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Atopic dermatitis: skin care and topical therapies

David M Fleischer, MD;[1]* Jeremy Udkoff, MA;[1,2]* Jenna Borok, BS;[2,3] Adam Friedman, MD;[4] Noreen Nicol, PhD, RN, FNP;[4,5] Jeffrey Bienstock, MD;[6] Peter Lio, MD;[7] Megha Tollefson, MD;[8] and Lawrence F Eichenfield, MD[2,3]

Abstract

Atopic dermatitis (AD) pathogenesis is strongly influenced by Type 2 innate lymphoid cell and T-helper cell type 2 lymphocyte-driven inflammation and skin barrier dysfunction. AD therapies attempt to correct this pathology, and guidelines suggest suggest basics of AD therapy, which include repair of the skin barrier through bathing practices and moisturizers, infection control, and further lifestyle modifications to avoid and reduce AD triggers.While some patients' AD may be controlled using these measures, inflammatory eczema including acute flares and maintenance therapy in more severe patients are treated with topical pharmacologic agents such as topical corticosteroids, topical calcineurin inhibitors, and, more recently, topical PDE-4 inhibitors. This model of basic skin therapy and, as needed, topical pharmacologic agents may be used to treat the vast majority of patients with AD and remains the staple of AD therapy.

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Atopic dermatitis (AD) pathogenesis is driven by T-helper cell type 2 (Th2) lymphocyte-driven inflammation and skin barrier dysfunction.[1,2] This compromised skin barrier increases moisture loss and creates dry, easily irritated, and hypersensitive skin. In this state, the skin is more prone to infections with bacteria, fungi, or viruses. Topical therapies can impact AD skin pathology and decrease inflammation, play an important role in improving pruritus,[3] are low in cost, and have limited systemic absorption and focused local effects. Accordingly, they are the current mainstay of AD therapy.[4] New topical AD medications are being developed, with the first new medication, crisaborole, recently released as the first new therapy approved for AD in over 15 years.

General guidelines

Most guidelines address AD care in a stepwise fashion.[5-9] Treatments are aimed at preventing dry skin, treating the rash, improving the itch, and minimizing exposure to triggers. These guidelines recommend 3 components of basic, nonacute, AD skin care: (1) frequent and liberal use of moisturizers or emollients in conjunction with warm baths or showers to repair the skin barrier; (2) antiseptic measures including dilute bleach baths twice weekly or more; and (3) identification and avoidance of common irritants, temperature extremes, and identified allergen triggers. Depending on the severity of AD, treatment of inflammatory

*These authors contributed equally.
[1]Department of Pediatrics, Children's Hospital Colorado, University of Colorado Denver School of Medicine, Aurora, Colorado.
[2]Division of Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego, California.
[3]Departments of Dermatology and Pediatrics, University of California, San Diego School of Medicine, La Jolla, California.
[4]College of Nursing, University of Colorado, Aurora, Colorado.
[5]Department of Nursing, Children's Hospital Colorado, Aurora, Colorado.
[6]PediatriCare Associates, Fairlawn, New Jersey.
[7]Chicago Integrative Eczema Center, Chicago, Illinois.
[8]Department of Dermatology and Pediatrics, Mayo Clinic Rochester, Minnesota.
Disclosures: Dr Fleischer reports nonfinancial service on scientific advisory council for National Peanut Board, nonpaid board membership for FAACT Medical Advisory Board and FARE Medical Advisory Board; provides consultancy services as an advisory board member for DBV Technologies, Aimmune Therapeutics, Monsant and Kaleo Pharma; institutional grants pending with Monsanto Company, Nestle Nutrition Institute, DBV Technologies and Aimmune Therapeutics; has received payment for lectures including service on speakers bureaus from Nestle Nutrition Institute, CSACI and ACAAJ (CME talks only); has received payment for manuscript preparation from Nestle Nutrition Institute; received royalties from UpToDate; outside the submitted work. Mr Udkoff reports personal fees from Lucid Group 3AD Bibliographic Fellowship outside the submitted work. Ms Borok, Drs Waldman, Ahluwalia, Nicol, Bienstock, Tollefson have nothing to disclose. Dr. Lio reports personal fees from Valeant, personal fees from Johnson & Johnson, personal fees from Anacor/Pfizer, personal fees from Galderma, personal fees from IntraDerm, personal fees from Pierre Fabre Dermatology, grants from AO Biome, personal fees from Realm Therapeutics, outside the submitted work. Dr Eichenfield has received honoraria as a consultant for Allergan, Anacor/Pfizer, DS Biopharma, Galderma Labs, Genentech, Lilly, Medimetriks, Otsuka/Medimetriks, Ralaxar, and Regeneron/Sanofi; he is an investigator for Regeneron/Sanofi, receiving no compensation; receives equity options as a consultant for TopMD; and receives honoraria as a consultant, advisory board member, and speaker for Valeant.
Correspondence: David M Fleischer, MD, david.fleischer@childrenscolorado.org and Jeremy Udkoff, MA, judkoff@ucsd.edu

