




## ATOPIC DERMATITIS: A SYSTEMATIC REVIEW ON EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT IN PEDIATRICS

 <https://doi.org/10.56238/levv16n46-023>

Submitted on: 10/02/2025

Publication date: 10/03/2025

Mirela Rocha Lascalla<sup>1</sup>, Isadora Lopes Silva<sup>2</sup>, Naiádine Sforcini Baldo<sup>3</sup>, Lara Morial Martins<sup>4</sup>, Lucas Ruffo de Medeiros<sup>5</sup>, Emerson de Lima Borba<sup>6</sup>, Marina Borges Lopes de Carvalho<sup>7</sup>, Julia Sammour<sup>8</sup>, Mariana Sciampaglia de Carvalho<sup>9</sup>, Robert Daniel Riveros Ramirez<sup>10</sup>, José Franco de Angelis<sup>11</sup>, Júlia Nery Tavares<sup>12</sup>, Rafael Natali do Amaral<sup>13</sup> and Maria Eugênia Alves Martins de Araújo Tristão<sup>14</sup>

### ABSTRACT

**Objective:** The general objective of the present study is to analyze the scientific production on atopic dermatitis in pediatrics, seeking to identify the main methods used in the diagnosis and treatment of this pathology. **Methodology:** This is a systematic review focused on understanding the main aspects that permeate atopic dermatitis in the pediatric population. The research was guided by the question: "What are the main aspects that permeate the development of atopic dermatitis in pediatrics, as well as what are the main

<sup>1</sup> Undergraduate student in Medicine at the University of Franca (UNIFRAN) - Franca/SP

E-mail: Mirelarochalascalla@hotmail.com

<sup>2</sup> Graduating in Medicine at the University of Franca (UNIFRAN) - Franca/SP

E-mail: isadoralopesjpa@gmail.com

<sup>3</sup> Graduating in Medicine from the University of Franca (UNIFRAN) - Franca/SP

E-mail: naiadinebaldo@gmail.com

<sup>4</sup> Graduated in Medicine from the University of Franca (UNIFRAN) - Franca SP

E-mail: laramorial@hotmail.com

<sup>5</sup> Graduating in Medicine at the Municipal University Center of Franca (UNIFACEF), Franca SP

E-mail: Lucasruffomedeiros@hotmail.com

<sup>6</sup> Graduated in Medicine from the Faculty of Medical Sciences of Paraíba

E-mail: emersonarquivos2020@gmail.com

<sup>7</sup> Graduated in Medicine from the University of Franca (UNIFRAN) - Franca, SP

E-mail: marinabldecarvalho@hotmail.com

<sup>8</sup> Undergraduate student in Medicine at the University of Franca (UNIFRAN) - Franca/SP

E-mail: jsammour50@gmail.com

<sup>9</sup> Undergraduate student in Medicine at Universidade de Franca (UNIFRAN) - Franca- SP

E-mail: marianasciampaglia10@gmail.com

<sup>10</sup> Medical Degree at Anhembi Morumbi University - Piracicaba SP

E-mail: robertriverosdr@gmail.com

<sup>11</sup> Graduated in medicine from Estácio de Ribeirão Preto SP

E-mail: dr.josefrancoangelis@gmail.com

<sup>12</sup> Undergraduate student in Medicine at Centro Universitário Presidente Antônio Carlos (Unipac JF)

E-mail: julia\_neryt@hotmail.com

<sup>13</sup> Graduated Federal University of Mato Grosso do Sul (UFMS) - Campo Grande MS

E-mail: rafael.amaral@ufms.br

<sup>14</sup> Dr. and Advisor

Pediatrician, Post graduate in Pediatric Palliative Care, Pediatric and Neonatal ICU and Pediatric Nutrition, acting as a professor of the medical course  
University of Franca

Institution: University of Franca (UNIFRAN)

E-mail: Maria Eugênia \_059@hotmail.com

clinical repercussions and the diagnostic and therapeutic methods used in clinical practice?"element. To find answers, searches were performed in the PubMed database using four descriptors combined with the Boolean term "AND". This resulted in 511 articles. 20 articles were selected for analysis and 12 articles were used to compose the collection.

