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Recent Developments and Advances in Atopic Dermatitis: A Focus on Epidemiology, Pathophysiology, and Treatment in the Pediatric Setting

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Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disorder that affects a substantial number of children and has a significant negative impact on affected patients and their caregivers/families. Recent studies have led to significant evolutions in the understanding of AD pathogenesis, epidemiology, and treatment. The first point of contact for many patients with new-onset AD is usually with their primary care provider or pediatrician. This underscores the importance for pediatricians to understand the basic pathophysiology and current standards of care for AD. This article provides up-to-date information and reviews the basic principles of AD pathophysiology, diagnosis, and management. In addition, the article highlights recent advances in scientific research regarding the mechanisms involved in the pathogenesis of atopic dermatitis that have resulted in the discovery of novel therapeutic targets and the development of targeted biologic therapies with the potential to revolutionize AD therapy.

Key Points

Major advances in AD research in the past decade have expanded our knowledge of the disease, supporting the concept of AD as an inflammatory skin disease with a systemic component.

AD places a substantial burden not only on affected children, but on their families and caregivers as well. Clinicians should make a holistic attempt to control the disease to mitigate this burden.

Novel targeted biologic therapies are being developed that target the underlying causes of AD, which may help define the future of AD therapy.

1 Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that typically manifests in early childhood and may precede the development of other atopic disorders, including asthma, allergic rhinitis, and food allergies [1–3]. The onset of AD most commonly occurs between 3 and 6 months of age, with approximately 60% of children with AD presenting symptoms in the first 12 months [4]. Consensus guidelines indicate that AD is characterized by essential features such as pruritus and eczema (acute, subacute, or chronic), with eczema lesions displaying typical morphology or age-specific patterns and having a chronic or relapsing history [5]. The presence of these essential features in combination with an early age of onset, atopy, and xerosis support a diagnosis of AD [5].

The prevalence of AD varies widely across the globe due to regional, country-specific, age group, and data-capturing methodological differences, affecting 0.2% to 36% of the pediatric population (ages < 18 years) [2, 6, 7]. This high prevalence, coupled with high patient/caregiver burden and increased healthcare utilization, highlights the considerable public health burden associated with AD [8–10]. Furthermore, approximately 50% of patients with AD are treated in the primary care setting [3], with community-based primary care practices reporting a high prevalence of AD among

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their pediatric patients [11]. Therefore, pediatricians have a key role in the management of AD.

This review aims to highlight the recent breakthrough advances in research that have the potential to revolutionize AD therapy. In addition, the article will provide pediatricians with the most up-to-date epidemiology, pathophysiology, and treatment information on AD, and serve to inform clinicians and parents of age- and severity-specific treatment options for AD.

2 Epidemiology

The evaluation of AD prevalence is impacted by challenges inherent in the disease, including a lack of objective diagnostic tests, few widely accepted biomarkers, and a relapsing disease, leading to differing estimates across studies [8, 12]. However, several well-designed US caregiver-centered surveys have reported prevalence estimates of 11–13% for healthcare-diagnosed eczema, with notable variation between states (9–18%), which is in line with global data [2, 8, 11]. In the US primary care setting, a cross-sectional survey study reported an AD prevalence 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 [11]. In this survey, an assessment of AD severity indicated that most patients presented with 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 non-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]; $p = 0.005$) [11]. Previous studies have also reported correlations between AD and several comorbidities, including asthma, allergic rhinitis, food allergy, and mental health disorders including attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD), autism, and depression [13–17].

3 Pathophysiology

The pathophysiology of AD is complex and multifactorial, and there is increasing recognition of the heterogeneous nature of AD [18, 19]. Although the exact mechanisms of the pathogenesis are still unclear, major advances in AD research in the past decade have expanded our knowledge on the disease, supporting the concept of AD as an inflammatory skin disease with a systemic component.

AD is precipitated by an interaction between environmental factors, disturbed skin barrier, the skin microbiome, and immune dysregulation among individuals with susceptibility genes for AD (Fig. 1) [20]. AD is a highly heritable disease, with phenotype-specific genes likely playing an

important role alongside ‘generic’ atopy genes. Genome-wide association studies have identified loci correlated with autoimmune regulation, including genes associated with regulation of innate host defenses and T-cell function; these studies have also linked AD to other autoimmune or inflammatory diseases [18]. Linkage studies have also implicated loci containing clusters of genes associated with skin barrier dysfunction, such as the filaggrin (*FLG*) gene, which has the highest association with AD [18, 21].

