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Allergy, Asthma, and Immune Deficiency

Atopic Dermatitis

Peck Y. Ong MD^a,   **and Mark Boguniewicz MD^b**

^aDivision of Clinical Immunology–Allergy, Childrens Hospital Los Angeles, University of Southern California Keck School of Medicine, 4650, Sunset Boulevard, MS# 75, Los Angeles, CA 90027, USA

^bDivision of Pediatric Allergy-Immunology, National Jewish Medical and Research Center, The University of Colorado Health Sciences Center, 1400 Jackson Street, Denver, CO 80206, USA

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Atopic dermatitis is a complex, chronic inflammatory skin disease. Affected individuals, particularly those with moderate to severe disease, often suffer from significant morbidity, such as sleep loss, skin infections, and school or work disruption. Treatment for these patients can be especially challenging. Restoring skin barrier function, eliminating allergic and nonallergic triggers, and properly using anti-inflammatory and antimicrobial medications are all important components of a comprehensive treatment plan. Wet wraps and systemic immunosuppressants are alternative treatments for patients with severe, refractory atopic dermatitis.

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Atopic dermatitis (AD) is a common chronic inflammatory skin disease in childhood, affecting up to 17% of children in the United States [1]. This skin disease is characterized by intense pruritus and cutaneous inflammation. The quality of life of affected individuals can be significantly affected, particularly in those with moderate to severe disease [2]. In addition, AD patients are predisposed to a variety of skin infections, including *Staphylococcus aureus* and herpes simplex virus. Up to 50% of children with AD go on to develop asthma [3]. AD also carries with it a significant financial burden to the family and society [4].

Pathogenesis

The pathogenesis of AD is complex, involving genetic factors, skin barrier defects, and immune dysregulation (reviewed in reference [5]). The genetics of AD is an area of intense research. Genetic polymorphisms have been associated with chromosome 5q22-23, which contains a cluster of T helper type 2 (Th2) cytokine genes (IL-4 and IL-13). Those genes play a significant role in IgE production and allergic sensitization. More recently, the association of AD with filaggrin gene mutations has pointed to the role of skin barrier defects in the pathogenesis of AD [6]. Filaggrin is a protein essential to the normal barrier function of the skin. Deficiency in this protein may contribute to the physical barrier defects in AD and predispose patients to increased transepidermal water loss, infections, and inflammation associated with exposure of cutaneous immune cells to allergens [7]. A recent study showed that the level of filaggrin can be modulated by cytokines [8]. This may present specific therapeutic opportunities, although, at this time, maintaining a normal epidermal barrier is key.

Diagnosis

There is currently no diagnostic laboratory test for AD. Although the majority of AD patients have elevated total serum IgE, up to 30% of these patients have normal total serum IgE and show no allergic sensitization to food or aeroallergens [9]. The diagnosis of AD is based on clinical criteria. Itch must be present for the diagnosis of AD. In addition, the patient should have three or more of the following criteria [10]:

- Visible rashes on the flexural areas (elbows, back of knees, front of neck, or eyelids); in infants, the rash may be present on the cheeks or extensor areas of the knees or elbows
- History of rashes on the flexural areas
- Personal or family history of respiratory allergies (asthma or allergic rhinitis)
- History of dry skin in the past year
- Onset before 2 years of age

Ninety percent of AD patients have onset of the disease before 5 years. Therefore, new-onset AD in older children or adults should raise suspicion for other skin conditions. [Box 1](#) shows the differential diagnosis of AD.

Box 1. Differential diagnosis of AD

Dermatologic diseases

Seborrheic dermatitis

Irritant or allergic contact dermatitis

Psoriasis

Nummular pilaris

Keratosis pilaris

Lichen simplex chronicus

Pityriasis rosea

Nonbullous congenital ichthyosiform erythroderma

Neoplastic diseases

Cutaneous T cell lymphoma (mycosis fungoides, Sezary syndrome)

Letterer-Siwe disease (Langerhans cell histiocytosis)

Necrolytic migratory erythema associated with pancreatic tumor

Immunodeficiencies

Immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome

Hyper-IgE syndrome

Wiskott-Aldrich syndrome

Severe combined immunodeficiency syndrome

Infectious diseases

Human immunodeficiency virus–associated eczema

Scabies

Candidiasis

Tinea vesicolor

Congenital and metabolic disorders

Netherton's syndrome

Phenylketonuria

Zinc deficiency

Essential fatty acid deficiency

Histidine deficiency

Infantile-onset multiple carboxylase deficiency

Management

Basic skin care

Daily skin care is key in the control of AD symptoms. The following list provides some of practical actions to take in the treatment of AD:

