



REVIEW

Current and Emerging Therapies in Pediatric Atopic Dermatitis

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Received: September 1, 2022 / Accepted: September 28, 2022 / Published online: October 18, 2022
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ABSTRACT

Atopic dermatitis (AD) is the most common inflammatory skin disease seen in children. It is a heterogeneous disorder, with a variety of associated manifestations and symptoms. Cases may range from mild to severe. As a result, a spectrum of prescription and nonprescription therapies may be utilized when managing this condition. This article provides an extensive overview of these therapies, with equal consideration provided to current, emerging, and alternative options used in the pediatric population.

Keywords: Atopic dermatitis; Pediatric; Allergies; Topicals; Phototherapy; Systemics; Biologics; JAK inhibitors; Alternatives; Complementary

Key Summary Points

The burden of atopic dermatitis on children is considerable; it may have a significant impact on a patient's health and quality of life.

The pathophysiology of atopic dermatitis is complex, involving factors such as genetics, an altered immune response, and the environment. As a result, there are a variety of therapeutic targets to consider.

Patients may utilize conventional pharmaceuticals or over-the-counter therapies to manage their symptoms, the choice of which often depends on the severity of disease.

Those with refractory cases or those who prefer another treatment option may consider an alternative treatment approach.

New strategies have emerged for pediatric atopic dermatitis over the past few years, and as advancements are made in research, novel therapies are likely to soon be introduced.

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INTRODUCTION

Atopic dermatitis (AD) is a prevalent inflammatory skin condition that affects up to 20% of children worldwide [1]. Common clinical features include xerosis, pruritus, and pink, scaly patches and plaques that appear in an age-dependent distribution [2]. Patients with AD often present with other comorbidities such as asthma, allergic rhinitis, and food allergies. Cutaneous bacterial or viral infections, sleep disturbances, and mental health disorders have also been described with increased frequency in patients with AD [3]. The pathophysiology of AD is a complex interplay of genetic predisposition, altered immunity, cutaneous microbiome, and environmental factors contributing to its onset and persistence [4]. As such, there are multiple potential targets in the treatment of AD. Herein, we discuss the vast and growing array of both prescription and nonprescription therapies currently available for the treatment of pediatric AD. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

PRESCRIPTION THERAPIES

Topical Corticosteroids

Topical corticosteroids (TCS) remain the mainstay of treatment for AD. Their mechanism of action is considered to be both antiinflammatory and immunomodulatory [5]. They are available in a wide variety of potencies and vehicles, including ointments, creams, lotions, gels, and foams, the choice of which depends on the location and severity of AD [6]. For example, gels, solutions, oils, and foams are particularly useful for dermatitis of the scalp and other hair-bearing regions as they tend to penetrate through the hair and down to the skin [6]. When used appropriately, TCS are safe and generally well tolerated. Despite the common fear of skin atrophy, a comprehensive review found no evidence of skin thinning with TCS when used intermittently or as “weekend therapy” to prevent flares [7]. Other potential

side effects to be aware of include striae, rosacea, perioral dermatitis, acne, and rarely systemic absorption [8]. Many of these effects can be mitigated by using steroids of lowest appropriate potency, by limiting application to less than 2 weeks a month or weekends only, and by tapering off after the healing period is complete [8]. This can often be achieved by alternating TCS with other AD therapies.

Topical Calcineurin Inhibitors

Pimecrolimus cream and tacrolimus ointment are two topical calcineurin inhibitors (TCIs) that are used in the treatment of pediatric AD, often as adjuncts to TCS. Currently, pimecrolimus 1% cream is approved by the US Food and Drug Administration (FDA) for mild to moderate AD in children 2 years of age and older [9]. Similarly, tacrolimus 0.03% ointment is FDA approved for AD in children 2 years of age and older, while tacrolimus 0.1% ointment is approved in children 16 years of age and older [10]. Both have an antiinflammatory effect and have been shown to improve the integrity of the epidermis, which may explain their benefit in the treatment of AD [11]. As they are nonsteroidal, TCIs can be used more frequently in areas of thinner skin, such as the face, neck, or intertriginous areas. The most common adverse effect of this therapy is a burning sensation with application, which can be alleviated by refrigerating the product before use [11, 12]. Notably, in early 2006, the FDA added a black-box warning to the labels of TCIs as there was a rare concern that they may increase the risk of certain forms of cancer [13]. However, there remains limited evidence for this adverse effect in long-term safety studies [14, 15].