TABLE 1 Suggested weekly quantity of topical therapies

Moisturizer	Basic management (grams per week)
Child	150-200
Adolescent or Adult	500
Ointment	**Twice daily acute therapy (grams per week)**
Child	125-250
Adolescent or Adult	260-330
Cream	**Twice daily acute therapy (grams per week)**
Child	140-275
Adolescent or Adult	290-330

eczema and maintenance with topical corticosteroids (TCS) or other therapeutic agents may be initiated in a stepwise fashion. During AD flares, TCS and/or topical calcineurin inhibitors (TCI) are typically prescribed and may be used in conjunction with wet wrap therapy (WWT).[10]

Basic AD Skin Care

Moisturizers

Moisturizers include emollients, humectants, and occlusive agents. They are a steroid-sparing standard of care and are useful for both AD prevention and maintenance therapy. Current national and international guidelines recommend daily application of moisturizers.[11-14] Mechanistically, topical formulations help treat the dysfunctional epidermal barrier in AD, thereby lessening transepidermal water loss (TEWL) and resulting xerosis, and can increase natural moisturizing factors (NMF).[15] NMFs are endogenous molecules that increase skin hydration and water retention.[16]

Moisturizers alone can be used to treat mild AD. Two prospective studies of daily moisturizing demonstrated a lengthened time until an AD flare compared to a control group without daily moisturization.[17,18] Thus, daily moisturization, with appropriate quantities, should be utilized and may significantly improve the course of AD in many patients (Table 1).[19-22] Creams and ointments are thicker than lotions and are therefore preferred. However, patient adherence is extremely important, and patients should be encouraged to choose a regimen that will best meet their lifestyle. Providing written patient instructions with demonstrative training sis very helpful, as health care -observed technique is important to educate patients to apply moisturizers (and other topical therapies) correctly and in sufficient quantities.[23,24]

Prescription emollient devices and eczema-specific moisturizers

Prescription emollient devices (PED), or "barrier repair devices" are a class of moisturizering agents that are formulated to target specific deficiencies in the AD skin barrier composition. Many are composed of lipids such as ceramides, fatty acids, glycyrrhetinic acids and palmitoylethanolamide, and they attempt to reproduce the optimal ratio of these components in the skin.[25] Colloidal oatmeal 1% is a moisturizer with purported antipruritic, anti-oxidant, and anti-inflammatory properties that may be a useful alternative moisturizer or adjuvant to AD therapy.[26,27] Other possible adjuvants include menthoxypropanediol, which is associated with a cooling sensation, and licochalcone A, an anti-inflammatory agent.[28,29] These devices, however, are expensive and lack strong head-to-head trials demonstrating their superiority over typical moisturizing products.[30]

Bathing

Bathing is essential to human health and hygiene and plays an important role in AD treatment and maintenance; however, there is no standard for the frequency or duration of bathing. Daily bathing with limited cleanser use or the use of neutral, low pH, hypoallergenic, fragrance free cleansers is often recommended, while there is little evidence to support daily versus every other day or less frequent bathing. Antibacterial skin cleansers may dry and aggravate the skin, so less irritating and moisturizing soaps may be used after initial soaking. After bathing, the skin should be patted down and not wiped completely dry, using a towel and not an abrasive washcloth. Chiang and Eichenfield performed a study demonstrating that bathing without moisurizing resulted in skin drying, while moisturizing after bathing increased skin hydration and reduced TEWL.[31] Showers are an acceptable alternative to bathing; however, some experts prefer baths during AD flares.