**Results:** Atopic dermatitis (AD) is a chronic inflammatory condition that affects millions of people, with a higher incidence in children. The efficacy of topical corticosteroids (TCS) is recognized, but concerns about their side effects, especially in pediatric patients, lead to the underutilization of these treatments. Proactive approaches, such as the appropriate use of TCS and the introduction of topical calcineurin inhibitors (TCI), are important for effective treatment. **Conclusion:** Future research should focus on understanding the regional factors that influence the prevalence of AD and developing new treatments with lower risks of adverse effects. In addition, educational programs and action plans are essential to increase treatment adherence, especially among children, thus ensuring a better quality of life for patients.

**Keywords:** Pediatrics. Atopic dermatitis. Treatment. Diagnosis.

## INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease that usually manifests in early childhood and can precede the development of other atopic disorders, including asthma, allergic rhinitis, and food allergies. The onset of AD most commonly occurs between 3 and 6 months of age, with approximately 60% of children with AD showing symptoms within the first 12 months. Consensus guidelines indicate that AD is characterized by essential features such as pruritus and eczema (acute, subacute, or chronic), with eczema lesions exhibiting typical morphology or age-specific patterns, and having a chronic or relapsed history. The presence of these essential features in combination with an early age of onset, atopy, and xerosis support the diagnosis of AD (EICHENFIELD et al., 2022).

The prevalence of AD varies widely around the world due to regional, country-specific, age group, and data capture methodological differences, affecting 0.2% to 36% of the pediatric population (ages < 18 years). This high prevalence, coupled with the high patient/caregiver burden and increased health care utilization, highlights the considerable public health burden associated with AD. In addition, approximately 50% of AD patients are treated in the primary care setting (EICHENFIELD et al., 2022).

The pathogenesis of the disease is complex and multifactorial, involving skin barrier failure, local and systemic immune dysregulation, intestinal and skin dysbiosis, and also genetic factors interacting with each other (ANANIA et al., 2022). Transcriptomic analysis of the skin of AD patients revealed a predominant increase in type 2 cytokines in acute and chronic skin lesions, including interleukin (IL)-13, IL-4, IL-5, and IL-31, indicating strong activation of type 2 T helper (Th2) immune responses. Type 2 cytokines, particularly IL-4 and IL-13, orchestrate the generation of immunoglobulin E (IgE) by B cells, along with the stimulation of immune cells such as eosinophils and mast cells. These processes collectively contribute to the inflammatory environment and the manifestation of pruritus symptoms (ZHAO et al., 2023).

The clinical manifestations of AD vary with age. In infants, the scalp, face, neck, trunk, and extensor (outer) surfaces of the extremities are usually affected, while the diaper area is usually spared. Children often have involvement of the flexural surfaces of the extremities (i.e., bend/bend at the elbow and back of the knee), neck, wrists, and ankles. In adolescence and adulthood, the flexural surfaces of the extremities, hands, and feet are usually affected. Regardless of age, the itching associated with AD usually continues during the day and worsens at night, leading to sleep loss and substantial impairments in quality of life (CARR et al., 2024).

This systematic review article aims to compile and evaluate the existing scientific evidence on atopic dermatitis in the pediatric population. The intention is to provide a comprehensive and up-to-date view, which not only synthesizes current knowledge about the condition, but also identifies gaps in research and directs future investigations and clinical practices. By offering an in-depth analysis of the evidence, this study aims to serve as a resource for health professionals, researchers, and academics, helping to optimize diagnostic and therapeutic approaches to this condition.

## **METHODOLOGY**

This is a systematic review that seeks to understand the main aspects of atopic dermatitis in the pediatric population, as well as to demonstrate the main diagnostic and pharmacological methods used in the treatment of the condition. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: "What are the main aspects that permeate the development of atopic dermatitis in pediatrics, as well as what are the main clinical repercussions and the diagnostic and therapeutic methods used in clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. 4 descriptors were used in combination with the Boolean term "AND": Topical Therapy, Atopic Dermatitis, Diagnostic Methods and Pediatric Atopic Dermatitis. The search strategy used in the PMC database was: Topical Therapy AND Atopic Dermatitis AND Diagnostic Methods and Atopic Dermatitis AND Pediatric Atopic Dermatitis. From this search, 511 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2020 to 2025 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 511 articles were found. After applying the inclusion and exclusion criteria, 20 articles were selected from the PubMed database, and a total of 12 studies were used to compose the collection.