- Rather than soaps, use cleansers with minimal defatting activity and a neutral pH.
- Avoid alcohol and astringents in skin care products.
- Avoid wool clothing or other materials that may be irritating to the skin; cotton or cotton blends are generally preferred.
- Launder clothing to remove formaldehyde and other chemicals.
- Use liquid detergents, which are easier to rinse out than powder detergents.
- Add a second rinse cycle to facilitate further removal of detergents.
- Avoid extremes of environmental temperatures or humidity; prolonged exposure to sun may lead to overheating and evaporation, as well as perspiration, all of which can be irritating.
- Use sunscreens with low irritancy potential, such as those made specifically for the face.
- After swimming, shower with a cleanser to remove chlorine or bromine.
- Avoid proven allergens (discussed further in the next sections).
- Most importantly, take time for daily skin care with hydration followed by moisturizers. The rationale and approach are discussed below.

Skin hydration and moisturizers

Skin hydration is best accomplished through daily soaking baths for 10 to 20 minutes. It is important to remind patients and caregivers to apply a topical medication or moisturizer immediately after bathing. This is to seal in the water that has been absorbed into the skin and prevent evaporation that can lead to further drying of the skin. The combination of skin hydration and the use of a moisturizer may help to reestablish and preserve the skin barrier function. In addition, moisturizers can also decrease the need for topical corticosteroids [\[11\]](#).

Moisturizers are available as ointments, creams, lotions, and oils. Due to their occlusive nature, ointments are ideal for maintaining skin hydration after bathing or shower, but they may also trap perspiration, resulting in increased pruritus. Therefore, they may be more suitable

for use in dry environments or in younger children or infants, who are generally more tolerable of the “greasy” feel. Lotions and creams, due to added preservatives or fragrances, may have more irritating effects. In addition, lotions contain more water than creams and may therefore have a drying effect through evaporation of their contents from the skin. Although oils (eg, mineral oil) can be applied easily, they often prove to be less effective moisturizers based on their emollient properties and occasionally irritant potential. Ceramides are lipids important to the barrier function of the skin and are shown to be deficient in AD skin. The use of a ceramide-dominant emollient has been found to decrease transepidermal water loss and the disease activity of AD in children [12]. Several ceramide-based creams are currently available and a new ceramide-containing cream, Epiceram, is expected to be available in 2007. In addition, nonsteroidal creams marketed as medical devices (thus requiring prescriptions) include Atopiclair and Mimyx [13]. They have unique ingredients, different proposed mechanisms of action, and do not have any restrictions for age or length of application.

Control of pruritus

Itch is usually the most distressing symptom of AD. Even patients whose AD is under good control may continue to be affected by itch. First-generation antihistamines might be of benefit primarily through their sedating effects at bedtime. On the other hand, topical antihistamines and analgesics, due to their potential for contact allergy, should be avoided. There is increasing evidence that neuropeptides and opioid receptors are involved in the pathogenesis of itch in AD [14]. A recent placebo-controlled trial that included patients with AD showed that a cream containing naltrexone, an opioid receptor antagonist, was effective in relieving pruritus [15]. In addition, the study showed that the clinical efficacy of the medication correlated with changes in opiate receptor expression [15].

Management of sleep disturbance

Sleep disturbance is a significant problem in AD. Pharmacologic management for sleep disturbances in AD has recently been reviewed [16]. Doxepin is a tricyclic antidepressant with both H₁ and H₂ receptor antagonist activity and may be helpful to aid the sleep of AD patients [16]. In addition, doxepin possesses anxiolytic and antidepressant effects, which may be helpful in select AD patients. However, the dose used to help with sedation is generally lower than the dose needed for antidepressant effects, and patients may have difficulty tolerating daytime sedation with higher doses [16]. Other medications that may improve the sleep of AD patients include benzodiazepine and nonbenzodiazepine hypnotics, chloral hydrate, and clonidine [16]. However, there are limited data on the use of these medications in AD. Therefore, potential risks and benefits of these medications need to be considered.