The etiology of AD appears to be driven by the reciprocal interaction between two biological pathways: skin epithelial function and innate/adaptive immune responses [22, 23]. Skin barrier dysfunction is a well-defined essential component in the pathogenesis of AD [21, 22]. In healthy skin, the epidermal barrier is a matrix of structural lipids and proteins that displays antimicrobial properties, functioning to maintain skin hydration and prevent penetration of allergens, and disruption to any one of these components contributes to AD [19]. The skin microbiome plays a key role in the skin’s innate immune response through the maintenance of immunological homeostasis and reduction of skin colonization by pathogenic bacteria [19, 24, 25]. Although numerous microbial species are involved in optimal function of the skin microbiome, *Staphylococcus aureus* has been found to colonize AD skin lesions in up to 90% of patients and can contribute to disease exacerbations or flare [24].

Recent developments in AD research have provided evidence supporting the contribution of immune mechanisms to AD pathogenesis. In particular, a number of immune biomarkers of inflammatory mediators have been identified, including T helper (Th)2, Th22, interleukin (IL)-4, IL-13, IL-31, Th1, and Th17 [26]. The onset of acute AD is characterized predominantly by the activation of Th2 and Th22 pathways, which are subsequently intensified in chronic disease, along with upregulation of the Th1 pathway [26, 27]. In the pediatric setting, studies of new-onset pediatric AD 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 patients with AD [28–30]. Consequently, the current understanding of pediatric AD has become one wherein Th2 signaling remains the main driver; however, Th17 signaling is more pronounced when compared with adults with AD [26, 28]. This Th17-skewed molecular profile more closely resembles immune signaling observed in patients with psoriasis rather than adult AD, and this difference may indicate a further need for different therapeutic approaches to pediatric and adult AD [28].

Multiple studies have underscored the importance of Th2 cytokines in the pathogenesis of AD, namely IL-4, IL-13 and IL-31, the Th22 cytokine IL-22, and the epithelial-derived cytokine thymic stromal lymphopoietin [18, 21, 27]. Phosphodiesterase 4 (PDE4), an isoenzyme