## **DISCUSSION**

Atopic dermatitis (AD, also known as eczema or atopic eczema) is now recognized as a systemic condition and is the most common chronic inflammatory skin disease

worldwide, affecting up to 20% of children (KERN et al., 2024). Since the 1970s, the incidence of AD has increased 2 to 3 times in industry developed countries, affecting approximately 15% to 20% of children, 5% to 20% of adolescents, and 1% to 3% of adults. However, the International Study of Asthma and Allergies in Childhood (ISAAC), reported that the prevalence varies widely depending on the geographic region (NAPOLITANO et al., 2022).

The onset of AD occurs during the first years of life in approximately 80% of individuals and approximately 60% have remission in adolescence (BYLUND et al., 2020). In the U.S. primary care setting, a cross-sectional research study reported a prevalence of AD of 24% among pediatric patients aged 0–5 years, ranging from 15% of children aged 1 year < to 38% of children aged 4–5 years. In this study, an assessment of AD severity indicated that most patients had mild AD (58%) or moderate AD (39%), with only 3% of children having severe AD. Comorbidities that were more prevalent in the AD population than in the AD population included asthma (12 vs 4%; age-adjusted prevalence ratio, 3.0 [95% CI 1.8–4.9];  $p < 0.001$ ) and food allergy (8 vs 2%; 3.7 [1.5–9.2];  $p = 0.005$ ) (EICHENFIELD et al., 2022).

AD is precipitated by an interaction between environmental factors, disrupted skin barrier, skin microbiome, and immune dysregulation among individuals with AD susceptibility genes. AD is a highly inherited disease, with phenotype-specific genes likely to play an important role alongside 'generic' atopy genes. Genome-wide association studies have identified loci correlated with autoimmune regulation, including genes associated with the regulation of host innate defenses and T cell function; these studies have also linked AD to other autoimmune diseases or cardiovascular diseases (EICHENFIELD et al., 2022).

The etiology of AD seems to be driven by the reciprocal interaction between two biological pathways: skin epithelial function and innate/adaptive immune responses. Skin barrier dysfunction is a well-defined essential component in the pathogenesis of AD. In healthy skin, the epidermal barrier is a matrix of structural lipids and proteins that exhibits antimicrobial properties, functioning to maintain skin hydration and prevent allergen penetration, and disruption of any of these components contributes to AD (EICHENFIELD et al., 2022).

Skin barrier abnormalities are often associated with mutations within, or impaired expression of, the filaggrin (FLG) gene, which encodes a structural protein essential for skin barrier formation, although genome-wide analyses have now identified at least 30 different susceptibility regions for AD. The skin of individuals with AD has also been shown to be deficient in ceramides (lipid molecules) as well as antimicrobial peptides such as

cathelicidins, which represent the first line of defense against many infectious agents. These skin barrier abnormalities lead to transepidermal water loss (passage of water from inside the body through the epidermal layer of the skin to the surrounding atmosphere) and increased penetration of allergens and microbes into the skin. The infectious agents most frequently involved in AD are *Staphylococcus aureus* (*S. aureus*), which colonizes in approximately 90% of patients with AD, herpes simplex virus, and molluscum contagiosum virus (CARR et al., 2024).

The skin microbiome plays a key role in the skin's innate immune response through maintaining immune homeostasis and reducing skin colonization by pathogenic bacteria. Although numerous microbial species are involved in the optimal function of the skin microbiome, *Staphylococcus aureus* has been found to colonize AD skin lesions in up to 90% of patients and may contribute to exacerbations or worsening of the disease (EICHENFIELD et al., 2022).

