Recent Developments in Atopic Dermatitis

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Atopic dermatitis (AD) is a bothersome and common skin disease affecting ~10.7% of children in the United States. This skin condition significantly decreases quality of life in not only patients, but in their families as well. Pediatricians are often the first physicians to diagnose and manage these patients and thus are relied on by families to answer questions about this disease. AD is complex, multifactorial, and has historically had limited therapeutic options, but the landscape of this disease is now rapidly changing. Pathways contributing to the pathogenesis of this disease are continually being discovered, and new therapies for AD are being developed at an unprecedented rate. With this article, we will review the current guidelines regarding the management of AD, outline updates in the current understanding of its pathophysiology, and highlight novel developments available for the treatment of this burdensome disease.

ATOPIC DERMATITIS

AD is a chronic inflammatory skin disease that affects ~10.7% of children in the United States and is becoming increasingly prevalent. Pediatricians are often the first physicians providing treatment to patients with new-onset AD and disease flares, and ~50% of patients with AD are treated in a primary care setting. Therefore, pediatricians play a key role in the overall management of patients with AD and should be well informed about recent developments in the clinical management of this disease.

Despite its high prevalence, this complex disease has historically been poorly understood. With this article, we provide an update on recent advances in our understanding of the clinical presentation and pathophysiology of AD and highlight new therapeutic developments for this disease.

CLINICAL COURSE

AD is a bothersome skin condition often referred to as the “itch that rashes” because of the pruritus that patients experience. This hallmark symptom of AD is responsible for its significant negative impact on quality of life (QoL). Patients with AD often present with severe pruritus and xerosis, with variable lesion distribution based on age. Young infants up to 2 years of age often present with scaly, crusted erythematous patches on the scalp, face, and extensor surfaces, whereas prepubertal children present with erythematous patches in a flexural distribution. Adolescents and adults typically present with more lichenified skin changes.

The progression of AD is unpredictable, but the following 4 phenotypes have recently been identified: early-onset transient (9.2% of children), early-onset persistent (6.5%), late-onset (4.8%), and absent or infrequent AD (79.5%). Patients with AD have alternating periods of exacerbated disease and symptom resolution. Thus, both the alleviation of symptoms and prevention of flares are important in the management of AD.

Diagnosis

Patients commonly present during acute flares with intense pruritus,
xerosis, erosions, excoriations, and ill-defined patches of erythema with a distribution that varies with age. AD is clinically diagnosed on the basis of history, morphology, distribution of skin lesions, and associated clinical signs. Other important factors suggesting a diagnosis of AD include early onset (<2 years of age), atopy, and family history of disease. This diagnosis should be reevaluated frequently, particularly in patients not responding to appropriate treatment, to verify the accuracy of this diagnosis and exclude the possibility of other conditions, such as scabies, contact dermatitis, psoriasis, tinea infections, or viral exanthems.

**Comorbidities and Complications**

AD is thought to “kick off” the atopic march, predisposing patients to other atopic disorders later in life. Patients with AD with early sensitization to foods have an increased risk of developing asthma, allergic rhinitis, and food allergies. Therefore, early diagnosis and management of AD and its associated risk factors may reduce the risk of developing other allergic diseases and improve overall QoL.

AD has been associated with an increased risk of developing a peanut allergy specifically, but previous clinical practice guidelines on food allergy prevention were constantly changing. Most recently, the Learning Early About Peanut Allergy trial revealed that an early introduction of peanut-containing foods reduces the risk of developing a peanut allergy in high-risk patients, including infants with severe AD. Current consensus guidelines recommend an introduction of peanut-containing foods such as peanut butter or peanut puffs as early as 4 months of age to patients with AD to reduce this risk of future allergy.

Children with AD have significant cutaneous immune dysregulation and an impaired skin barrier, which contribute to an increased susceptibility of developing skin infections. Because of a decreased antimicrobial peptide expression, >75% of affected children are colonized by *Staphylococcus aureus*, compared with <25% of healthy children in control groups. *Staphylococcus* colonization worsens inflammation and pruritus, increasing the risk of colonization and/or superinfection with *Streptococcus pyogenes*, viruses, or fungi. AD can also predispose patients to disseminated eczema herpeticum and molluscum contagiosum outbreaks.