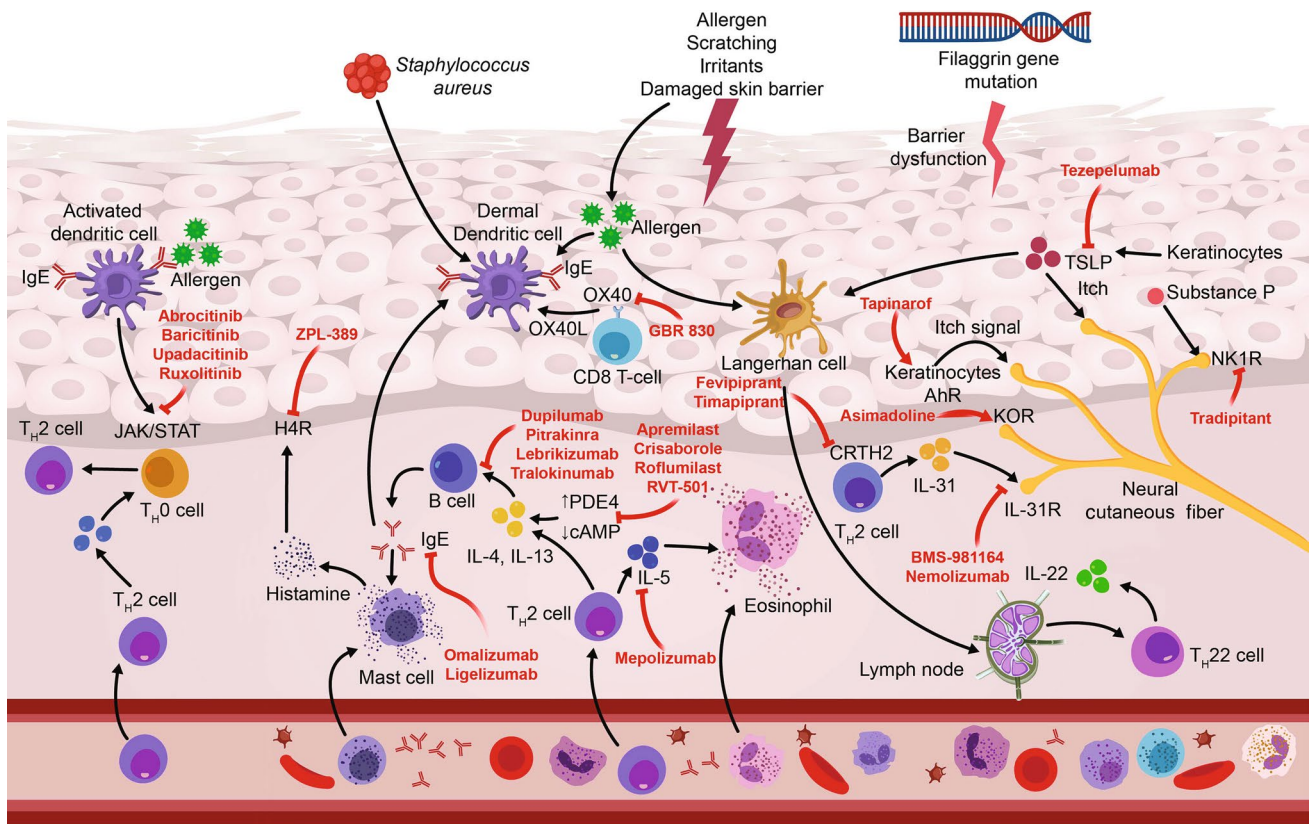


Fig. 1 Atopic pathogenesis and mechanisms of action of approved and emerging agents. Adapted with permission from Nguyen et al. [77]. *AhR* aryl hydrocarbon receptor, *cAMP* cyclic adenosine monophosphate, *CRTH2* chemoattractant receptor homologous molecule expressed on TH2 cells, *H4R* histamine-4 receptor,

IgE immunoglobulin-E, *IL* interleukin, *JAK/STAT* Janus kinase/signal transducer and activator of transcription, *KOR* κ -opioid receptor, *NK1R* neurokinin-1 receptor, *PDE4* phosphodiesterase 4, *R* receptor, *TSLP* thymic stromal lymphopoietin

that regulates cytokine production, has also been identified in immune and inflammatory cells (i.e., T cells, B cells, monocytes, macrophages, neutrophils, etc.), suggesting that PDE4 may play a role in controlling AD-associated inflammation [21, 31]. Indeed, selective inhibition of PDE4 was associated with reductions in several proinflammatory mediators, including tumor necrosis factor, IL-2, IL-5, IL-8, IL-12, and IL-22 [32]. The Janus kinase (JAK) pathway is a signal transduction pathway for several cytokines and growth factors and is thought to be involved in the inflammatory immune responses in AD, primarily through enhancement of the Th2 cell differentiation [21, 33]. Recently, a natural killer (NK) cell deficiency was also observed in the blood of AD patients, and this may be associated with enhanced Th2-driven skin inflammation [34]. Taken together, elucidation of the proinflammatory immune mechanisms that drive AD pathogenesis has important implications, resulting in the identification of novel therapeutic targets that can inform future advances in AD therapy.

4 Burden of Atopic Dermatitis (AD)

The hallmark symptom of AD is pruritus, which is responsible for most of the negative impact on quality of life experienced by patients with the disease [3]. Accordingly, the treatment of acute AD prioritizes the mitigation of this pruritus [3]. Beyond itch, children with AD experience a range of comorbidities related to the disease, including a higher risk for skin infections due to AD-associated skin barrier defects, cutaneous dysbiosis, and innate immune suppression via type 2 inflammatory signaling [35]. Children with AD also exhibit increased healthcare utilization, including healthcare provider visits, relative to children of the same age without AD, and this healthcare use increase rises in tandem with AD severity [1, 36]. Furthermore, AD is associated with a significant psychosocial burden that impacts patients, their caregivers, and wider society that can be traced back to the significant pruritus experienced by these patients [3, 37]. In particular, sleep disturbances characterized by difficulty with both sleep initiation and sleep maintenance appear to have

a notable impact, even among patients in clinical remission, potentially resulting in daytime drowsiness and resultant poor academic performance at school [37–39]. In addition, the literature suggests that the magnitude of effects on sleep increases as AD severity increases [1]. In a longitudinal cohort study following 13,988 children in the United Kingdom from the ages of 2 to 16 years, it was found that children with any form of AD, even mild or inactive AD, had statistically significantly increased odds of poor sleep quality, and that children with active AD were almost 50% more likely to encounter increased disturbances to their sleep throughout childhood [40]. Similarly, a questionnaire-based survey of 91,642 children in the United States between the ages of 0 and 17 years found that children with AD had a higher chance of experiencing four or more nights of impaired sleep per year [1, 41]. This effect was even more pronounced in children with severe AD than in those with mild or moderate AD [1, 41].