Recent developments in AD research have provided evidence supporting the contribution of immunological mechanisms to the pathogenesis of AD. In particular, several immunological biomarkers of inflammatory mediators have been identified, including T helper (Th)2, Th22, interleukin (IL)-4, IL-13, IL-31, Th1 and Th17. The onset of acute AD is predominantly characterized by activation of Th2 and Th22 pathways, which are subsequently intensified in chronic disease, along with upregulation of the Th1 pathway. In the pediatric setting, recent-onset pediatric AD studies have demonstrated strong immune activation of Th2, Th9, and Th17 in skin lesions, as well as increased levels of Th2 and Th17 markers in the blood of pediatric AD patients. Consequently, the current understanding of pediatric AD has become one in which Th2 signaling remains the primary driver; however, Th17 signaling is more pronounced when compared to adults with AD (EICHENFIELD et al., 2022). In addition, the cutaneous endophenotype of paediatric AD is substantially different from that of adult/adolescent AD. In fact, the lesion in children was evidenced through comparable or greater epidermal hyperplasia and cell infiltration than adults with AD (NAPOLITANO et al., 2022).

Innate and adaptive immune cells, such as basophils, eosinophils, and macrophages, contribute strongly to the pathogenesis of AD. Basophils participate in AD initiation through increased IL-4 expression and interactions with keratinocytes and dermal macrophages, resulting in epidermis, malignant hyperplasia, and skin barrier dysfunction. Circulating eosinophils in AD patients express increased upregulated histamine 4 receptor (H4R), mediated by IL-4 and IL-13 via the JAK/STAT pathway, leading to increased IL-31 production (SAVVA et al., 2024).

Skin lesions, which are usually accompanied by severe pruritus, include infiltrated erythema, erythema with erosions caused by scratches, lichenified areas, and pruritic papules and nodules. The childhood nummular variant resembles adult nummular eczema (e4). Atopic dermatitis significantly impairs quality of life. Minimal manifestations include inflammation of the dry lips (cheilitis sicca), inflammatory fissures in the corner of the mouth, infranasal erosion, infra-auricular lacerations, retroauricular intertrigo, eczema on the tips of the fingers and toes ("winter atopic feet"), eczema on the nipples, and pityriasis alba (WOLLENBERG et al., 2023).

The typical skin manifestations of atopic dermatitis usually appear at three months of age or later. Their predilection sites change over time, in infants the lesions predominate on the cheeks, scalp (capitulum), extensor surfaces of the limbs, while in young children and schoolchildren, they are located on the flexor surfaces (elbows, popliteal region, neck); and in adolescents, eczema on the hands and feet. (WOLLENBERG et al., 2023).

Eczematous lesions usually have an age-related distribution. Infants under 2 years of age present with acute lesions, characterized by pruritic papules and vesicles raised <1 cm, often associated with serous exudate and crusts. Typically, these lesions present with ill-defined erythema and involve the face, trunk, extensor surfaces of the limb, and sometimes the diaper area. In childhood at age two and older, AD is characterized by the appearance of dry skin, lighter erythema, and lichenified papules and plaques that affect the flexor surfaces, hands, and feet. Facial involvement is less prominent, but when present, perioral and periorbital distribution may be observed. However, from the age of three, different types of skin lesions are observed, such as nummular eczema or morphological variants including the follicular type characterized by densely aggregated follicular papules (NAPOLITANO et al., 2022).

Patients often have associated diseases, including other atopic conditions (asthma, allergic rhinoconjunctivitis), rarely vernal keratoconjunctivitis, giant papillary conjunctivitis, superficial punctate keratitis, atopic keratoconjunctivitis, or otitis externa and media. Food allergies are demonstrable in 30% of children with more severe atopic dermatitis, and immediate hypersensitivity (type 1) to cow's milk, chicken eggs, peanuts, soy, and tree nuts is common (WOLLENBERG et al., 2023).

The diagnosis of AD depends on the clinical presentation because there is currently no reliable biomarker. Diagnostic criteria for AD have evolved, with the seminal diagnostic criteria developed by Hanifn and Rajka modified in 1994 by the UK Working Party and again in 2003 by the American Academy of Dermatology (AAD) in an attempt to generate and refine a diagnostic tool that is suitable for clinical practice. The AAD guidelines indicate



that a clinical diagnosis should be based on historical features, morphology and distribution of skin lesions, and associated clinical signs. Criteria to be considered in the diagnosis of AD patients include essential features such as pruritus and eczema; important features that support a diagnosis of AD, such as early age of onset, atopy, and xerosis; and associated features that suggest a diagnosis of AD, such as atypical vascular responses, keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis, ocular/periorbital changes, other regional findings, and perifollicular accentuation/lichenification/prurigo lesions (EICHENFIELD et al., 2022).