Bath additives and bleach baths

Dilute bleach baths may help reduce the number of local skin infections in AD patients with heavy bacterial colonization of the skin.[32] Bleach baths may also have positive effects on AD by modulating inflammatory pathways and repairing skin integrity.[33-37] Patients can prepare a bleach bath by mixing ¼ to ½ a cup of 6% sodium hypochlorite solution (chlorine liquid bleach) into a bathtub full of lukewarm water; the final bleach concentration approximates a modified Dakin's-like solution with a bleach concentration of 0.005%.[38] The patient may soak in this bath for 5 to 10 minutes and may subsequently rinse the skin with fresh water.[39-41] Proprietary bleach containing products are also available and may be formulated as bath additives, body washes, sprays, or gels.

Bath oils, acidic spring water and water softeners should be avoided as a general rule. However, salt baths may be soothing and helpful.[42] Apple cider vinegar baths were proposed as an adjuvant to AD therapy; however, there is insufficient evidence to support their use.

AD management beyond basic skin care

Topical corticosteroids

TCS are considered to be the mainstay of AD therapy and have been used for decades.[4] They are recommended for treating active eczematous lesions, lichenification, and other chronic cutaneous manifestations of AD, and for managing pruritus. More than 110 randomized control trials (RCT's) have proven their safety and efficacy.[5,43,44]

There is a wide-range of potency of TCS and varying methods of prescribing them for disease flares. One approach is to initiate

lower potency TCS, with an increase in strength if there is a lack of response, while another is to start with bursts of mid to higher strength TCS with subsequent taper. There is a wide-range of potency of TCS and varying methods of prescribing them for disease flares. One approach is to initiate lower potency TCS, with an increase in strength if there is a lack of response, while another is to start with bursts of mid to higher strength TCS with subsequent taper. Due to the potential morbidity associated with AD, short bursts of medium-potency TCS may be utilized for most disease flares (Table 2). Thomas and colleagues found this to be a safe regimen even for young children, with an increased surface area to volume ratio.[45]

TABLE 2 Class and relative potencies of topical corticosteroids

Class and potency	Drug name, concentration (vehicle)
I, Very high	Halobetasol propionate, 0.05% (cream, ointment)
	Diflorasone diacetate, 0.05% (ointment)
	Clobetasol propionate, 0.05% (cream, foam, ointment)
	Augmented betamethasone dipropionate, 0.05% (ointment)
II, High	Triamcinolone acetonide, 0.5% (cream, ointment)
	Mometasone furoate, 0.1% (ointment)
	Halcinonide, 0.1% (cream)
	Fluocinonide, 0.05% (cream, gel, ointment, solution)
	Diflorasone diacetate, 0.05% (cream)
	Desoximetasone, 0.05% (gel)
	Desoximetasone, 0.25% (cream, ointment)
	Betamethasone dipropionate, 0.05% (cream, foam, ointment, solution)
	Augmented betamethasone dipropionate, 0.05% (cream)
	Amcinonide, 0.1% (cream, lotion, ointment)
III-V, Medium	Triamcinolone acetonide, 0.1% (cream, ointment)
	Prednicarbate, 0.1% (cream)
	Mometasone furoate, 0.1% (cream)
	Hydrocortisone valerate, 0.2% (cream, ointment)
	Hydrocortisone butyrate, 0.1% (cream, ointment, solution)
	Fluticasone propionate, 0.05% (cream)
	Fluticasone propionate, 0.005% (ointment)
	Flouocinolone acetonide, 0.025% (cream, ointment)
	Desoximetasone, 0.05% (cream)
	Clocortolone pivalate, 0.1% (cream)
	Betamethasone valerate, 0.1% (foam, lotion, ointment)
VI, Low	Fluocinolone acetonide, 0.01% (cream, solution)
	Desonide, 0.05% (cream, gel, foam, ointment)
	Alclometasone dipropionate, 0.05% (cream, ointment)
VII, Lowest	Hydrocortisone acetate, 0.5%-1% (cream, ointment)
	Hydrocortisone, 0.25%-1% (cream, ointment, solution)
	Dexamethasone, 0.1% (cream)