Currently well-known comorbidities of AD are mostly atopic, but AD may have a broader impact on health. Authors of recent studies have shown that patients with AD are more likely to be obese and have elevated serum cardiovascular risk markers than healthy patients, contributing to increased cardiovascular disease risk. However, severe AD in children and adolescents has also been associated with impaired growth and short stature.

Patients with AD are also at an increased risk of developing depression, anxiety, attention-deficit/hyperactivity disorder, and conduct disorder, with risk correlated with AD disease severity. AD is not just skin deep, and management should be used to address the comorbidities, in addition to skin symptoms, associated with this systemic disease.

**QoL Impairments**

Although skin disease is often perceived to be relatively benign, children with generalized AD report QoL deficits similar to that of children with other serious chronic diseases, including renal disease and cystic fibrosis. Because of the ever-present nature of the itch–scratch cycle, AD can be extremely burdensome and infringe on all areas of affected patients’ lives, including sleep, social functioning, work productivity, and income.

AD has a well-characterized negative impact on sleep in children and their families because of debilitating pruritus and the constant care needed for this disease. Children with moderate-to-severe AD experience more restless sleep, increased waking, greater difficulty falling asleep, and increased daytime sleepiness compared with healthy patients; these are behaviors that worsen with the severity of AD and with flares. Parents of affected children also experience significant sleep loss (~1–3 hours per night) while providing overnight care to soothe their children and help them return to sleep. The severity of sleep disruption associated with AD is comparable to that of other chronic conditions requiring constant care, including autism spectrum disorder, mental retardation, and seizure disorders. An effective treatment plan is necessary to minimize the QoL impairment because of poor sleep in both affected patients and their families.

AD affects children during critical stages of childhood development, causing significant QoL impairment at ages when patients are most vulnerable. Children with AD can be severely impacted by fear of embarrassment and constant anxiety about future flares. Patients with AD are often socially isolated and bullied because of the fear of contagion and stigma, leading to poor self-esteem in these young and impressionable patients. As a result, patients with AD often withdraw socially, avoid group activities, or may even skip school to prevent further embarrassment. Affected patients will often also have impaired concentration because of sleep loss, antihistamine sedation, and irresistible itch, which, combined with stunted social development and missed school time, may decrease scholastic achievement and
ultimately diminish future career prospects.66,69,52–54

Additionally, AD is economically burdensome, costing the United States $5.3 billion in 2004,55 a number that will likely rise with the rapidly increasing price of topical corticosteroids (TCSs).56 In 1 study, families of affected patients spent 34.8% ($274) of their available monthly income on AD care, which can be a significant financial burden especially for low-income families.57

Caregivers for patients with AD often miss work to care for their children’s health issues,42 which can contribute to impaired work performance and decreased income. It is important for pediatricians to be aware that the negative impact of AD on the QoL for patients and their families is multimodal. Skin symptoms represent a small portion of the negative impact of AD, which also profoundly affects sleep, childhood development, and finances.

PATHOPHYSIOLOGY AND PATHOGENESIS

The pathogenesis of AD involves a complex interplay of immunologic dysfunction, genetics, environmental exposures, and skin barrier disruption. Loss-of-function filaggrin gene mutations were implicated early on as a major predisposing risk factor for AD.58 suggesting skin barrier defects to be key drivers of this disease. However, authors of more recent research have found that filaggrin is deficient in most affected adults regardless of genotype59 but not in patients with new-onset AD.60 Therefore, filaggrin deficiency is not necessary for disease onset but may be a downstream result of disease chronicity. Authors of recent findings have also found skin barrier disruption to occur early in life, with increased neonatal transepidermal water loss predicting future development of AD.61 Nevertheless, most recent developments with respect to therapeutics and pathogenesis of this multifactorial condition have been in the understanding of the immunology of this disease.