Sleep disturbances due to pruritus have also been identified as a major cause of stress within the family unit and consequent sleep deprivation affects all family members [3, 37, 39]. Loss of 1–2 h of sleep per night has been shown to lead to suboptimal performance in the workplace and a reduction in coping skills at work and home [37]. Self-reported sleep measures from a longitudinal study in the United Kingdom of 11,649 mothers and their children with and without AD indicated that mothers of children with AD were approximately 40% more likely to report each of the following: difficulty falling asleep, insufficient sleep, and daytime exhaustion [42].

Pediatric patients with AD may present with a number of behavioral problems, potentially exacerbated by impaired sleep quality, that can have multifarious negative impacts on their social and intellectual development [37]. Cross-sectional data from 19 US population-based surveys has demonstrated that children with AD have an increased likelihood of being diagnosed with ADD/ADHD [14]. AD has also been associated with school absenteeism [43–45], and children may feel socially isolated by their peers as a result of bullying and teasing due to the physical appearance of their AD lesions; this can negatively affect a child's self-perception and self-esteem [46]. The International Study on Life with Atopic Eczema revealed large impacts on self-esteem in children with AD, with 27% of children with AD indicating that they'd been bullied due to their AD and 36% reporting feeling less self-confident because of their AD [47]. In focus sessions where expert clinicians interviewed the parents of 26 American children with AD, more than half of parents reported that their children with AD were avoided by other children and adults [48]. Although the impact of AD on stigmatization/discrimination has not been well studied, children

with lesions on visible sites of the skin may be at higher risk of discrimination [49].

Adolescents with AD may also be more likely to experience symptoms of depression and psychological distress [50, 51]. In South Korea, surveys have reported that patients with AD are significantly more likely to experience suicidal ideation and suicide attempts, leading researchers to speculate that the exacerbating effects of AD on negative psychological states can create a vicious cycle, especially in adolescents, who are already more vulnerable to suicidality on average [50, 51]. An increasingly large data set in pediatric patients with AD corroborates this negative impact of AD with regard to depression and anxiety, both of which appear to be largely driven by pruritus, sleep disturbances, and social stigmatization due to visible skin lesions [52]. Quality of life and disease severity are also linked in pediatric patients with AD, with long-term effects on childhood behavior and development [53]. Findings from a cross-sectional study in Brazil reported a moderate positive correlation between disease severity, as assessed by the SCORing Atopic Dermatitis (SCORAD) scale, and quality of life, as assessed by the Children's Dermatology Life Quality Index (CDLQI), in patients aged 5–16 years receiving care at a pediatric dermatology clinic [53].

It is important to recognize the negative impact on decreased quality of life of the parents/caregivers and siblings of children and adolescents with AD; this effect is also correlated with disease severity, with greater severity linked with increased family disruption [37, 53]. In a cross-sectional study of children aged < 16 years with AD, caregivers' mental and physical health were negatively affected by children's health-related quality of life [54]. A recent online caregiver-centered survey assessing the burden of AD on children and families noted frequent sleep disturbances, exhaustion, worry, and social isolation related to their child's AD [55]. Even as the impact of pediatric AD on caregivers and family units as a whole have been documented, effects on patients' siblings have not been well studied. However, there is evidence that siblings of patients with chronic physical disorders are more likely to internalize their problems, experience emotional stress, and have decreases in school attendance and impaired academic performance [56, 57]. When considering the evidence in the literature, it is clear that the impact of AD is wide-ranging, spanning sleep disturbances, lifestyle changes, treatment issues, social disruptions, school performance, time lost from work, family activities, and financial and mental strain [37]. Therefore, the impact of pediatric AD extends beyond the pathological nature of the disease, highlighting the need to consider the psychosocial aspects of AD for both patients and their families.

5 Diagnosis of Pediatric AD

Diagnosis of AD relies on clinical presentation because there is currently no reliable biomarker. The diagnostic criteria for AD have evolved, with the seminal diagnostic criteria developed by Hanifin and Rajka [58] modified in 1994 by the UK Working Party [59] and again in 2003 by the American Academy of Dermatology (AAD) in an attempt to generate and refine a diagnostic tool that is suited for clinical practice [60, 61]. The AAD guidelines indicate that a clinical diagnosis should be based on historical features, morphology and distribution of skin lesions, and associated clinical signs [5]. Criteria to be considered in the diagnosis of patients with AD 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 are suggestive of 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 [5].