PDE-4 Inhibitors

Crisaborole, a phosphodiesterase 4 (PDE-4) inhibitor, was approved by the FDA in 2016 [16]. It is currently indicated for topical treatment of mild to moderate AD in children 3 months of age and older [16]. PDE-4 is theorized to play a role in the production of key inflammatory cytokines responsible for the AD

disease process [17]. Phase 3 clinical trials demonstrated improvement in both AD skin manifestations and the severity of pruritus with use of crisaborole ointment [18]. Adverse effects were generally limited to stinging and burning at the site of application, and no serious adverse effects were noted [18]. Furthermore, it continues to have a favorable safety profile within the first year of use; longer-term data remain limited at this time [11].

Phototherapy

Phototherapy is a beneficial adjunct to topical therapies used in the treatment of severe, refractory pediatric AD. Of the various light modalities, narrowband ultraviolet B (NBUVB) is generally preferred due to its superior safety and efficacy profile. Treatment is offered two to three times weekly. NBUVB is thought to suppress a diverse range of inflammatory pathways involved in AD, including Th₂ [19]. A retrospective review found that 40% of children achieved complete clearance or minimal residual AD activity after completing ten or more exposures of NBUVB [20]. Follow-up data also revealed a long period of disease remission even after completion of therapy [20]. Adverse effects of phototherapy may include skin burning, transient erythema, pruritus, herpes simplex virus reactivation, and a potentially increased risk for skin cancer, particularly with psoralen (PUVA) [21, 22]. These effects warrant attention in the pediatric population, given their longer life expectancy and potential risk for long-term damage [22]. Combined with the challenge of scheduling phototherapy on a weekly basis and ensuring proper protection throughout the treatment course, many authors recommend against use of phototherapy in infants and young children [19, 21]. Though long-term data on the safety of phototherapy are still lacking, numerous studies currently support the safety of administering NBUVB to children [21, 22].

Systemic Immunosuppressant Therapies

A variety of systemic therapies may be used in the treatment of pediatric AD refractory to other

first-line options. Commonly used agents include cyclosporine A, azathioprine, methotrexate, mycophenolate mofetil, and corticosteroids. An overview of these agents is presented in Table 1 [19–27]. Though the pediatric patient may achieve adequate control of their AD with systemic therapy, the side effect profile will often limit its long-term use. In the advent of newer, safer, and more effective therapies for pediatric AD, use of these agents may be less common in the future.

Biologics

Targeted biologic therapy has become increasingly important in dermatology over the last 5 years. Of those that currently exist, only dupilumab is FDA approved for treatment of pediatric AD in patients aged 6 months and older [28]. Through inhibition of the IL-4 and IL-13 signaling cascade, dupilumab dampens the Th₂ inflammatory response key to the pathophysiology of AD [29]. In a phase 3 trial conducted on pediatric patients aged 6–11 years, dupilumab improved the signs, symptoms, and quality of life of those with refractory, severe AD when used in conjunction with TCS [30]. Adverse effects include injection site reactions, ocular side effects (i.e., conjunctivitis, pruritus, blepharitis), and head/neck erythema [28, 30, 31]. However, dupilumab is not known to be immunosuppressive.

Additional biologics are in development for pediatric AD. Lebrikizumab, an IL-13 inhibitor, showed promising results in a phase 2b trial conducted on adult patients with moderate to severe AD [32]. Phase 3 trials in adolescent patients with moderate to severe AD are nearing completion [33, 34].

Tralokinumab, another IL-13 inhibitor, is already approved for use in adult patients with moderate to severe AD. A phase 3 trial studying tralokinumab monotherapy for adolescent patients has reached completion, with promising early results [35].