High-potency, or class I. TCS may be used for severe AD, but should not be applied to the face and other sensitive areas such as the axillae or groin. Medium to high potency (class II-V) TCS can be used for mild to moderate AD. Low potency (class VI-VII) TCS can be used to treat AD on thinner-skinned areas such as the eyelids, face, genitals and intertriginous areas.

Patients can estimate their use of TCS using the fingertip method (FTU; Figure 1). A FTU is equivalent to approximately 0.5 grams of ointment or cream and is the amount expressed over an adult fingertip length from a tube with a 5 mm diameter nozzle. This may be converted into gram units for an approximation of the optimal weekly usage (Table 1).[19-22]

Side effects

Although rare, complications from TCS can occur at any age. Due to their increased surface area to weight ratio, children have a higher probability of systemically absorbing TCS, which can result in elevated blood concentrations and systemic side effects.[46] Hypothalamic-pituitary-adrenal (HPA) axis suppression following systemic absorption of TCS is a potential, but fortunately very rare, serious systemic complication.[43,47,48] High-potency TCS do carry a greater risk for HPA suppression than lower-potency TCS. However, HPA axis suppression is rarely observed in the absence of an extreme situation, such as large amounts of high-potency TCS under plastic occlusion or for extended duration. In a typical-use study, Eichenfield and colleagues did not note any HPA axis suppression or treatment adverse effects in patients who completed 4 weeks of 0.05% desonide hydrogel therapy for moderate AD.[43]

In addition, TCS carry a small risk of causing striae, and in extreme overuse, may cause ophthalmo logic effects.[49] The use of TCS may also result in thinning of the skin, especially in certain areas that are more prone to it, such as the face, axillae, and groin; infants and small children may be at a higher risk of local atrophic effects from TCS, since they often have AD affecting the face. Although multiple studies found a slightly higher rate of systemic infections with TCS use, no skin atrophy was observed with intermittent TCS use.[41] Thus, complications of TCS use in children are almost always related to an inappropriate class of steroid for the patient, inappropriate duration of therapy, inappropriate anatomical sites, and the use of extreme occlusive techniques. In addition to developing complications from TCS, withdrawal from long-term and inappropriate use of potent TCS, especially to the face and genital areas, is associated with application site burning, stinging, erythema, and edema.[50]

Proactive therapy

"Proactive therapy," in contrast to "reactive therapy" with TCS has become increasingly popular for treating relapsing AD. Schmitt and colleagues performed a systematic review and meta-analysis of TCS RCTs and found that applying TCS (or TCI) to inactive areas of AD 2 to 3 times a week reduced AD flares compared with vehicle.[51] Indirect evidence from this study found intermittent therapy with TCS decreased the relative risk of a disease flare compared with a similar regimen with TCI. A prospective, vehicle control study by Wahn and colleagues demonstrated similar results and found daily topical pimecrolimus was effective at decreasing AD flares and reducing or eliminating the need for the acute use of TCS (see TCI discussion below).[52] The risk-to-benefit ratio of long-term, scheduled, intermittent steroids is favorable, and a consensus conference on AD stated that areas of frequent, relapsing AD should be treated with TCS twice weekly.[53] They recommended monthly medium to high potency TCS maintenance doses to not exceed 15 grams for infants, 30 grams for children, and 60 to 90 grams for adolescents or adults.