It is important to note that the differential diagnosis for AD can be extensive given the heterogenous nature of the disease. 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, immune deficiency diseases, and erythroderma of other causes [5]. Table 1 provides a more extensive list of potential differential diagnoses of AD, with impetigo, molluscum contagiosum, tinea corporis, and viral exanthems being most common in children [62]. The exclusion of conditions like impetigo and molluscum contagiosum can be particularly difficult, as these conditions may occur concomitantly with, as well as exacerbate, a patient's AD [5].

Identification and assessment of disease severity may be useful for a differential diagnosis of AD, to monitor disease progression, and to evaluate treatment outcomes. Measurement of disease severity or intensity can be characterized by numerous severity indices, including body surface area, Investigator's 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) (Table 2) [63–65]. Recently, a consensus statement for the global, multi-professional Harmonising Outcome Measures for Eczema (HOME) initiative indicated that patient-reported symptoms were a top-prioritized domain, recommending use of the POEM index [66], a clinically validated patient-derived measure of seven symptoms

Table 1 Differential diagnosis of atopic dermatitis. Modified with permission from Frazier and Bhardwaj [62]

Diagnosis	Age	Morphology	Etiology	Other features
Impetigo	Common in children	Honey-colored crusts	Bacterial	Very contagious
Molluscum contagiosum	Common in children	Skin-colored or erythematous papules	Viral	May induce eczematous responses
Tinea corporis	Common in children	Erythematous, annular patches with raised scaly borders	Fungal	May occur in addition to Tinea capitis
Viral exanthems	Common in children	Diffuse erythematous macules and papules	Viral	Resolves after illness
Contact dermatitis	All ages	Erythematous vesicles, papules, or plaques	Hypersensitivity reaction	Rash occurs at site of exposure
Scabies	All ages	Intertriginous, erythematous papules with serpiginous burrows	Parasitic	Intense itching at night
Seborrheic dermatitis	All ages	Yellow, greasy scales	Unknown	Scalp and face distribution
Urticaria	All ages	Erythematous papules or plaques	Immune-mediated	Individual lesions usually resolve within 24 hours
Cutaneous T-cell lymphoma	Rare in children	Erythematous, dry patches	Unknown	Rash develops slowly
Dermatitis herpetiformis	Rare in children	Symmetrical vesicles and papules	Autoimmune	Association with gluten sensitivity
Lichen simplex chronicus	Rare in young children	Well-circumscribed, thick scales	Chronic scratching	Association with stress and anxiety
Nummular eczema	All ages	Annular erythematous patches	Variable	Patches can last weeks to months
Psoriasis	Rare in children	Erythematous patches with silvery scale	Immune-mediated	Can have nail involvement

on a 5-point scale, for evaluating severity of atopic dermatitis, and an updated version of SCORAD known as the patient-oriented SCORAD index [67]. By utilizing these tools, pediatricians can more accurately track the course of their patients' disease and tailor their treatment regimens accordingly.

6 Management of Pediatric AD

A US survey of children presenting to primary care practice indicated that most patients are employing skin care practices that may be detrimental to the skin barrier, highlighting the need for recommendations to guide appropriate treatment practices [11]. A range of treatments are recommended for AD, including emollients (e.g., creams, lotions, ointments), topical corticosteroids (e.g., hydrocortisone, triamcinolone acetonide), topical calcineurin inhibitors (tacrolimus, pimecrolimus), PDE4 inhibitors (crisaborole 2%), systemic oral and injectable treatments, and phototherapy.