Management of triggers and infections

Food allergens

About 30% to 40% of AD children with moderate to severe AD have immediate IgE-mediated food reactions [17]. Patients or families also describe delayed cutaneous reactions after ingesting certain foods. These reactions are more difficult to reproduce or characterize as to mechanism of action. In children older than 1 year, negative allergy skin tests for foods have high negative predictive value (>95%), essentially ruling out IgE-mediated food allergy [18]. On the other hand, a positive skin test to a food allergen has a positive predictive value of only approximately 50% [18]. More recently, food-specific IgE levels measured by serum ImmunoCAP assay have been shown to have predictive values up to 95% for selected foods at specific levels [19]. These foods include cow's milk, eggs, peanuts, and fish. However, it is crucial to recognize the limitations of this assay. It is especially important to note that the lower end of sensitivity for the assay is not zero, but less than 0.35kU/L. Rarely do patients still react at very low levels of food-specific IgE. In addition, specific IgE levels do not define severity of the clinical reaction. The clinical history of the patient remains important in conjunction with the use of in vivo or in vitro allergy tests. This is important because unnecessary limitation of diet based on testing can severely compromise the patient's nutrition status. Ultimately, food challenges may be needed for diagnosing clinically relevant food allergies. These should be done with the involvement of an allergist familiar with the procedure. Foods that are confirmed to cause allergic reactions should be eliminated from the patient's diet as repeat ingestion may cause a spectrum of allergic reactions. The ImmunoCAP assay may also be useful in following the natural history of a patient's food allergy with repeat measurements obtained approximately 12 months apart because most children become tolerant to cow's milk and egg protein, as opposed to peanuts, tree nuts, fish, or shellfish.

Aeroallergens

Although there is limited data on the role of domestic animals or pollens as triggers for AD, case reports and atopy patch testing suggest a

role for these allergens in sensitized AD patients [20] and [21]. The best-studied aeroallergen in AD is house dust mite (HDM) [22]. However, blinded placebo-controlled studies have shown conflicting results on the role of HDM-control measures in AD [23] and [24]. Nevertheless, HDM control measures should be considered in sensitized patients, as these patients often have concurrent respiratory allergies or are at risk for developing these allergies [25]. The control measures include the use of HDM-proof encasings, frequent vacuuming (eg, once a week) and washing linens in hot water. At this time, specific allergen immunotherapy ("allergy shots") is not indicated for AD, although limited studies suggest benefit in HDM-sensitized adult AD patients [26].

Microbial pathogens

S aureus can be cultured from the skin lesions of most AD patients [27]. AD patients are predisposed to colonization and infections by *S aureus* through deficiency in endogenous antimicrobial peptides as well as through a defective skin barrier [28]. *S aureus* from patients with AD typically secrete toxins that can cause T cell activation by acting as superantigens, which can exacerbate and perpetuate cutaneous inflammation [29]. AD patients also make specific IgE directed against these toxins, thus further triggering activation of mast cells and other IgE receptor-bearing cells in AD lesions [30]. Although AD patients are at risk for infections by *S aureus*, use of antibiotics in the absence of clinical signs of infection is not recommended because of the risk of bacterial resistance. A first-generation cephalosporin, such as cephalexin, for 7 to 10 days for overt infections is effective unless the patient is infected by a resistant strain of *S aureus*. Baths and cleansers as part of routine care can reduce *S aureus* colonization. Most AD patients do not tolerate harsh antiseptic cleansers, such as chlorhexidine or bleach baths, although some dermatologists recommend dilute bleach baths for AD patients with recurrent methicillin-resistant *S aureus* superinfections. Antibacterial cleansers, such as Lever 2000, can be considered, although some patients may still find these to be irritating to their skin. The nose is a major reservoir of *S aureus* and intranasal mupirocin (Bactroban) applied twice daily for 5 to 7 days may eradicate *S aureus* and improve AD.

Herpes simplex virus can cause life-threatening eczema herpeticum in AD patients. Therefore, physicians who treat AD must be vigilant for this infection. The infected area may not present with vesicular lesions or the area may appear as punched-out lesions with an erythematous base (Fig. 1). Ideally, viral polymerase chain reaction (PCR), Tczank smear, and/or culture should be obtained by unroofing an intact vesicle because the yield from excoriated lesions is low. The mainstay of treatment is systemic acyclovir. Patients with disseminated lesions who appear toxic should be admitted to the hospital for intravenous acyclovir and antistaphylococcal antibiotic pending PCR and culture results. Patients with periocular or suspected ocular involvement should be evaluated by an ophthalmologist emergently. AD patients are also more susceptible to molluscum contagiosum (MC) virus infection. The lesions typically present as single or multiple flesh-colored papules, which may be distributed on the trunk, extremities, or face. The treatment of MC depends on the location and number of the lesions, and the ability of the patient to tolerate painful procedures. If lesions are not periocular, they can be observed, as spontaneous resolution does occur. However, they are contagious and can spread through autoinoculation. In addition, they can occasionally scar with resolution. Treatment options include curettage under topical anesthetic cream, cryotherapy, cantharidin (a blistering agent), or topical imiquimod and tretinoin, although none of the treatments are currently approved by Food and Drug Administration for MC.