However, much of the current understanding of AD immunology is based on studies in adults, who present different clinically and have a longer duration of disease than pediatric patients. Given that the immune system changes with age,62 findings in adults may not represent the immunologic processes occurring in children. Authors of recent studies have characterized immunologic differences in AD observed with age,63 ethnicity,64 and disease subtype,65 suggesting that several distinct inflammatory mechanisms likely contribute to this complex, heterogeneous skin disease. Significant recent advances have increased our understanding of the underlying mechanisms of both adult and pediatric AD, contributing to the development of novel therapies for this complex disease.

AD has historically been described as a biphasic T-cell–mediated disease, in which an initial T helper (Th) 2 (Th2) activation drives acute disease, whereas a later Th1 response maintains chronic AD.66 Authors of recent studies corroborate the role of early Th1 axis suppression in this disease, finding low Th1 T-cell levels in acute AD lesions in adults67 and children recently diagnosed with AD.63 However, chronic AD lesions reveal intensification, rather than withdrawal, of Th2-related inflammation.67 Strong activation of the Th2 and Th22 inflammatory responses are observed in the lesional skin of both children and adults with AD, but affected children demonstrate greater induction of the Th17 axis to levels comparable to that of patients with psoriasis.60 Interestingly, the nonlesional skin of young children66 and adults68 also already harbors significant inflammation with increased Th2 and Th17 expression, suggesting that AD involves early systemic involvement.

Thus, the progression of AD may not be as clear-cut as previously thought.

Despite major immunologic similarities to AD in adults, pediatric AD also reveals features that may be unique to new-onset disease. The skin of affected children reveals T-cell predominance as compared with healthy children and affected adults, implicating T-cell activation as a key driver of early AD.69 Additionally, these children exhibit lymphocyte distributions similar to that of healthy adults, implying that accelerated lymphocyte development may play a role in disease initiation.69 The lesional skin of affected children also uniquely reveals gene expression more similar to psoriatic lesions than that of adult AD or healthy pediatric skin, which may have implications for future treatment.60 Significant inroads are being made to understand the pathogenesis of both adult and pediatric AD and the overlap and differences between the 2, which may help guide the development of future, more targeted therapies.

Although various additional pathways contribute to AD, the Th2 immune response remains the main focus of AD pathogenesis and therapeutic development. Th2 cells are the main producers of Th2 cytokines interleukin 4 (IL-4), interleukin 5 (IL-5), and interleukin 13 (IL-13) in AD, but type 2 innate lymphoid cells (ILC2s), found in increased numbers in lesional AD skin,60 have recently been characterized as an additional source of Th2 cytokine release.70–72 The recent discovery of these cells in AD may link several abnormalities known to occur with AD and may serve as a target for new therapies in the near future.

ILC2s express killer cell lectin-like receptor G1, which normally binds E-cadherin to inhibit ILC2 proliferation and IL-5 and/or IL-13 production.70 E-cadherin is normally expressed by epidermal cells but is downregulated in AD73 and
patients with filaggrin deficiency. Because barrier dysfunction is a key pathogenic factor for AD, this model provides a novel barrier-sensing mechanism that contributes to the pathogenesis of AD.

Additionally, ILC2s proliferate in response to elevations in thymic stromal lymphopoietin (TSLP), a pro-inflammatory cytokine produced by epithelial cells in response to stress found at increased levels in AD skin lesions. TSLP selectively increases basophil hematopoiesis and promotes peripheral basophilia. These basophils subsequently release IL-4, causing ILC2s to proliferate in an IL-4–dependent manner. ILC2s release IL-5 and IL-13, further contributing to the upregulated Th2 response observed in AD. IL-13 also upregulates TSLP release by keratinocytes, creating a positive feedback loop for the worsening of AD. However, the role of ILC2s specifically in AD pathogenesis is poorly understood and in the early stages of investigation. Further characterization of the mechanisms of AD-related immune dysfunction will aid the development of future therapeutics.