It is important to note that the differential diagnosis for AD can be extensive, given the heterogeneous nature of the disease. The AAD guidelines indicate that a diagnosis of AD is dependent on the exclusion of conditions, such as impetigo, scabies, seborrheic dermatitis, contact dermatitis, ichthyoses, cutaneous T-cell lymphoma, psoriasis, photosensitivity dermatoses, immunodeficiency diseases, and erythroderma of other causes. Identification and assessment of disease severity may be useful for a differential diagnosis of AD, to monitor disease progression, and to assess treatment outcomes. Measurement of disease severity or intensity can be characterized by several indices of severity, including body surface area, Investigator Global Assessment (such as the V-IGA, a validated global assessment score), Eczema Area and Severity Index (EASI), SCORAD, and Patient-Oriented Eczema Measure (POEM). Recently, a consensus statement for the global, multiprofessional Harmonizing Outcome Measures for Eczema (HOME) initiative indicated that patient-reported symptoms were a high-priority domain, recommending the use of the POEM index, a clinically validated patient-derived measure of seven symptoms on a 5-point scale, to assess the severity of atopic dermatitis, and an updated version of SCORAD known as the patient-oriented SCORAD index. By utilizing these tools, pediatricians can more accurately track the course of their patients' disease and tailor their treatment regimens accordingly (EICHENFIELD et al., 2022).

If atopic dermatitis is suspected, potential psychosomatic, allergic, or environmental triggers should be identified (eBox). The importance of these triggers varies widely among individuals, and avoiding them is a component of the personalized treatment plan. The role of dietary factors is often overestimated, particularly in childhood; instead, acute and chronic skin irritations and low temperatures should always be considered as potential triggers of skin barrier dysfunction. Infections and vaccinations can also aggravate atopic dermatitis, but children and adults with atopic dermatitis should nevertheless be vaccinated as usual, as recommended by STIKO (German Standing Committee on Vaccination). Neither infection nor vaccination against SARS-CoV-2 increases the risk of developing



atopic dermatitis. In acute exacerbations, it is recommended to postpone vaccination until the skin condition has stabilized (WOLLENBERG et al., 2023).

The exact role of food and aeroallergens in the pathogenesis and exacerbation of AD is controversial. Although most AD patients demonstrate food- and/or aeroallergen-specific IgE antibodies on skin prick testing (SPT) and measurements of serum specific IgE levels, their clinical significance remains unclear. Although a positive SPT or specific serum IgE test indicates sensitization to a particular allergen, this does not prove clinical hypersensitivity or causality. For the vast majority of children with AD, food is not a trigger. In clinical studies, up to 35% of children with moderate to severe AD have clinically relevant food allergies, however, these are most often associated with immediate symptoms after ingestion and are usually clearly identifiable from the clinical history. In contrast, food allergies appear to have little or no role in adult AD (CARR et al., 2024).

Unnecessary dietary restrictions can result in nutritional deficiencies, negatively impact child development (e.g., food aversions, and

abnormal dietary habits) and may paradoxically increase the risk of developing immediate and potentially fatal food allergies for some patients. Therefore, the decision to perform food allergy testing should be based on whether the patient's history is consistent with or highly suggestive of IgE-mediated food allergies. Exposure to aeroallergens, such as dust mites, animal dander, pollen, and fungi, can exacerbate AD in some patients. In these cases, identification of TPS sensitization may be helpful. Specific prevention measures should be considered, as removing the allergen from the patient's environment may improve AD symptoms (CARR et al., 2024).