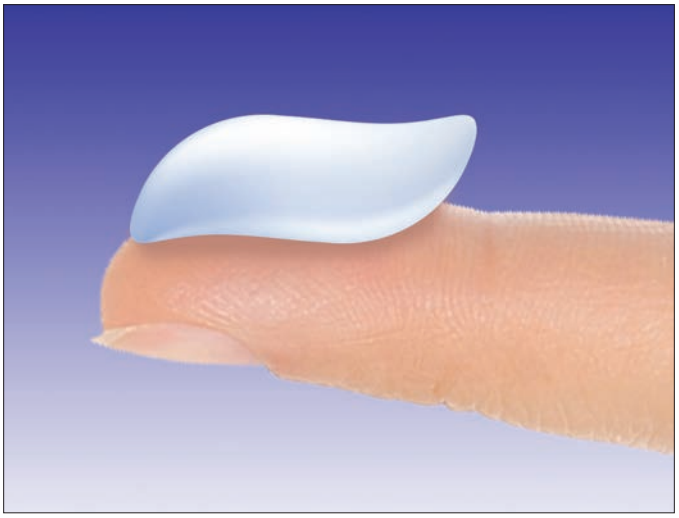

FIGURE Fingertip unit. The amount of ointment or cream expressed from a 5 mm diameter nozzle over the length of the fingertip. One fingertip unit (FTU) is approximately equivalent to 0.5 grams of product.

Steroid phobia

Unfortunately, TCS therapy is stigmatized within the medical community, and patient education is necessary to reduce steroid phobia.[54] Steroid phobia results in under-treatment of AD and is correlated with poor knowledge of steroid potencies and differences in the pharmacology of topical versus systemic agents.[55,56] A survey of dermatology outpatients and their parents by Charman and colleagues found that 24% admitted to not being adherent to their TCS regimens due to concerns about adverse effects.[57] Patients were most frequently concerned about skin thinning (34.5%) and systemic absorption that could cause delayed growth and development (9.5%). Another study by Mueller and colleagues noted similar results, but also found a significant decrease in patient concerns after an educational intervention.[58] Accordingly, patient education to address steroid phobia is crucial in ensuring patient adherence to TCS therapy.[25]

Wet-wrap therapy

Wet-wrap therapy (WWT) utilizes a topical therapeutic agent covered first by a wet layer of occlusive bandages or tighter-fitting, cotton clothes followed directly by a similar dry outer layer. Studies have shown WWT to be an effective adjuvant therapy in refractory or severe AD.[59-61] A recent observational cohort study of 72 children found a large decrease in AD severity following WWT therapy, with 1 month of lasting benefits.[10] Mechanistically, WWT increases contact time with topical therapies allowing for better topical absorption. In addition, WWT

provides a physical barrier to prevent TEWL and skin excoriation, and decreases pruritus as a result of the cooling effects of the wet layer. Wolkerstorfer and colleagues showed that 1:20, 1:10, and 1:4 dilutions of fluticasone propionate under WWT were equally effective, but the 1:20 and 1:10 dilutions demonstrated less HPA suppression. Thus, WWT should be used with caution to prevent HPA axis suppression, and lower-potency TCS or higher-potency TCS dilutions are appropriate to use in conjunction with WWT. TCI, however, should not be used with WWT. Some conjecture exists regarding WWT and an increased risk of cutaneous infection, but whether this association truly exists is unclear.[63,64]

Other topical therapies:

Topical calcineurin inhibitors

TCI are therapeutic agents that act on T-cells and decrease the expression of inflammatory cytokines.[65] They are typically considered second-line agents, but do not cause cutaneous atrophy and may be included in standard therapeutic regimens for thin and sensitive skin areas such as the face and intertriginous areas.[66,67] Current TCI available are tacrolimus ointment (0.03% for patients >2 years old and 0.1% for patients >15 years old) and pimecrolimus cream (1% strength for patients >2 years old). Tacrolimus is currently FDA-approved for moderate to severe AD, while pimecrolimus is approved for mild to moderate AD. While both are only approved for children older than 2 years, pimecrolimus has been studied extensively under two years of age, and both TCIs have been recommended for "off-label" use as needed.[5,58,68] Both available TCI decrease the cutaneous manifestations of AD; however, two 6-week comparative studies demonstrated a greater effect with tacrolimus therapy than pimecrolimus.[69,70]