**MANAGEMENT**

AD is often managed successfully in the pediatric primary care setting with topical agents, but recalcitrant disease has been historically difficult to address because of a lack of approved second-line therapies for AD. However, great strides have been made recently in the development of treatments for AD.

**Basic Management**

The basic management of AD has not changed significantly in recent years, still centering around gentle skin care and the prevention of disease exacerbation. Skin hydration and liberal use of moisturizers is essential for all patients with AD both during flares and for maintenance, because skin barrier disruption in this disease results in xerosis and increased transepidermal water loss. Adequate moisturization significantly decreases AD symptoms, including pruritus and lichenification, and decreases the amount of prescription medications needed for treatment. In fact, applying moisturizer to neonates with a family history of AD reduces the risk of future development of the disease and should be considered for patients at high risk of developing atopic disease.

Trigger avoidance is also important to prevent recurrent symptoms or disease worsening. A careful history should be taken to characterize relationships between suspected triggers and skin symptoms. Age can be used to guide the discussion of likely triggers (ie, younger children are more likely to have a food allergy than older children, who are more often triggered by aeroallergens). Indiscriminate allergy testing without a history that suggests allergic triggers is not recommended, because these tests have low positive predictive values. Skin-prick or specific immunoglobulin E testing should only be done when there is a high clinical suspicion of allergy-induced dermatitis. If patients are found to have trigger-induced disease exacerbation, trigger avoidance can greatly decrease the frequency and severity of flares.

Acute management of AD is largely focused on controlling pruritus, which is responsible for significant QoL impairment. Acute flares are often managed with topical therapies, but oral antihistamines may provide additional benefit in certain situations. Non-sedating antihistamines are not recommended for routine treatment of AD, but short-term use of first-generation antihistamines such as diphenhydramine, in combination with topical therapies, may be helpful for patients with sleep loss secondary to itch because of their sedative effect. Young patients should be monitored for paradoxical excitation, a sign of antihistamine toxicity that occurs at higher rates in children. Sedating therapies should only be used short-term, because long-term use can be detrimental to school performance.

Although their clinical evidence is conflicting, bleach baths are recommended for patients with moderate-to-severe AD with signs of secondary bacterial infection because of their presumed antistaphylococcal and antiseptic properties. These may also be useful for maintenance treatment of patients suffering from recurrent infections to decrease bacterial colonization and the risk of secondary skin infection and to improve disease severity. These patients should bathe twice weekly in 0.05% sodium hypochlorite (~0.5 cups of 6% bleach in a full bathtub of water (~40 gal)) but may use bleach baths daily if they have severe disease. Intranasal mupirocin and sodium hypochlorite cleansers may provide additional benefit, but consensus guidelines for these have not yet been developed.

Vigilant skin care and trigger avoidance may often be sufficient for patients with mild disease, but patients with symptoms not adequately managed by these measures require further pharmacologic interventions, including topical and systemic agents.

**Topical Therapies**

The recommended first-line pharmacologic therapy for AD continues to be TCSs, which have proven to be effective for children over several decades. However, TCS phobia remains a significant concern for patients and providers, and is a significant source of treatment nonadherence. AD persists on average for 6.1 years and can be active well into adulthood for some
patients, so physicians often fear long-term TCS effects such as skin atrophy, striae development, or systemic effects. This has resulted in an increased use of second-line treatments, such as the topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus, in the management of pediatric AD. However, TCIs are associated with increased rates of burning sensations and pruritus and have higher costs, with no additional benefit over TCSs with respect to long-term safety or efficacy. Thus, TCSs, when used appropriately, are a safe and effective first-line option for the treatment of pediatric AD.