AD is usually present early in life and confers a high burden of disease on both the patient and their care; therefore, the potential to prevent disease onset is a highly coveted and continuously pursued therapeutic goal. In addition, AD is commonly among the first manifestations of atopic march, providing further justification for exploring preventive measures for the disease in an attempt to prevent other future atopic comorbidities (MORENO et al., 2023). Treatment of AD should be directed at restoring the skin barrier, which includes moisturizing and repairing the skin, limiting itching, and decreasing inflammation when necessary. Therefore, successful treatment of AD requires a multi-pronged approach that involves patient and caregiver education, optimal skin care practices, anti-inflammatory treatment such as topical corticosteroids (first-line), topical calcineurin inhibitors (ICTs), and/or phosphodiesterase-4 (PDE-4) inhibitors, as well as the treatment of skin infections (CARR et al., 2024).

Dysfunction of the skin barrier, leading to increased allergen penetration and transepidermal water loss, is a major cause of AD. Therefore, frequent use of moisturizers and emollients is the mainstay of over-the-counter therapy for pediatric AD. Guidelines currently recommend liberal and frequent reapplication of moisturizers throughout the day to prevent skin dryness. Applying it right after a daily 5-10 minute warm water bath can be helpful in locking in moisture and removing scabbing. Gentle, hypoallergenic, fragrance-free products should be used to prevent further skin irritation and decrease the risk of subsequent development of contact dermatitis. Barrier creams that contain occlusive agents (e.g., petrolatum) or humectants (e.g., glycerol) are also helpful in protecting and maintaining the skin barrier (JOHNSON; YU, 2022).

The use of natural oils can be considered an alternative treatment approach for pediatric AD. Evening primrose oil (EPO), from the *Oenothera biennis* plant, is a source of omega-6 fatty acids and is believed to be anti-inflammatory. A small study conducted in 50 AD patients reported that 96% of patients treated with EPO showed improvement after a 5-month course of daily dosing. Sunflower seed oil (SSO), from the *Helianthus annuus* plant, is another option, given its anti-inflammatory and barrier-repairing properties. A steroid-sparing effect was observed in a study involving 86 children with moderate AD treated with alternating TCS and 2% SSO (JOHNSON; YU, 2022).

Supplementation with vitamins and antioxidants can positively impact pediatric AD. Some studies investigating vitamin D have observed improvement in eczema severity with oral supplementation, particularly when provided in the winter months. This suggests that vitamin D deficiency may contribute to the pathophysiology of AD. However, topical vitamin D can worsen AD and is often avoided. In contrast, topical vitamin B12 is thought to prevent AD flare-ups, possibly by inhibiting an important step in the inflammatory pathway (JOHNSON; YU, 2022).

The first topical corticosteroid (TCS), hydrocortisone acetate, was introduced in 1952 for the treatment of inflammatory skin diseases. Today, TCS are the most commonly used topical agents in dermatology and are still the mainstay for the treatment of AD, both in children and adults. TCS largely modulate and suppress the immune system, including various types of immune cells, by downregulating robust pro-inflammatory drivers, including TNF, granulocyte-monocyte colony-stimulating factor, IL-2, and IL-1 (MORENO et al., 2023).

However, pediatric patients with AD are often undertreated due to concern about adverse effects associated with TCS; These concerns are heightened for high-potency formulations, chronic application, use on extensive areas of the skin, or use on sensitive

areas. While TCS are effective in treating pediatric AD when used as prescribed, 90% of physicians treat their pediatric population differently than adults due to concerns about long-term side effects, with 98% of physicians reporting "treatment-related adverse effects" as a major concern. Currently, the average adherence rates for 5-day and 8-week AD treatment regimens are 40% and 32%, respectively. The most effective methods for increasing treatment adherence include written action plans, reducing follow-up time, and educational workshops (MORENO et al., 2023).

In children with moderate to severe AD, proactive therapy with twice-weekly application of medium-potency TCSs (e.g., fluticasone or mometasone) to previously affected skin areas for up to 16 weeks may help prevent relapse. TCS can be grouped into seven power classes. High-potency TCSs on highly sensitive areas of skin (face, neck, and skinfolds) should be used with caution to avoid skin atrophy. Low to medium power TCS can be used for longer periods for chronic AD involving the trunk and extremities. Infants and young children with AD should be treated with less potent medications (YAO et al., 2022).

