# Atopic Dermatitis Prevention and Treatment

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## PRACTICE **POINTS**

- Prevention of atopic dermatitis is desired in high-risk settings (ie, 1 or more relatives with atopy).
- Emollient therapy from early infancy has been described as one method.
- Other forms of disease prevention have not yet been adequately developed.

Atopic dermatitis (AD) is the cause of substantial morbidity including severe pruritus and impaired personal and familial quality of life. Furthermore, the rising incidence and familial association of AD have highlighted the need for disease prevention. It is largely genetic in nature and cannot be avoided in all cases. However, low-risk prevention strategies have been attempted to reduce triggering of first onset of AD in predisposed individuals. Therapeutics for active disease include trigger avoidance, barrier repair, topical medicaments including topical corticosteroids (TCs) and nonsteroidal agents, phototherapy, and antibacterial interventions.

*Cutis.* 2017;100:173-177, 192.

Atopic dermatitis (AD) is a disease that finally is coming of age in dermatology research. New topical agents and systemic biologic agents offer patients with AD other options for medical management. This article provides a practical review of prevention strategies and treatment guidelines for AD.

## PREVENTION

Prevention strategies for AD have been largely unsuccessful in the past, which may relate to factors such as prenatal triggers.[1] However, some newer interventional studies have shown some promise in AD prevention in specific settings. For example, a randomized trial of infants in the United States and United Kingdom at high risk for AD (ie, family history of atopy) reported that the AD risk was reduced by 50% when patients were treated with at least once-daily application of full-body emollients for 6 months (beginning by 3 weeks of life).[2] The strategy of daily application of emollients for avoidance of AD in infants with a family history of AD is reasonable but may not offer lifetime prevention, and the benefit in children not from AD families is unknown.

Other trials to prevent AD have included usage of dust avoidance and dust covers for mattresses. This strategy showed modest benefit in reducing the incidence of atopic diatheses in the first year[3] but did not gain endorsement by the most recent guidelines of the American Academy of Dermatology (AAD).[4]

Prenatal and postnatal (maternal and child) supplementation of *Lactobacillus rhamnosus* has shown promise in prevention.[5] The exact regimen likely makes an impact on efficacy. An early study showed the usage of probiotics (eg, *Lactobacillus reuteri*) prenatally in pregnant women and postnatally in infants resulted in no reduction in occurrence of AD and possible reduction in IgE-associated AD.[6] Kalliomäki et al[7] demonstrated that *L rhamnosus* GG alone reduced AD by half in at-risk infants in a double-blind, placebo-controlled trial. On the other hand, Taylor et al[8] performed a study of probiotic supplementation in which patients at high risk for AD developed higher rates of allergen sensitization. The most successful recent trial involved the randomization of

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415 pregnant women to receive interventions from 36 weeks' gestation until 3 months postpartum.[9] The intervention was a randomized comparison of milk without probiotics versus a blend of probiotic milk containing *L rhamnosus* GG, *Lactobacillus acidophilus* La-5, and *Bifidobacterium animalis* subsp *lactis* Bb-12. At 6 years of age, 81 babies who consumed probiotic milk and 82 babies who consumed milk without probiotics were available for testing. The strategy caused a statistically significant reduction in AD in the complete case analysis (odds ratio, 0.48; 95% confidence interval, 0.25-0.92; *P*=.027; number needed to treat, 6). Sadly, other allergic diseases were not prevented in this study.[9]

## MANAGEMENT OF AD

There currently is no cure or perfected prevention technique for AD. As a result, therapy focuses on avoiding triggers and alleviating symptoms.[10] Recent guidelines from the AAD state that"[t]he ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biologic behavior of the disease."[11] Skin-directed therapies are the first line of treatment including emollients, gentle skin care, and topical medicaments. In AD, therapies are needed to reduce disease activity and flare severity, clear flares, and provide relief.