A selective IL-31 inhibitor, nemolizumab, is also under investigation given the relationship of IL-31 to Th₂ inflammation and the itch signaling pathway [37]. Multiple phase 3 trials are

Table 1 Overview of systemic therapies used in pediatric AD

Agent	Mechanism of action	Administration route	Efficacy	Recommended laboratory monitoring	Side effect profile
Cyclosporine A (CsA) [19, 21, 23]	Calcineurin inhibitor	Oral	A systematic review found 14 trials demonstrating benefit of CsA in improving the clinical signs of recalcitrant AD in children and adults [23]. It is a first-line systemic agent with use up to 1 year	Blood pressure, complete blood count (CBC), and comprehensive metabolic panel (CMP) with liver function tests (LFTs) and creatinine. A lipid panel may also be obtained [19]	Gastrointestinal upset, headache, parasthesia, hypertension, hypertrichosis, gingival hyperplasia, nephrotoxicity, carcinogenicity [19, 21]
Azathioprine (AZA) [19, 21, 23]	Purine analog, antimetabolite	Oral	AZA may provide a modest reduction in the signs and symptoms of AD as demonstrated by several case series and three trials [19, 23]. It is generally considered to be less effective than CsA and is therefore a second-line therapy	Thiopurine methyltransferase enzyme analysis, CBC, and CMP with LFTs. Consider a pregnancy test if indicated [19]	Gastrointestinal upset, hepatotoxicity, abnormalities in blood counts, myelosuppression, teratogenicity, carcinogenicity [19, 21]
Methotrexate (MTX) [19, 21, 23, 24]	Folate antagonist	Oral, intramuscular, subcutaneous	A small retrospective review of 55 pediatric patients with severe AD found approximately 76% improved with MTX. Decreased area of involvement was the most common effect observed, followed by decreased TCS use [24]. It is thought to have similar efficacy to AZA [19, 23]	CBC, CMP with LFTs and creatinine, and viral hepatitis panel. Consider a pregnancy test if indicated [19]	Gastrointestinal upset, hepatotoxicity, stomatitis, abnormalities in blood counts, myelosuppression, pulmonary fibrosis, teratogenicity/abortifacient [19, 21]

Table 1 continued

Agent	Mechanism of action	Administration route	Efficacy	Recommended laboratory monitoring	Side effect profile
Mycophenolate mofetil (MMF) [19, 23, 25]	Inhibitor of inosine monophosphate dehydrogenase, antimetabolite	Oral	A trial comparing MMF with CsA revealed similar efficacy between the two when used as maintenance therapy. MMF was found to have a delayed response with increased need for rescue medication during the early maintenance phase. However, MMF was also found to have a more stable response even after withdrawal than did CsA [25]. A proposed strategy would be to induce AD remission with CsA, followed by MMF for maintenance therapy [19, 23]	CBC and CMP with LFTs. Consider a pregnancy test if indicated. Consider a tuberculosis test [19]	Gastrointestinal upset, headache, fatigue, abnormalities in blood counts, myelosuppression, teratogenicity, carcinogenicity [19]
Corticosteroids [19, 26, 27]	Alters multiple pathways; antiinflammatory, immunosuppressive	Oral, intramuscular	Two trials and a case series provide evidence for short-term use of beclomethasone, flunisolide, and methylprednisolone in AD [19]. These agents have a rapid onset of action and are thought to have a moderate impact on the clinical signs of AD [27]	None in the short term	Stunting of vertical growth, weight gain, hypertension, adrenal suppression, osteoporosis, cataracts/glaucoma, diabetes, mood disturbance, broad immunosuppression [26]

underway to study its impact on pediatric and adult AD [38, 39].