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Fig. 1. Eczema herpeticum. (Courtesy of Ronald Ferdman, MD, Los Angeles, CA.)

Sensitization to the yeast *Malassezia* species has also been demonstrated in a subgroup of AD patients. Specific IgE levels to *Malassezia furfur* (previously known as *Pityrosporum orbiculare*) have been correlated with severity of AD [31]. Antifungal therapy has been shown to be effective in a subgroup of AD patients in several studies, with most studies showing a correlation between response to antifungals and the levels of specific IgE [32]. However, the mechanism of antifungal therapy in AD remains to be clarified. It is likely that antifungal therapy may exert anti-inflammatory effects in addition to the fungicidal activity [32]. Further studies are needed to confirm the use of antifungal agents in AD patients who are colonized by these organisms.

Anti-inflammatory treatment

Topical corticosteroids

Topical corticosteroids are the first-line treatment for AD. They are available in potencies ranging from extremely high (class I) to low (class VII) ([Box 2](#)). In general, a corticosteroid formulated in an ointment base is more potent than one in a cream or lotion base. Ointment-based preparations are also more occlusive and have the fewest number of additives. They provide better delivery of the medication and decrease evaporative loss. Cream-based preparations, however, may be better tolerated during conditions of excessive heat or humidity. Although lotions are easier to apply, they may contribute to irritation and xerosis. Solutions are useful for the scalp, although their high alcohol content can be irritating and drying. A lotion-based corticosteroid may be better tolerated. The choice of topical corticosteroid potency depends on the severity and distribution of AD. Although using the least potent corticosteroid is typically a good rule to follow, this approach should be balanced by the possibility that treatment with a preparation that is too weak may result in persistence or worsening of AD, which can in turn result in decreased adherence or the need for high-potency topical or systemic corticosteroids. A stepped approach starting with a mid-potency preparation (except for eczema involving the face, axillae, or groin) and, with clinical improvement, use of a lower-potency preparation may be a more effective strategy. High-potency corticosteroids may be needed for severe hand and foot eczema. In general, use of topical corticosteroids under occlusion should be avoided. Prescribing topical corticosteroids in inadequate amounts can also contribute to suboptimal control of AD or nonadherence. The rule of thumb is that 30 g of medication are needed to cover the entire body of an average adult [\[33\]](#). Therefore, patients with widespread disease need to be prescribed sufficient quantities of medication. In addition, obtaining medications in larger quantities may result in significant savings for the patient. A major reason for treatment failure with topical corticosteroids is noncompliance as a result of parental or patient fear of side effects [\[34\]](#), including skin atrophy, telangiectasias, and possibly systemic absorption resulting in hypothalamic-pituitary-adrenal (HPA) axis suppression. A study with fluticasone propionate 0.05% cream (group V) in children as young as 3 months with AD showed that this medication was safe and effective even when applied twice daily to the face and over significant areas of the body for up to 1 month [\[35\]](#). Studies using desonide 0.05% ointment (group V) or aqueous gel (group VI) found no evidence of HPA axis suppression in children with AD for up to 4 weeks of twice daily applications [\[36\]](#) and [\[37\]](#).

Box 2. Topical corticosteroid potency ranking

Group I (most potent)

Betamethasone dipropionate 0.05% (Diprolene; cream, ointment)

Clobetasol propionate 0.05% (Temovate; cream, ointment)

Diflorasone diacetate 0.05% (Psorcon; ointment)

Halobetasol dipropionate 0.05% (Ultravate; cream, ointment)

Group II

Amcinonide 0.1% (Cyclocort; ointment)

Betamethasone dipropionate 0.05% (Diprosone; cream, ointment)

Desoximetasone (Topicort; 0.05% gel; 0.25% cream, ointment)

Fluocinonide 0.05% (Lidex; solution, gel, cream, ointment)

Halcinonide 0.1% (Halog; solution, cream, ointment)

Mometasone furoate 0.1% (Elocon; ointment)

Group III

Amcinonide 0.1% (Cyclocort; lotion, cream)

Betamethasone valerate 0.1% (Valisone; ointment)

Diflorasone diacetate 0.05% (Florone; cream)

Fluticasone propionate 0.005% (Cutivate; ointment)