Adverse effects associated with TCS are divided into two categories: local and systemic effects. Local side effects such as stretch marks, skin atrophy, and pigmentation changes are less common in the pediatric population, but the pediatric population is at higher risk of systemic side effects due to the higher skin surface area to body volume ratio and thinner epidermis, resulting in higher absorption and elevated blood concentrations of corticosteroids. Potential systemic adverse events include hypothalamic pituitary axis and adrenal suppression, along with stunted linear growth. However, early adrenal suppression was considered transient and spontaneously normalized, even with continued corticosteroid use (MORENO et al., 2023).

Topical calcineurin inhibitors (TCI) are considered strong second-line agents for the treatment of AD in the pediatric population. However, there are some situations in which TCIs may be preferable to TCS, including: recalcitrant TCIs, tender areas (such as face, anogenital, skin folds), sites with TCS-induced atrophy, and long-term uninterrupted use of TCS. TCIs currently approved for pediatric AD include pimecrolimus cream 1% in children >2 years, tacrolimus 0.03% for children >2 years, and tacrolimus 0.1% for adolescents >16 years of age, all for indication of mild to moderate disease (MORENO et al., 2023).

ICTs form a complex that inhibits calcineurin and prevents the transcription of multiple pro-inflammatory mediators such as TNF- $\alpha$ , IFN $\gamma$ , and IL-2, resulting in a broad suppression of the cutaneous immune milieu of AD. Tacrolimus inhibits histamine release from IgE-mediated skin mast cells, an additive mechanism that further enhances the

resulting clinical response. The most beneficial effect of TCI on AD is its ability to decrease pruritus. The antipruritic effects of TCI can also be attributed to its ability to inhibit cutaneous sensory nerve endings, decrease the release of substance P in these nerve endings, and decrease the release of neuropeptides—all of which decrease nerve sensitization and inflammation. The most common side effects associated with the use of TCI include skin irritation at the site of application, such as burning, stinging, and itching. However, irritation at the application site usually disappears within an hour of application, which ensures that these local adverse effects are very limited (MORENO et al., 2023).

Crisaborole is a topical steroid-sparing agent that works as a phosphodiesterase-4 (PDE4) inhibitor. It is approved for the treatment of mild to moderate AD in patients two years of age and older. PDE4 is elevated in AD and plays an active role in the production of pro-inflammatory cytokines, including Th2-related (IL-5, IL-10), Th1-related (IFN $\gamma$ , TNF $\alpha$ ), and Th17/Th22-related (IL-17, IL-22). Bidaily application of crisaborole resulted in improvement in AD severity as early as the eighth day of treatment, as well as sustained improvement in pruritus. In both the pediatric and adult populations, crisaborole provided early relief from pruritus as early as the sixth day (MORENO et al., 2023).

In recent years, two biologic agents have been approved in Canada for moderate to severe AD that does not respond to topical therapies. Dupilumab (Dupix-ent) was the first biologic to be approved in adults and now has approval for patients 6 months of age and older. Tralokinumab (Adtralza) is approved for patients 12 years of age and older. Dupilumab is an interleukin (IL)-4 receptor alpha antagonist that leads to inhibition of IL-4 and IL-13 signaling. Tralokinumab binds to and counteracts the effects of IL-13. These cytokines play an integral role in the overactive T2 inflammatory cascade found in eczema patients, and blocking them significantly reduces the activity of this pathway. Dupilumab and tralokinumab are injection therapies that can be self-administered via pen or pre-filled syringe, depending on the patient's age. Both biologic agents have been shown to significantly improve eczema scores (Eczema Area and Severity Index [EASI], Investigator's Global Assessment [IGA], and others), pruritus scores, and quality of life scores when used as monotherapy or concomitantly with topical corticosteroids (CARR et al., 2024).

JAK inhibitors have been used for several years for rheumatological conditions. In 2021, upadacitinib was the first JAK inhibitor to be approved for moderate to severe AD, followed by abrocitinib in 2022. Both agents are approved for patients 12 years of age and older. JAK inhibitors for eczema selectively inhibit the JAK-STAT pathway, significantly reducing pro-inflammatory cytokine activity but sparing the side effects of JAK-2 inhibition

(neutropenia and anemia) Both AD-approved JAK inhibitors are once-daily oral tablets and have low and high doses available prior to initiation of treatment with JAK inhibitors, Patients need to be screened for chronic infections, including tuberculosis and hepatitis. Other laboratory monitoring required at the start of treatment and during follow-up include: complete blood count, lipids, and liver and kidney function. The most common side effects associated with JAK inhibitors are mild and include acne and nausea. However, opportunistic infections such as herpes zoster and eczema herpeticum have also occurred (CARR et al., 2024).