Parental education and written eczema action plans are recommended to help patients and parents/guardians follow recommended regimens[12]; Tollefson and Bruckner[13] for the American Academy of Pediatrics provide an action plan to guide the care of children with atopic dermatitis that is simple, but many others exist online. The eczema action plan usually provides information on how to bathe and what to do when the skin is actively inflamed.

In 2014, a 4-part series of guidelines of care for the management of AD was published by the AAD, replacing prior guidelines.[4,11,14,15] The following sections review some of the important parameters of care highlighted in these management guidelines.

### Psychological Support

Appropriate psychological support for AD patients can be sought through counselors, therapists, psychiatrists, and support groups such as the National Eczema Association (https://nationaleczema.org/).

### Education

Education is the leading form of medical therapy in patients with AD. Eczema schools are popular in Europe and are just beginning to form in the United States (http://tuh.templehealth.org/content/eczema_school.htm), which can be helpful to educate caregivers and patients with AD. Patient resources online and through support groups with an online presence, in-person meetings, and patient/family conventions can be helpful to AD patients. Often, an initial office visit with a dermatologist involves a review of avoidance of triggers, usage of gentle skin care including bland emollients, and therapeutic regimens for disease activity. This form of verbal education is to be paired with an eczema action plan, a written document that allows individuals to reference recommendations and share information with other caregivers.[12,13,16]

### Emollients and Gentle Skin Care

Gentle skin care regimens, which includes the usage of synthetic cleansers with a low pH to help maintain the acidity (acid mantle) of the skin, seek to reduce irritation and have been rated as level IA (highest level) in recent AAD guidelines.[14] Although bathing frequency has been emphasized in the guidelines, AD severity as reflected by SCORAD (SCORing Atopic Dermatitis) was not different for daily bathing versus twice weekly.[17] The American Academy of Pediatrics recommended a skin care regimen of bathing every 2 to 3 days in lukewarm water for 10 to 15 minutes, followed by application of emollients that are fragrance free and have few preservatives.[13] Topical emollients with additives such as colloidal oatmeal, avenanthramides, or ceramides can be used to enhance the skin barrier and are well tolerated in all age groups.[18,19] Despite enhanced emollients, the therapy of AD still requires usage of prescription or over-the-counter TCs and/or topical calcineurin inhibitors (TCIs) in many cases.[20]

### Topical Medication

Children have a relatively higher body surface area–to-weight ratio, allowing for greater potential absorption of topical medicaments and potential side effects from absorption. Types of vehicle, cost, site of application, and availability may impact patient and physician preference in choice of therapeutic topical agent.[14]

*Topical Corticosteroids*—Topical corticosteroids (TCs) are the mainstay of treatment for AD and have been used for more than 60 years.[14,20] Topical corticosteroids provide anti-inflammatory effects on T cells, monocytes, and macrophages, producing altered cytokine activity locally. Topical corticosteroids inhibit collagen synthesis, potentially causing skin atrophy. They also inhibit IL-1, IL-2, IL-6, IFN-α, and tumor necrosis factor α.[21] Topical corticosteroids are classified as class I (ultra-high potency) to class VII (low potency). In children, low-potency TCs generally are applied to the face, intertriginous areas, groin, and genitalia, and mid-potency corticosteroids are applied to the body, arms, and legs. An even higher-strength agent can be prescribed as a rescue medication in severe cases. After clearance with once- or twice-daily therapy, twice-weekly usage can benefit disease activity.[22] Topical corticosteroids reduce inflammation as well as *Staphylococcus aureus* load through inhibition of cytokines that inhibit antimicrobial peptides. Topical corticosteroids have been endorsed as level IA evidence therapy by the AAD guidelines.[14]