Group IV

Triamcinolone acetonide 0.1% (Kenalog; cream, ointment)

Fluocinolone acetonide 0.025% (Synalar; ointment)

Mometasone furoate 0.1% (Elocon; lotion, cream)

Group V

Hydrocortisone valerate 0.2% (Westcort; cream, ointment)

Betamethasone valerate 0.1% (Valisone; lotion, cream)

Fluticasone propionate 0.05% (Cutivate; cream)

Fluocinolone acetonide 0.025% (Synalar; cream)

Desonide 0.05% (Tridesilon; ointment)

Group VI

Alclometasone dipropionate 0.05% (Aclovate; cream, ointment)

Flucinolone acetonide 0.01% (Synalar; solution, cream)

Desonide 0.05% (Tridesilon; cream, aqueous gel)

Group VII (least potent)

Hydrocortisone 1%/2.5% (Hytone; lotion, cream, ointment)

Topical calcineurin inhibitors

Topical calcineurin inhibitors approved for AD include tacrolimus ointment (Protopic) 0.03% and pimecrolimus cream (Elidel) 1% (both for children 2 years and above), and tacrolimus ointment 0.1% (for adults). These medications use different anti-inflammatory mechanisms as compared with topical corticosteroids. Because they do not cause skin atrophy, these medications are especially useful for treatment of AD involving the face, including periorcular and perioral areas [\[38\]](#). However, based on animal studies and case reports, the Food and Drug

Administration has issued a “black box” warning for continuous use of both tacrolimus ointment and pimecrolimus cream because of concerns for possible development of malignancies. Since the issue of the warning, case-control studies involving up to 300,000 patients have not shown any association between the use of these medications and the risk of malignancy [39] and [40]. Systemic exposure in study animals treated with high oral doses or nonstandard formulations of pimecrolimus that result in immunosuppression and development of lymphoma have been 31 to 343 times higher than the highest individual systemic exposure ever observed among pediatric patients with extensive AD lesions treated with pimecrolimus cream [41]. The Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology reviewed all available data and concluded that the risk/benefit ratio of topical pimecrolimus and tacrolimus were similar to those of most conventional therapies for the treatment of chronic relapsing AD [42]. Therefore, as-needed use of these medications should continue to be considered in patients with persistent AD, especially on skin areas prone to develop atrophy from topical corticosteroids.

Alternative and experimental treatments

Treatments for patients with recalcitrant AD can be challenging [43]. Wet-wrap treatment with topical corticosteroids has been shown to be efficacious although potential side effects include secondary infection and HPA suppression. Therefore such treatments should be performed under the supervision of physicians who are familiar with them. A short course of an oral corticosteroid can also be considered for severe flare of AD, but the corticosteroid dose should be tapered over 1 week to decrease the chance of a rebound effect off the systemic corticosteroid [44]. Cyclosporin A and ultraviolet phototherapy have been shown to be efficacious for severe AD, but their systemic side effects (eg, renal toxicity with Cyclosporin A) and the risk of malignancy are of concern [43]. Other experimental treatments include mycophenolate mofetil, azathioprine, methotrexate, and intravenous immunoglobulin [43]. These treatments are also associated with significant systemic side effects and therefore should only be considered for the most severe AD patients. Often, hospitalization of patients with a comprehensive approach, including addressing psychosocial aspects of this chronic relapsing disease, can lead to dramatic clinical improvement [45].

The use of probiotics to treat or prevent AD has been an area of controversy. To date, no convincing evidence shows that probiotics are effective in AD [46]. Studies on the use of probiotics to prevent the development of AD have yielded conflicting results [47] and [48]. Evening primrose oil has also been shown to be ineffective in the treatment of AD [49]. There is also no convincing data to support the use of Chinese medicinal herbs in AD [50]. In addition, the potential side effects of these medications are of concern [50]. Omalizumab or anti-IgE (Xolair) is approved for use in patients 12 years or older with allergic asthma that is inadequately controlled on high-dose inhaled or systemic corticosteroids. There have only been few case reports on the use of this medication in AD [51] and [52] and the results in these studies conflicted. Therefore, well-designed controlled trials are needed [53]. Finally, controlled studies with montelukast have not shown benefit in AD [54].

Summary

In conclusion, AD is a multifactorial, chronic inflammatory skin disease susceptible to numerous environmental triggers. Management of this condition should emphasize measures to preserve skin barrier function, elimination of triggers, and timely, consistent use of topical anti-inflammatory medications. Patients who repeatedly fail these interventions should be referred to a specialist for further evaluation and alternative treatment.

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