AD is typically treated as a single entity despite its heterogeneous nature [68], with numerous guidelines recommending stepwise therapy initiated according to disease severity [60, 68–73]. Current practice has evolved away from an emphasis solely on controlling acute flares to a more holistic, long-term approach that focuses on comprehensive disease management via the combination of baseline maintenance treatments in tandem with intermittent use of topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), or a PDE4 inhibitor (crisaborole 2%) as needed for more acute manifestations of AD. Figure 2 summarizes a proposed approach to the management of pediatric AD patients. Prior to escalating or stepping up therapy, patients should undergo assessment for nonadherence, potential comorbidities, and to confirm that the increased level of symptoms warranting a step up in therapy is related to AD [71]. Basic management of AD comprises two important nonpharmacologic interventions that should be implemented in all patients at all levels of disease severity: (i) skin care involving regular emollient use and regular (daily or every other day) bathing in warm water using nonsoap cleansers or mild soaps, and (ii) avoidance of irritants (e.g., soaps, wool), temperature extremes, and proven allergens [71, 74]. Treatment of acute flares with topical therapies, including corticosteroids, calcineurin inhibitors, and PDE4 inhibitors (crisaborole 2%) can be administered as needed in pediatric patients for maintenance therapy and the prevention of flares [69–71, 74]. Notably, the treatment options for infant patients with AD are more limited. Fluocinolone acetonide, fluticasone propionate, desonide, and hydrocortisone butyrate are the only topical corticosteroids that are FDA-approved in infants (≥ 3 months old) [75, 76]. Crisaborole is the only FDA-approved topical PDE4 inhibitor for pediatric AD, and a

recent study demonstrated crisaborole's safety and efficacy in infants aged ≥ 3 to < 24 months with mild-to-moderate AD [70, 77, 78]. TCIs are not approved by the US Food and Drug Administration (FDA) for use in children < 24 months of age [79, 80].

Patients with mild-to-moderate AD who remain symptomatic despite optimal basic management and use of low-to-medium-potency topical therapies are candidates for stepping up therapy [71]. Treatment options in these patients include adding a TCS or TCI or crisaborole into their basic maintenance treatment routine.

Approximately one-third of pediatric patients have moderate-to-severe AD, which may not be adequately managed with topical therapy/phototherapy—thereby necessitating a step-up in therapy that includes the initiation of systemic therapy [81, 82]. Current guidelines recommend systemic therapy for pediatric patients with AD who have inadequate disease control despite appropriate topical therapy and/or phototherapy [69–71, 74]. Despite conventional systemic immunomodulators being recommended for the management of moderate-to-severe AD, only a few are licensed for this indication (i.e., systemic corticosteroids in the United States). The findings from a pivotal phase III trial resulted in FDA approval of the targeted biologic therapy, dupilumab, in children aged 6–11 years old with moderate-to-severe, inadequately controlled eczema [77, 83]. Methotrexate, along with cyclosporine, mycophenolate mofetil, and azathioprine, can also be considered as off-label treatments for pediatric patients with severe disease, although data supporting their use are sparse [69–71, 81]. There is limited evidence supporting the prophylactic use of systemic antibiotics in the AD setting, and improvement in outcomes with the addition of topical or oral antibiotics to topical steroid and emollient treatment in children with eczema has not been shown [84]. However, antibiotics are customarily used for the treatment of clinically evident secondary bacterial infections, and many experts have seen success using oral antibiotics to treat infected eczema [71, 72, 81]. There is also little data supporting the use of oral antihistamines in the treatment of AD, though nonsedating antihistamines may be considered in the presence of urticaria and sedating antihistamines may be considered in patients with sleep disturbance secondary to pruritus [5, 62, 72].

It is important to note that patients with severe disease should be referred to an AD specialist [60, 71]; indications for referral include those for whom diagnosis is not confirmed, who have poor disease control with appropriate first-line treatments, who have severe or recurrent skin infections (viral or bacterial), who are possible candidates for systemic therapy or phototherapy, who have significant allergies such that they could benefit from allergy evaluation and/or specific immunotherapy (i.e., immunoglobulin E > 150 IU/mL), or who have significant AD-related psychosocial problems [62, 85].

Table 2 Severity scales for assessment of atopic dermatitis (AD) (modified from Lara-Corrales et al., 2019 [61])