Topical corticosteroids, particularly prolonged usage of mid- to high-potency products, have been associated with side effects such as skin atrophy, striae, telangiectases, hypopigmentation, rosacea, acneiform eruptions, focal hypertrichosis, perioral dermatitis, and acne[23]; potential systemic side effects include hypothalamic-pituitary-adrenal axis suppression, cataracts, glaucoma (with periocular application), Cushing syndrome, hyperglycemia, hypertension,[23] and growth retardation.[14] Long-term corticosteroid therapy is associated with tachyphylaxis and potential rebound of disease with discontinuation.[24] Based on the potential risk of side effects with TCs, the least potent product for the shortest time needed is recommended, with special care for thin skin. Discontinuation when clearance occurs is advised. Allergy to TCs and/or vehicle ingredients such as propylene glycol should be suspected in severe unremitting cases.[14] A recent registry review of children screened for contact dermatitis demonstrated that children with AD had higher sensitization to the steroid tixocortol pivalate.[25]

*Topical Calcineurin Inhibitors*—Topical calcineurin inhibitors include pimecrolimus cream 1%, which is approved for mild to moderate AD in adults and children 2 years and older, and tacrolimus ointment 0.03% and 0.1%, which are approved for moderate to severe AD in adults and children aged 2 to 15 years (0.03% formulation only). Topical calcineurin inhibitors can be used as second-line agents in AD in patients who have inadequate response to TCs or who may not be able to use TCs due to the disease site.[10,13,14] Guidelines from the AAD also have endorsed TCIs as level IA evidence for steroid-sparing agents.

Concerns about the reporting of cancers and lymphomas prompted the US Food and Drug Administration to issue a black box warning on TCIs more than 10 years ago. Pimecrolimus, which has little absorption and no notable immunosuppressive effects, has been used without detrimental effect on vaccination and delayed-type hypersensitivities, but many decades of data are lacking.[10,13,14,17,26-29] Topical calcineurin inhibitors can be used as steroid-sparing agents in lieu of corticosteroids in specific locations such as the face and eyelids and for long-term suppressive therapy twice weekly.[30] Intermittent usage and cycling with corticosteroids is advisable,[28] but usage intermittently beyond 1 year has not been evaluated.

Topical calcineurin inhibitors are recommended as effective for acute and chronic AD. Their use as maintenance therapy in adults and children, for AD recalcitrant to steroids, for AD in sensitive areas, for steroid-induced atrophy, and for long-term uninterrupted topical steroid usage carries a level IA evidence recommendation. Furthermore, the AAD guidelines have recommended TCIs as steroid-sparing agents with level IA evidence and off-label use of TCIs in children younger than 2 years with level IA evidence. Pretreatment with TCs to reduce stinging has level IIB evidence. Usage for flare prevention is level IA evidence. Routine blood monitoring of TCI-treated patients was not recommended; in fact, the AAD guidelines provided this recommendation as level IA evidence against routine laboratory monitoring of TCI-treated patients.[14]

*Topical Antibiotics*—Topical antibiotics are indicated for the therapy of impetigo and can be used in the setting of impetiginized AD in conjunction with TCs. Recent AAD guidelines suggested against routine usage of topical anti-staphylococcal agents as level IA evidence.[14] There is one study supporting usage of topical mupirocin in addition to TCs to heal children with eczema area and severity index scores more than 7 more rapidly in the first week of AD therapy, but in the same study, additive benefit was not demonstrated in AD beyond the first week.[31] There also are data supporting usage of intranasal mupirocin adjunctively with bleach baths in patients with moderate to severe AD, which was rated as level IIB evidence in the AAD guidelines.[14,32] There are limited data on the long-term utility of topical anti-infectives in AD. The risks of long-term usage could include resistance formation to agents such as mupirocin, contact dermatitis, and lack of efficacy.

## Additional Therapeutics

*Wet Wraps*—Penetration through the stratum corneum is needed for drug activity in AD. Penetration can be enhanced using wet wrap therapy or using ointments, which produce higher relative potency.[13] Wet wraps overlying a dilute topical medicament have been described as effective in AD and are recommended in AAD guidelines as level IIB evidence.[14] Different wet wrap techniques can be used, including wet pajamas covered by dry pajamas or saline-soaked gauze wrapped around the affected areas and then dry gauze applied over the wet gauze. The methodology used should be tailored to the patient as well as to whether the individual is an inpatient or outpatient.