JAK Inhibitors

Janus kinase (JAK) inhibitors are a newer class of oral and topical medications that have emerged as a promising treatment modality in pediatric AD. In the topical form, ruxolitinib is FDA approved as a 1.5% cream for treatment of mild to moderate AD in non-immunocompromised patients 12 years of age and older on less than 20% of body surface area daily [40]. Significantly more patients with AD attained treatment success, as determined by the Investigator Global Assessment (IGA) score, with use of topical ruxolitinib versus vehicle in two phase 3 trials [41]. Of particular interest, topical ruxolitinib was also found to have a rapid effect on the severity of itch, possibly due to the effects of the JAK signaling cascade on sensory nerve fibers [41]. Topical ruxolitinib is generally well tolerated, with lower rates of burning or pain on application compared with TCIs or crisaborole [41]. It also carries the same boxed warning as the oral JAK inhibitors, despite limited evidence for systemic absorption with topical use [42]

Upadacitinib, an oral JAK inhibitor, was recently approved in January 2022 for pediatric patients 12 years of age and older with refractory moderate to severe AD [43]. Phase 3 trials found that patients treated with upadacitinib had at least a 90% improvement in Eczema Area and Severity Index (EASI) score when compared with placebo [44]. Improvement of other aspects of AD were also achieved in these studies, including itch and quality of life [44]. In a head-to-head trial conducted on adult patients with moderate to severe AD, upadacitinib was also deemed to be more efficacious than dupilumab in achieving skin clearance and itch relief [45].

Abrocitinib, another oral JAK inhibitor, is currently approved for use in adult patients with AD [46]. In phase 3 trials, it has shown promising results in the adolescent population, however it is yet to be approved for this age

group [47]. Abrocitinib at 200 mg has been shown to be superior to dupilumab in improving the itch response; no difference has been found in the EASI or IGA scores [48].

Nausea, acne, nasopharyngitis, and headache appear to be the most common treatment-related adverse effects from oral JAK inhibitor use [43–48]. Increased incidence of upper respiratory tract infections, AD, folliculitis, and herpes zoster have also been seen [43–48]. Elevations in creatine phosphokinase levels may occur, particularly with exercise [43–48]. Oral JAK inhibitors also carry a boxed warning for risk of infection, malignancy, thrombosis, cardiovascular events, and all-cause mortality [43, 46]. The safety data for use of oral JAK inhibitors in pediatric AD are still evolving. For this reason, it is recommended to obtain laboratory testing upon initiation of the JAK inhibitor, 1 month following, and every 3 months thereafter to ensure maintenance of appropriate laboratory values.

NONPRESCRIPTION THERAPIES

Moisturizers and Emollients

Skin barrier dysfunction, leading to increased penetration of allergens and transepidermal water loss, is a major cause of AD [49]. Therefore, frequent usage of moisturizers and emollients is the mainstay of nonprescription therapy for pediatric AD. Guidelines currently recommend liberal and frequent reapplication of moisturizers throughout the day to avoid drying of the skin [21, 50]. Application soon after a daily 5–10-min warm-water bath may be useful to retain moisture and remove crust [50]. Bland, hypoallergenic, fragrance-free products should be used to avoid further irritation of the skin and to decrease the risk for subsequent development of contact dermatitis. Barrier creams that contain occlusive agents (i.e., petrolatum) or humectants (i.e., glycerol) are also useful in the protection and maintenance of the skin barrier [50].

Wet Wraps

During an AD flare, wet-wrap therapy (WWT) may also be a useful method to rehydrate the skin. This process involves application of a moisturizer or TCS to involved skin, followed by a damp bandage or gauze and then a dry cotton overlay. The wrap is typically left on for 8–24 h [51]. Aside from decreased transepidermal water loss, WWT is beneficial as it increases penetration of the moisturizer or TCS and prevents scratching of the skin [50]. An observational cohort study of 72 children with moderate to severe AD found that WWT improved the Scoring Atopic Dermatitis (SCORAD) index after 2–16 days of application with effects lasting up to 1 month even after discontinuing treatment [52]. WWT should not be used for prolonged periods of time due to cutaneous side effects including skin atrophy from TCS and folliculitis from occlusion emollients [51, 53].