Diagnostic index	Description of assessment	Benefits	Limitations
EASI	Validated scale utilizing 7-point assessment of disease extent in 4 defined body regions, with severity of 4 clinical signs on a 4-point scale, to a maximum score of 72	Evaluates both extent of eczema and lesion severity Good to fair intra-evaluator reliability	Less sensitive in patients with very low %BSA Inter-evaluator variability lies in the dimension of induration/papulation Patient-reported symptoms are not evaluated
SCORAD [65]	Clinically validated scale assesses disease extent based on the rule of 9s, intensity based on 6 clinical signs rated on a 4-point scale, plus patient-reported pruritus and sleep loss	Evaluates both BSA and lesion severity	Measures such as pruritus and sleep loss can be influenced by factors other than AD
PO-SCORAD [99]	Patient self-assessment scale developed based on SCORAD criteria, but optimized for use by patients and their families by the inclusion of images and other assessment support	Evaluates both BSA and lesion severity Patients can monitor AD symptoms between clinical consultations	Measures such as pruritus and sleep loss can be influenced by factors other than AD
BSA	Disease extent assessed as a percentage of total BSA		Difficult to evaluate in patients with less severe lesions, especially in the presence of xerosis Does not assess lesion severity
IGA [63]	4 or 5-point scale of global disease severity based on morphological appearance of lesions, e.g., V-IGA, a validated global assessment score	Facilitates easy, rapid assessment of AD	No standardized ISGA, with variable definitions and implementations in clinical studies
POEM [66, 100]	Validated score assessing 7 symptoms over the preceding 7 days using a 5-point scale system (to maximum of 35)	Specifically developed for AD Scores are correlated with disease severity Appropriate to assess clinical trial populations Easily utilized in routine clinical practice Increasingly used in AD studies and clinical trials	High utility in clinical studies but low utility in a dermatology clinic

AD atopic dermatitis, BSA body surface area, EASI Eczema Area and Severity Index, IGA Investigator's Global Assessment, ISGA Investigator's Static Global Assessment, POEM Patient-Oriented Eczema Measure, PO-SCORAD Patient-Oriented SCORing Atopic Dermatitis, SCORAD SCORing Atopic Dermatitis

All pediatric patients with AD and their caregivers should receive ongoing disease education and develop an AD action plan

Mild AD Patches of dry skin, some itching, minimal impact on quality of life or sleep	Moderate AD Dry skin, frequent itching, excoriation, skin redness, significant impact on quality of life and sleep	Severe AD Large areas of dry skin, constant itching, redness, and excoriation that strongly impedes daily routine and sleep
Basic maintenance treatment <ul style="list-style-type: none"> • Skin care involving regular use of emollients and moisturizers as well as bathing in warm water using nonsoap cleansers or mild soaps • Avoidance of irritants (eg, soaps, wool), temperature extremes, and proven allergens 	Basic maintenance treatment <ul style="list-style-type: none"> • All elements of basic maintenance treatment for mild disease, PLUS: • Maintenance TCS • OR: Maintenance TCI • OR: Crisaborole 2% • AND/OR: Dilute bleach baths and other antiseptic measures, especially in patients with recurrent skin infections 	Basic maintenance treatment <ul style="list-style-type: none"> • Chosen elements of basic maintenance treatment for moderate disease, PLUS: • A <u>referral</u> to an AD specialist • Phototherapy • Dupilumab • Systemic immunosuppressant therapy • Other options if AD remains uncontrolled: <ul style="list-style-type: none"> – Wet wrap therapy – Hospitalization
Acute treatment <ul style="list-style-type: none"> • Low-to-medium potency TCS applied to inflamed skin • OR: TCI • OR: Crisaborole 2% 	Acute treatment <ul style="list-style-type: none"> • A medium-to-high potency TCS applied to inflamed skin, low potency TCS for other sensitive areas • OR: TCI • OR: Crisaborole 2% 	Acute treatment <ul style="list-style-type: none"> • Medium-to-high potency TCS applied to inflamed skin, low potency TCS for other sensitive areas • If unresolved after 7 days, consider the following: <ul style="list-style-type: none"> – Potential nonadherence – Infection – Misdiagnosis – Contact allergy to treatment – <u>Referral</u> to an AD specialist
Advancing from mild to moderate: When symptoms persist despite appropriate use of TCS, antiseptic measures, and irritant avoidance. Advancing from moderate to severe: When symptoms persist despite an aggressive course of TCS/TCI/crisaborole prescription therapy, especially when there is a large negative impact on daily routine, sleep, or psychosocial health.		

Fig. 2 Comprehensive long-term approach to the management of atopic dermatitis in children. Adapted with permission from Boguniewicz et al. [71]. AD atopic dermatitis, TCI topical calcineurin inhibitor, TCS topical corticosteroids

Any comprehensive management plan should also incorporate ongoing disease education and an AD action plan [69–71, 74, 86]. Ongoing parental education is particularly important with regard to the phenomenon of steroid phobia, which may result in poor treatment adherence if not addressed and minimized [71]. The development of an action plan is also crucial for the long-term care of patients with pediatric AD, as the current treatment paradigm necessitates the stepping up of therapies in response to acute or poorly controlled disease [71]. Any action plan should be malleable in response to factors including patient satisfaction and treatment tolerability to optimize results for each patient [74]. In the context of AD, early and aggressive treatment response to worsening signs and symptoms can yield significant benefits with regard to health outcomes, and an action plan with predetermined responses and prevention strategies can help increase adherence, decrease treatment failure, and minimize the long-term effects of AD in the pediatric population [71, 74].