*Bleach Baths*—Dilute sodium hypochlorite solution 0.005% (one-quarter cup bleach in 20 gallons of water) has been demonstrated to be beneficial in reduction of disease activity in AD patients with recurrent bacterial infections.[32] This simple technique in addition to intranasal mupirocin can reduce AD severity and improve quality of life and is the only ongoing *S aureus* therapeutic management endorsed by the AAD guidelines for the management of AD.[14,32]

## Topical and Oral Delivery

*Antihistamines*—Topical antihistamines are ineffective in AD. Oral antihistamines can be used to reduce pruritus and are most effective when given as sedating agents for sleep enhancement but may be given as nonsedating agents for patients with concomitant allergic disorders such as allergic rhinoconjunctivitis. Paradoxical hyperreactivity with sedating antihistamines is not uncommon in small children, and sedating antihistamine usage should be discontinued in these instances.[13] Parents of children with AD have reported giving the child antihistamines to sleep was helpful, as well as putting on creams, using special clothes (eg, all cotton), and keeping the room cool.[33] There is level IIIC evidence against use of systemic

antihistamines and level IIA evidence for sedating and nonsedating, according to the AAD guidelines.[14]

## Systemic Therapeutics

Oral therapeutics range from oral antihistamines to oral antibiotics and immunosuppressive medications. Oral antibiotics (level IIB evidence) are reserved for superinfected AD, which is not easily defined for the following reasons: there is no consensus definition of superinfected AD; the majority of active AD lesions when cultured will demonstrate *S aureus* growth; and most AD lesions ooze, thereby creating the appearance of superinfection. In real-world practice, superinfection can be diagnosed based on the presence of pustules; furuncles; or signs of infection such as tracking erythema, tenderness, severe erosions, or maceration. Clinical judgment is always required.

The immunosuppressive medications used in AD include leukotriene inhibitors, which rarely are effective for AD.[34] More effective systemic agents for AD include cyclosporine (level I to IIB evidence), azathioprine (level IIB evidence), mycophenolate mofetil (level IIIC evidence), and methotrexate (level IIB evidence). These agents are indicated for pediatric or adult patients when topical agents and/or phototherapy have failed.[15] Monitoring these agents for side effects includes ongoing evaluation for renal and liver toxicity. Short courses (ie, 6 months) are preferred to minimize side effects.[35]

Dupilumab, an injectable AD therapy, is approved in the United States. This agent is injected every 2 weeks and binds to the IL-4Rα shared by IL-4 and IL-13. In 4 weeks of monotherapy, 85% of adult patients treated had 50% or greater clearance.[36] Recently published consensus opinion from the International Eczema Council recommends assessment of a variety of factors before initiating systemic therapy including comorbid illnesses such as contact allergy, trigger avoidance, superinfection, and impact on quality of life.[37]

*Oral Corticosteroids*—Systemic corticosteroids clear patients quickly but provide no sustained improvement; in fact, many patients rebound or have tachyphylaxis. Although short-term corticosteroid usage can break the itch-scratch cycle, long-term usage is associated with osteoporosis, Cushing syndrome, and aseptic necrosis of the femoral head. Decreased linear growth will occur during therapy in children; therefore, systemic steroids are not recommended in children with AD, except for additional or comorbid conditions (eg, asthma or contact dermatitis).[4]

*Phototherapy*—Phototherapy has been recommended in the AAD guidelines as a second-line treatment after failure of first-line agents (ie, TCIs and TCs) for clearance and or maintenance and should be tailored to the patient's skin tone by an experienced physician. Narrowband UVB phototherapy may act through the suppression of T-cell activity in the skin and possibly via suppression of staphylococcal superantigens; however, many phototherapy types have been described for AD.[38,39] Usage can be effective in school-aged children and teenagers but may be limited due to school attendance. Phototherapy was graded as level IIB evidence in the AAD guidelines.[15] Side effects include aggravation of AD by exposure to heat and UV light, actinic damage, tenderness, erythema, pruritus, burning, and stinging. Lentigines; skin cancers (melanoma and nonmelanoma); folliculitis; and ocular toxicity, especially cataracts, can occur.[15] Children younger than 6 years will find it difficult to stand in a phototherapy booth and may be poor candidates.[15,38,39]