Bleach Baths

Bleach baths (half a cup of regular household bleach added to a 40-gallon adult bathtub full of water) are thought to be particularly useful in patients with recurrent skin infections or for those looking for an inexpensive treatment option [53]. In a mouse model, bleach was shown to inhibit epithelial cell cytokines, thereby decreasing skin inflammation and tissue damage [54]. A small randomized controlled trial (RCT) of 31 children with moderate to severe AD and clinical signs of secondary bacterial infection observed a decrease in disease severity with chronic use of dilute bleach baths and intermittent use of intranasal mupirocin [55]. Another similar study of 28 children with AD discovered a significantly lower burden of *Staphylococcus aureus* on the skin after treatment with emollients, TCS, and dilute bleach baths [56]. Further evidence supporting the use of bleach baths is limited, likely due to lack of funding and the inability to blind a study given its distinct odor [57].

Oils

Use of natural oils may be considered as an alternative treatment approach to pediatric AD. Evening primrose oil (EPO), from the *Oenothera biennis* plant, is a source of omega-6 fatty acids and is thought to be antiinflammatory [58]. A small study conducted on 50 patients with AD reported that 96% of patients treated with EPO showed improvement after a 5-month course of daily dosing [59]. However, another review found no statistically significant advantage to use of EPO in the treatment of AD [60]. As a result, the consensus on EPO remains neutral [58]. Sunflower seed oil (SSO), from the *Helianthus annuus* plant, is another option given its antiinflammatory and barrier repair properties [61]. A steroid-sparing effect was observed in a study involving 86 children with moderate AD treated with alternating TCS and 2% SSO [62]. Finally, extra virgin coconut oil from the *Cocos nucifera* tree can be utilized; its antibacterial effects are of particular interest [61]. As with any essential oil, discretion is advised to prevent irritation and sensitization of the skin. In addition, use of olive oil should be avoided. Studies have suggested that olive oil may cause skin inflammation and irritation without any significant treatment benefit [63].

Vitamins

Supplementation with vitamins and antioxidants may positively impact pediatric AD. A few studies investigating vitamin D saw improvement in eczema severity with oral supplementation, particularly when provided in the winter months [61, 64]. This suggests that deficiency of vitamin D may contribute to the pathophysiology of AD [61]. However, topical vitamin D may worsen AD and is often avoided [61]. In contrast, topical vitamin B12 is thought to prevent AD flares, possibly through inhibition of an important step in the inflammatory pathway [61]. A systematic review found a significantly lower AD severity score with use of topical vitamin B12 and no associated serious adverse events [64].

Probiotics

Of interest, some studies have investigated a link between the health of the gut and its relationship to the skin barrier. It is theorized that the gut regulates the immune system and, when the gut microbiome is altered, it may lead to host vulnerability and decreased immune tolerance [65]. This dysbiosis may result in a myriad of skin conditions, such as acne, psoriasis, and AD [65]. Probiotics, such as lactobacillus, were therefore thought to confer an additional benefit in the management of pediatric AD [61]. An early RCT saw a significant reduction in the SCORAD index of children with moderate to severe AD with twice daily oral *Lactobacillus fermentum* supplementation [66]. Another systematic review found preliminary studies supporting the use of topical probiotics in decreasing AD severity as well [67]. Nevertheless, concerns over proper dosing, formulation, efficacy, and the potential side effects of probiotics have limited their use in everyday practice [61].

Melatonin

Sleep disturbance is a well-known and common side effect associated with AD. Melatonin, a hormone produced by the pineal gland to regulate the sleep–wake cycle, may be supplemented in patients experiencing this symptom. In a randomized, double-blinded, placebo-controlled trial, 6 mg of melatonin nightly was shown to improve overall sleep quality in children with AD as evaluated by the Children's Sleep Habits Questionnaire [68]. Furthermore, melatonin was also found to improve the SCORAD index, objective SCORAD index, and the serum total IgE levels [68]. It did not, however, influence pruritus scores, sleep-onset latency, or serum high-sensitivity C-reactive protein (CRP) [68]. Nonetheless, it is thought to have a great safety profile with few adverse effects in comparison with other sleep aids [68]. Thus, it may be a useful adjunct to an existing treatment regimen. However, additional large-scale studies investigating melatonin are still

required as the current evidence for its use in pediatric AD is limited.