As our understanding of the mechanisms involved in the pathogenesis of AD has evolved with advances in AD research, novel biologic therapeutic targets have been identified that have the potential to change the treatment paradigm

in patients with AD. Targeted therapies provide treatment options that are more effective and less toxic, compared with broad immunomodulatory approaches. Dupilumab, available as a subcutaneous injection, is a first-in-class dual inhibitor of IL-4 and IL-13 signaling that has been approved for use in children aged 6–11 years old with moderate-to-severe, inadequately controlled eczema [77, 83], and has demonstrated efficacy in adolescents aged 12–17 years with refractory moderate-to-severe AD, providing rapid improvements in disease severity. Dupilumab pediatric studies have included patients 6 months of age and older. However, adverse effects, such as ocular complications (e.g., conjunctivitis) or joint pain should be carefully monitored in the pediatric population. A number of novel systemic agents in development for moderate-to-severe AD may be promising treatment options in the pediatric setting, including oral JAK inhibitors (i.e., abrocitinib, baricitinib, and upadacitinib) and injectable anti-IL-13 antibodies (i.e., tralokinumab and lebrikizumab). These systemic agent classes have shown promise in clinical studies in adults [77, 87–90], and are also in development for pediatric use [86]. Abrocitinib, a next-generation selective JAK 1 inhibitor that received breakthrough therapy designation in February 2018, has been investigated in

multiple phase III studies investigating its use in adults and adolescents aged > 12 years for the treatment of moderate-to-severe atopic dermatitis, and has been approved in the United States, European Union, Japan, and in other countries [91, 92]. A phase III extension study for abrocitinib is still underway (ClinicalTrials.gov identifier: NCT03422822) [77]. Upadacitinib, a reversible, selective JAK1 inhibitor, has completed phase III trials in atopic dermatitis [88], has been approved for the treatment of atopic dermatitis in the UK, European Union, and Japan [93, 94], and is under regulatory review in the United States. Baricitinib has been recently approved in adults by the European Medicines Agency [95, 96]. Topical ruxolitinib, a topical JAK1/JAK2 inhibitor, has also undergone clinical trials for AD in both children aged 12–17 years as well as adults and has been approved by the FDA for treatment of AD [77]. The anti-IL-31R α monoclonal antibody nemolizumab is specifically being developed to treat pruritus and is currently being investigated in children aged 6–17 years and has shown promising results regarding a reduction in pruritus [77].

7 Role of Telemedicine in AD

The current global pandemic of COVID-19 has highlighted the need for strong and robust telemedicine to deliver optimal patient care to patients with AD. Web-based consultation in children with AD has been shown to be equally effective in terms of patient self-management, health outcomes, and costs when compared with traditional delivery of care [97, 98]. However, given the technological advances of the past decade and the rapid innovation driven by COVID-19, more studies are needed to more fully determine how to integrate telemedicine into current treatment paradigms.

8 Summary

In the primary care setting, pediatricians play an important role in the management of AD, treating patients with mild-to-moderate disease themselves, referring those with moderate-to-severe disease for specialist care, and providing ongoing maintenance care after initial treatment by AD specialists. As a result, it is critical that pediatricians have a sound knowledge of AD pathophysiology, diagnosis, basic skin care, and management recommendations for mild-to-moderate disease. As our understanding of AD has grown to recognize the systemic components of this disease and the scope of its lifelong impact, it is incumbent upon treatment providers to shift their thinking away from merely addressing episodic, acute flares in their patients and work toward a more comprehensive paradigm of controlling the disease in all its manifestations. Given the substantial burden that AD

places on affected children and their families/caregivers, a holistic approach to assessing the disease should be considered by the pediatrician, taking into account both the physical nature of AD and its impact on the psychosocial wellbeing and quality of life of the child and his/her family. Finally, recent advances in research and breakthroughs in science have vastly improved our understanding of AD, particularly the crucial role that inflammatory immune responses play in the pathogenesis of this disease. As a result, novel targeted systemic therapies are being developed that target the underlying causes of AD, which have the potential to change the future of AD therapy.

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Author contributions All authors made substantial contributions to the conception or design of the work, revised it critically for important intellectual content, approved the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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