As the underlying mechanisms of AD have become better understood, new topical therapies have been developed for AD, most notably crisaborole. Crisaborole is a topical phosphodiesterase-4 (PDE-4) inhibitor approved in 2016 for the treatment of mild-to-moderate AD for patients ≥2 years of age. PDE-4 inhibition inhibits intracellular cyclic adenosine monophosphate degradation, ultimately decreasing pro-inflammatory cytokine release via downregulation of the nuclear factor kappa-light-chain-enhancer of activated B cells pathway. Two phase III trials revealed that nearly one-third of patients using twice-daily crisaborole therapy for 28 days demonstrated Investigator’s Static Global Assessment of clear or almost clear with at least a 2-grade improvement from baseline, significantly more than patients applying vehicle ointment (AD-301: 32.8% vs 25.4%; P = .038; AD-302: 31.4% vs 18.0%; P < .001). Notably, crisaborole is well tolerated by patients in the short-term and the long-term (48 weeks). Application-site burning and/or stinging was experienced by 4.4% of patients in the first 4 weeks, with decreased incidence over time. A far greater proportion of patients experience stinging in the authors’ clinical experience, but crisaborole still provides a fairly well-tolerated, albeit expensive, nonsteroidal alternative to TCSs and TCIs for the management of mild-to-moderate adult and pediatric AD.

Several other topical PDE-4 inhibitors have completed phase II studies and have revealed efficacy for AD. An ointment preparation of tofacitinib, a Janus kinase inhibitor, also significantly improved AD severity and pruritus in a phase II trial. Other topical agents being investigated for AD include toll-like receptor antagonists, serotonin inhibitors, aryl hydrocarbon receptor agonists, and leukotriene antagonists. Clinical trials are currently ongoing to investigate the efficacy and safety of crisaborole for patients 3 months to 2 years in age (NCT03356977).

**Topical Therapy Considerations**

Safe usage of topical therapies requires a careful and deliberate approach. Patients generally should be treated with the least potent TCS that is effective, to minimize the risk of TCS-related side effects. TCSs have greater penetration in sensitive and occluded areas such as the face, neck, and skin folds, so lower potency or nonsteroidal agents should be used in these areas to decrease the risk of systemic corticosteroid absorption. Because AD often persists for years, long-term maintenance management should alternate TCSs with nonsteroidal agents such as TCIs or crisaborole as appropriate to reduce the risk of treatment-related side effects.

Another important consideration in selecting topical therapies is vehicle choice. Children notoriously have poor adherence to topical medications, so physicians must prescribe treatments their patients will actually tolerate and
use. Ointments are considered the most efficacious vehicle because of their occlusive nature and are well tolerated by infants and young children. However, adolescents often dislike the greasy feel and thus avoid using ointments during the daytime. Physicians must aim to optimize treatment adherence and may compromise by recommending nighttime ointment use while suggesting daytime application of thinner vehicles, such as creams or lotions. However, choosing topical therapies requires a personalized approach, and vehicle selection should be evaluated on a case-by-case basis.

Systemic Therapies

Because of a historic lack of safe and efficacious options, the threshold for considering the initiation of systemic therapies has traditionally been high. UV-B phototherapy is a safe and effective treatment, without increased skin cancer risk, for patients with AD uncontrolled by topical agents. However, phototherapy can be inconvenient, requiring 2 to 3 treatments per week for several months. Patients deriving minimal benefit from phototherapy should consider systemic therapy. Traditionally, azathioprine, cyclosporine, methotrexate, and mycophenolate were the only systemic therapies that were efficacious for recalcitrant AD, but these therapies are associated with potentially serious side effects and require close monitoring (Table 1).

Because these medications are not frequently used by pediatricians in the outpatient setting, physicians may be hesitant in using them to treat patients with pediatric AD. Despite these potential side effects, the “cost of not treating” should be a key consideration in selecting treatment for patients. AD is often thought of as “just a skin disease,” but it is also associated with significant comorbidity and QoL deficits, as discussed previously. This disease typically affects patients during critical stages of development, and abnormal development may ultimately cause lifelong impairment. Pediatric providers must be mindful of these considerations when deciding the optimal course of therapy for their patients. Fortunately, more targeted biological therapies are in development for AD that will create more safe and effective systemic therapies for this disease.