Black Tea Bags

Facial dermatitis is a common but difficult-to-treat manifestation of pediatric AD. Black tea compresses have been studied in Germany for this purpose, likely owing to their astringent, antiinflammatory properties [69]. To make a black tea compress, nonflavored black tea is brewed in boiling tap water. The same tea bag is then allowed to brew in a second boiling tap water bath. After cooling to room temperature, a gauze, cloth, or bandage is then soaked in the second tea infusion, rung out, and applied to the face for 20 min [69]. A prospective study conducted on patients with facial dermatitis demonstrated reduction in a variety of disease severity scales after 3 days of treatment with black tea compresses, with sustained improvements up to day 6 [69]. Drawbacks to this therapy include the potential for nickel hypersensitivity given the high nickel content of black tea, as well as the level of compliance and time that it may require of the patient [69]. Likewise, few studies exist for this therapy, and thus more investigation is required.

Acupuncture and Traditional Chinese Herbal Medicine

Another complementary approach to consider is acupuncture, with or without combined traditional Chinese herbal medicine. A sham-controlled trial discovered that twice-weekly verum acupuncture improved both the SCORAD and EASI scores of patients diagnosed with AD [70]. Acupuncture is thought to alleviate histamine-mediated skin itching, which may explain some of its benefits [70, 71]. The risks of acupuncture are low but may include pain/soreness, numbness, or reaction to the contaminants found in Chinese herbs if used [70, 71]. Children may also exhibit needle anxiety. Individuals or families contemplating this therapy for AD should speak with their healthcare provider. Additionally, an experienced, licensed

acupuncturist should be sought out to ensure a safe and comfortable experience.

Stress-Reduction Techniques

Stress management may also be a powerful tool in combating the symptoms of AD. Interestingly, in healthy patients, increased stress has been linked to disruption of the skin barrier and impaired skin healing [71]. Stress-induced impairment of the skin barrier is also associated with an increase in inflammatory cytokines, which can worsen or trigger AD [72]. Interventions such as hypnosis, biofeedback, progressive muscle relaxation (PMR), meditation, guided imagery, and massage have been explored, with some successful results. For example, an early study conducted on adult and pediatric patients with refractory AD saw improvements in itch, scratch, sleep disturbance, and mood after treatment with hypnotherapy [73]. Another study utilizing PMR, a technique used to release tension in the body, found decreased levels of pruritus and sleep disturbance after only 1 month of therapy [74]. Further research on the benefits of stress-reducing techniques such as those described is needed. For now, they may be considered when a low-risk, relatively low-cost alternative is desired.

Alpine Climate Treatment

In Europe, a change in environment and climate has been studied as a therapy for allergic diseases. It is thought that the alpine environment may be beneficial for AD given its reduced aeroallergens, dust mites, and pollution [75]. To undergo alpine climate treatment, children are hospitalized in a specialized clinic at high altitude for up to 3 months and treated with anti-inflammatory medications [75]. A randomized trial conducted in Davos, Switzerland found that children with difficult-to-treat AD had significant improvement in disease activity when cared for in the alpine climate and for up to 6 weeks thereafter [75]. However, this effect was lost at the 6-month follow-up visit [75]. Given the absence of long-term effectiveness and its potential cost, alpine climate treatment may

only be useful when seeking quick results in severe cases.

Conclusions

While there remains no cure for pediatric AD, the list of potential treatments for this disease is long and not limited to those described above. Options may include the standard pharmaceutical agents, newly developed small-molecule inhibitors and biologics, nonprescription adjuvants, and alternative therapies. As our understanding of the pathophysiology of pediatric AD continues to grow, it is likely that this list will expand over the coming years. Ideally, these therapies will strike a unique balance between symptom control and minimal associated adverse effects.

ACKNOWLEDGMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Author Contributions. HJ and JY contributed equally to this manuscript, including concept and design and drafting of the manuscript.

Disclosures. Hadley Johnson has nothing to disclose. JiaDe Yu has nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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