## Complementary and Alternative Medicine

Complementary and alternative medicine (CAM) also has been used for AD in the United States. In a review of the 2007 National Health Interview Survey of 9417 children aged 0 to 17 years, CAM was used for AD by 0.99% of children. Some CAM techniques were associated with worsening severity of AD, including herbal therapy, vitamins, homeopathic agents, diet, and movement techniques.[40] Usage of Chinese herbal medications for AD can be associated with liver toxicity.[41] Only one CAM therapy—massage therapy—has some mild supportive data.[42]

*Allergen Avoidance and Diet*—Bronsnick et al[43] discussed the possible benefit of prenatal and postnatal probiotics for prevention of AD, which were not supported in the AAD guidelines for management of AD[4]; postnatal prebiotic supplementation; and exclusive breastfeeding and/or supplementation with hydrolyzed formula in at-risk children. Elimination diets for children and mothers were not recommended. The authors found no beneficial role of supplements including vitamin D, selenium, fish oil, borage oil, and zinc sulfate.[43]

A National Institute of Allergy and Infectious Diseases consensus group recommended avoidance of proven but not random elimination of food allergens in AD, asthma, and/or eosinophilic esophagitis.[44] Restricted maternal diet was not recommended, and breastfeeding exclusively for the first 4 to 6 months was recommended. Hydrolyzed formulas were suggested as a possible preventive strategy in at-risk infants as a breastfeeding alternative, with cost of these formulas being a problem.[44]

In children younger than 5 years, food allergy screening for the most common allergens (eg, milk, eggs, peanuts, wheat, soy) should be considered in children with persistent unremitting dermatitis and/or known food challenge–induced reactions.[4] Conservative measures to avoid house dust mite exposure in known sensitized individuals including dust covers for pillows and mattresses may be beneficial.[4,45]

## Emerging Therapies

Recently approved therapies include better-targeted agents that appear to have a reasonable safety profile and may fulfill unmet needs in AD care. Of these agents, crisaborole, a topical boron-based phosphodiesterase 4 inhibitor, was approved in December 2016 for mild to moderate AD in patients 2 years and older. Topically, this agent seems to be efficacious in the absence of notable carcinogenicity.[46]

The systemic (injectable) biologic agent dupilumab was approved in March 2017 for moderate to severe AD. Phase 3 studies in adults with AD showed excellent success in adults with moderate to severe AD.[37] This agent is a monoclonal antibody targeted at blockade of the crucial atopic inflammatory triggering pathway via blockade of the IL-4A receptor site, targeting IL-4 and IL-13 activity.[36,47] There are many medications in the pipeline, which Renert-Yuval and Guttman-Yassky[48] review. However, an overview of the landscape demonstrates that Janus kinase (JAK) inhibitors[49] and biologic medications in addition to dupilumab affecting targeted inflammatory cascades in AD are in development. In particular, the JAK inhibitors appear promising due to availability both as oral and topical agents.[49]

## Need for Ongoing Care and Monitoring

Atopic dermatitis is a chronic inflammatory skin disorder with a genetic basis. Once initiated, the process of AD may persist throughout the patient's life and become a systemic disorder with comorbidities including sleep disturbance, reduced quality of life, and cardiovascular disease.[50] Ongoing management of AD includes topical reduction in irritants and triggers, topical medicaments, and management of pruritus and infections. At this time, emollients and irritant avoidance paired with judicious topical medicaments including TCs and second-line or site-specific (eg, eyelids) usage of TCIs or phosphodiesterase 4 inhibitors remain the backbone of therapy. Ongoing review of therapeutics for associated morbidities is underway, which may guide future therapeutic interventions into AD. The future of prevention and therapy look bright, but time will tell.

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