The most common side effect of TCI therapy is application site burning or stinging that occurs during the first few applications. A brief course of TCS prior to TCI treatment has been recommended by some experts to minimize this.[71] In 2006, the FDA included a black box warning label cautioning against the theoretical risk of TCI-associated malignancy. However, no longitudinal registries (A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety [APPLE] and Pediatric Eczema Elective Registry [PEER]) have corroborated this claim.[72-74]

Topical coal tar

van den Bogaard and colleagues found in vitro coal tar increases levels of filaggrin expression and inhibition of the IL-4 signaling pathway.[75] Coal tar preparations have some clinical use, and one study found their efficacy to be similar to 1% hydrocortisone acetate cream.[76] However, they are messy and hard to apply, which lessens their clinical usefulness.

Topical phosphodiesterase 4 inhibitors

Crisaborole recently received FDA approval for use in patients 2 years or older with mild to moderate AD based on the efficacy and safety demonstrated in multiple RCTs.[77-80] The long-term safety of crisaborole was also demonstrated in an open-label, 48-week trial performed by Eichenfield and colleagues in which they administered 4-week cycles of crisaborole, as needed, to more than 500 patients.[81] In contrast to TCS therapy, crisaborole is not associated with atrophy, telangiectasia, or hypopigmentation. However, application site pain was more common with crisaborole than placebo in phase III clinical trials.[82] A study by Zane and colleagues showed that crisaborole ointment applied to sensitive areas was well tolerated as vehicle.[83]

Crisaborole may be a useful alternative to TCI and TCS therapies; however, comparative trials with TCI and TCS are needed. Cost and insurance coverage of crisaborole may impact patient access to the medication. Other topical PDE-4 agents are being studied for AD.

Other therapies:

Fabrics

Comfortable materials may decrease the itch associated with AD and increase quality of life. The skin should not be in direct contact with wool; instead, cotton or silk should be used.[84] Some silk-based products have been specifically engineered to reduce skin discomfort.[85] Silver-coated fabrics have been studied in AD and were associated with an increase in quality of life and AD severity metrics.[86]

Topical antibiotics

Staphylococcus aureus and other bacteria frequently colonize AD-affected skin. These bacteria may contribute to AD pathogenesis by producing toxins that damage the epidermal barrier, ultimately allowing allergen penetration.[25] Antimicrobial preparations were thought to treat AD by reducing the presence of these bacteria on the skin. However, a 2010 Cochrane review of RCTs found no sufficient evidence to support this claim.[87] In addition, topical antibiotics such as mupirocin may cause an allergic contact dermatitis and contribute to microbial antibiotic resistance.[88] Thus, mupirocin should be avoided as a general rule, though it may be useful in patients with limited areas of mildly impetiginized AD. While not supported by current evidence, there has been increased interest in antimicrobial-TCS combinations with some reports in support of their efficacy.[89]

Antihistamines

Topical antihistamines, such as diphenhydramine and doxepin, are not recommended for treating itch in patients with AD. They may cause local allergic contact dermatitis or other reactions such as burning or stinging.[90] In addition, they can be absorbed systemically and cause tiredness.[91,92] Oral first-generation antihistamines at night can be used to help patients fall asleep due to their sedating effects.[7] However, they are not useful for daytime disease and their is mixed evidence for their efficacy.

Conclusions

There are many therapeutic options available to control and treat AD. These range from the basics of AD skin management to WWT and potent TCS. Patients' AD may differ due to alternative environmental exposures, ethnicities, genetics, and specific pathophysiologic disease pathways.[93] Thus, they may respond differently to therapeutics, and healthcare practitioners should work with their patients to find a regimen that works for them. While much effort is typically placed upon treating acute AD flares, maintenance therapy, prophylactic management, and bathing regimens have been increasingly recognized as very im-

portant aspects of AD therapy and should not be dismissed. In addition to commonly used moisturizers, TCI, and TCS, crisaborole represents an exciting new non-steroidal medication in patients with mild to moderate AD.

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