One such biological therapy is dupilumab, a human monoclonal immunoglobulin G4 antibody targeting IL-4Ra that was approved in 2017 for the treatment of moderate-to-severe AD for adults. Dupilumab inhibits IL-4- and IL-13-mediated inflammatory responses, because the IL-4Ra subunit is shared by the receptor complexes for both of these cytokines. Two phase III trials revealed that more than one-third of patients on dupilumab monotherapy every 2 weeks for 16 weeks demonstrated Investigator’s Global Assessment (IGA) of clear or almost clear with at least a 2-grade improvement from baseline, significantly more than patients receiving the placebo (Study of Dupilumab Monotherapy Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis 1 [SOLO1]: 37.9% vs 10.3%; SOLO2: 36.1% vs 8.5%). Dupilumab use was associated with an increased risk of conjunctivitis (4%–5% of patients) and injection-site reactions (8%–14%) over the placebo.

Topical therapies can be combined with dupilumab for additional benefit and to treat patients with recalcitrant disease. In the phase III trial LIBERTY AD CHRONOS, 38.7% of patients receiving combination therapy with both twice-weekly dupilumab and TCS achieved an IGA of 0 or 1 at week 16 with a ≥2-grade improvement from baseline, as compared with 12.4% of patients using only TCS. This response with combination therapy persisted through week 52, with 36.0% of patients receiving combination therapy achieving this same end point, as compared with just 12.5% of patients in the control group. Additionally, combination therapy with TCS and twice-weekly dupilumab therapy improved disease severity in patients not responding to cyclosporine, with 40.2% achieving an IGA of 0 or 1 with a ≥2-grade improvement at week 16 as compared with 13.9% on TCS alone in the phase III LIBERTY AD CAFÉ trial. Patients receiving combination therapy demonstrated no increased risk of serious adverse events over TCS monotherapy but still yielded an increased risk of conjunctivitis and injection-site

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<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side Effects</th>
<th>Monitoring</th>
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<tbody>
<tr>
<td>Azathioprine</td>
<td>1–4 mg/kg per d</td>
<td>Myelosuppression, nausea, vomiting, hepatotoxicity</td>
<td>Baseline TPMT levels, CBC, CMP</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2.5–6 mg/kg</td>
<td>Hypertension, renal insufficiency</td>
<td>CBC, CMP, Mg&lt;sup&gt;2+&lt;/sup&gt;, uric acid, lipids, blood pressure</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>2–4 mg/kg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Conjonctivitis, injection-site reactions</td>
<td>None</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0.2–0.7 mg/kg per wk</td>
<td>Nausea, ulcerative stomatitis; hepatotoxicity, myelosuppression</td>
<td>CBC, CMP</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>20–50 mg/kg daily</td>
<td>Nausea, vomiting, abdominal cramping</td>
<td>CBC, CMP</td>
</tr>
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CBC, complete blood count; CMP, complete metabolic panel; Mg<sup>2+</sup>, magnesium ion; TPMT, thiopurine methyltransferase.

<sup>a</sup> The dose used in the phase 2a trial is not currently approved for pediatric use.
It is now apparent that AD extends beyond cutaneous manifestations to impair sleep, social function, school performance, and overall development. As such, the treatment paradigm for AD is shifting, and considering deficits beyond physical symptoms is recommended when developing treatment plans. The management of affected patients will likely continue to progress in the coming years as the underlying mechanisms of this disease become better understood and new therapies become available. Primary pediatric care providers must stay aware of these updates, because they are the go-to provider for most patients with AD and will continue to be the first-line defense against this burdensome disease.

### ABBREVIATIONS

- **AD**: atopic dermatitis
- **IGA**: Investigator’s Global Assessment
- **IL-4**: interleukin 4
- **TCS**: topical corticosteroids
- **ILC2**: type 2 innate lymphoid cell
- **QoL**: quality of life
- **SOLO1**: Study of Dupilumab Monotherapy Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis
- **SOLO2**: Study of Dupilumab [REGN668/SAR231893] Monotherapy Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis
- **TCI**: topical calcineurin inhibitor
- **TCS**: topical corticosteroid

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