## CONCLUSION

Atopic dermatitis (AD) is a chronic inflammatory skin condition that affects millions of children and adults around the world. The significant increase in the incidence of AD in recent decades highlights the urgent need for effective treatment and prevention strategies. Despite the widespread use and efficacy of topical corticosteroids (TCS), concerns about side effects, especially in children, lead to an underuse of prescribed treatments, compromising the proper management of the disease

The review highlights the importance of proactive and personalized approaches in the treatment of AD, including the use of appropriately potency TCS and the introduction of topical calcineurin inhibitors (TCI) as safe alternatives in certain situations. It is crucial that doctors and caregivers are well informed about treatment options and methods to increase adherence to therapies, aiming to minimize risks and improve patients' quality of life.

Future research should focus on better understanding the regional factors that influence the prevalence of AD and develop innovative treatments that can offer long-lasting relief with lower risks of adverse effects. In addition, educational programs and clear action plans are essential to ensure higher and more effective adherence to treatment, especially in the pediatric population.

## REFERENCES

1. ANANIA, Caterina et al. Probiotics function in preventing atopic dermatitis in children. *International Journal of Molecular Sciences*, v. 23, n. 10, p. 5409, 2022.
2. BYLUND, Simon et al. Prevalence and incidence of atopic dermatitis: a systematic review. *Acta dermato-venereologica*, v. 100, n. 12, 2020.
3. CARR, Stuart; PRATT, Rebecca; WHITE, Fred; WATSON, Wade. *Allergy, Asthma & Clinical Immunology*. v. 20, n. 63, 2024.
4. EICHENFIELD, Lawrence F. et al. Recent developments and advances in atopic dermatitis: a focus on epidemiology, pathophysiology, and treatment in the pediatric setting. *Pediatric Drugs*, v. 24, n. 4, p. 293-305, 2022.
5. JOHNSON, Hadley; YU, JiaDe. Current and emerging therapies in pediatric atopic dermatitis. *Dermatology and Therapy*, v. 12, n. 12, p. 2691-2703, 2022.
6. KERN, Chloe et al. Atopic dermatitis and cardiovascular risk in pediatric patients: a systematic review and meta-analysis. *Journal of Investigative Dermatology*, v. 144, n. 5, p. 1038-1047. e16, 2024.
7. MORENO, Ariana; RENERT-YUVAL, Yael; GUTTMAN-YASSKY, Emma. Shedding light on key pharmacological knowledge and strategies for pediatric atopic dermatitis. *Expert review of clinical pharmacology*, v. 16, n. 2, p. 119-131, 2023.
8. NAPOLITANO, Maddalena et al. Children atopic dermatitis: Diagnosis, mimics, overlaps, and therapeutic implication. *Dermatologic Therapy*, v. 35, n. 12, p. e15901, 2022.
9. SAVVA, Maria et al. Recent Advancements in the Atopic Dermatitis Mechanism. *Frontiers in Bioscience-Landmark*, v. 29, n. 2, p. 84, 2024.
10. WOLLENBERG, Andreas et al. Atopic Dermatitis in Children and Adults: Diagnosis and Treatment. *Deutsches Ärzteblatt International*, v. 120, n. 13, p. 224, 2023.
11. YAO, Tsung-Chieh et al. Taiwan guidelines for the diagnosis and management of pediatric atopic dermatitis: consensus statement of the Taiwan Academy of Pediatric Allergy, Asthma and Immunology. *Journal of Microbiology, Immunology and Infection*, v. 55, n. 4, p. 561-572, 2022.
12. ZHAO, Anqi; PAN, Chaolan; LI, Ming. Biologics and oral small-molecule inhibitors for treatment of pediatric atopic dermatitis: Opportunities and challenges. *Pediatric Investigation*, v. 7, n. 3, p. 177-190, 2023.