al.[157]
↑↑ = higher grade recommendation, ↑ = lower grade recommendation, UAI = Upper airway infections, CPK = creatine phosphokinase.

During recent years, based on understanding of the importance of the inflammatory process, systemic immunosuppressants such as cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil have become the last resort for inhibition of this process. Their use requires special precautions because of the significant possible side effects, particularly when prescribed for prolonged periods.

It is important to point out that other medications with anti-inflammatory activity, such as systemic corticosteroids, can also be prescribed in very specific situations and for a small number of days.[75]

Addition of immunobiologicals and JAK inhibitors to the arsenal for treatment of severe to moderate AD has made safe and effective treatment possible for this population of patients. In view of the high cost of these drugs, national and international guidelines recommend their use for severe forms of AD, based on well-defined severity criteria, and after failure of optimized topical treatment.[22,159]

Immunobiologicals inhibit the activity of proinflammatory cytokines or their receptors. Dupilumab (anti IL-4/IL-13) was the first immunobiological to be used and many others are being tested in phase III clinical trials. Some are already available or will soon be approved for clinical use, such as: anti-TSLP, anti-IL-13, anti-IL31, anti-IL33, and anti-IL17.[159] Small molecules and JAK inhibitors are also being prescribed with excellent results.[83] These new drug classes attenuate disease severity, reducing the inflammatory process, improving the appearance of the skin, and relieving cutaneous pruritus, which is being proven with tools such as SCORAD and EASI.

One expectation for the coming years is that we will increase our understanding of the factors that favor development of the disease, such as genetic and epigenetic factors, external and internal exposomes, and other factors that are part of its pathophysiology.[160] We also hope that biomarkers can be identified in the future that will enable an individualized approach based on phenotypes and endotypes and also new therapeutic options that will help us to better manage this extremely complex disease.[161,162]

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