FROM THE ACADEMY

Guidelines of care for the management of atopic dermatitis

Section 2. Management and treatment of atopic dermatitis with topical therapies

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Atopic dermatitis is a common and chronic, pruritic inflammatory skin condition that can affect all age groups. This evidence-based guideline addresses important clinical questions that arise in its management. In this second of 4 sections, treatment of atopic dermatitis with nonpharmacologic interventions and pharmacologic topical therapies are reviewed. Where possible, suggestions on dosing and monitoring are given based on available evidence. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2014.03.023.)

Key words: antihistamines; antimicrobials; atopic dermatitis; bathing; calcineurin inhibitors; corticosteroids; emollients; topicals; wet wraps.

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care, or be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding

Abbreviations used:

AAD:	American Academy of Dermatology
AD:	atopic dermatitis
PED:	prescription emollient device
RCT:	randomized controlled trial
TCI:	topical calcineurin inhibitors
TCS:	topical corticosteroids
WWT:	wet-wrap therapy

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Funding sources: None.

The authors' conflicts of interest/disclosure statements appear at the end of the article.

Accepted for publication March 13, 2014.

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Published online May 7, 2014.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2014.03.023

Table I. Clinical questions used to structure the evidence review for the management and treatment of atopic dermatitis with topical therapies

- What is the effectiveness of nonpharmacologic interventions such as moisturizers, prescription emollient devices, bathing practices and oils, and wet wraps for the treatment of atopic dermatitis?
- What are the efficacy, optimal dose, frequency of application, and adverse effects of the following agents used as monotherapy or in combination with other topical agents for the treatment of atopic dermatitis?
  - Topical corticosteroids
  - Topical calcineurin inhibitors
  - Topical antimicrobials/antiseptics
  - Topical antihistamines
  - Others (eg, coal tar, phosphodiesterase inhibitors)

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 biological behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

SCOPE

This guideline addresses the management of pediatric and adult atopic dermatitis (AD; atopic eczema) of all severities. The treatment of other forms of dermatitis, such as irritant dermatitis and allergic contact dermatitis in those without AD, are outside the scope of this document. Recommendations on AD treatment and management are subdivided into 4 sections given the significant breadth of the topic, and to update and expand on the clinical information and recommendations previously published in 2004.[1] This document is the second part of the series and covers the use of nonpharmacologic approaches (eg, moisturizers, bathing practices, and wet wraps), along with pharmacologic topical modalities, including corticosteroids, calcineurin inhibitors, antimicrobials, and antihistamines.

METHOD

A work group of recognized AD experts was convened to determine the audience and scope of the guideline, and to identify important clinical questions in the use of topical therapies for AD management (Table I). Work group members completed a disclosure of interests that was updated and reviewed for potential relevant conflicts of interest throughout guideline development. If a potential conflict was noted, the work group member recused himself or herself from discussion and drafting of recommendations pertinent to the topic area of the disclosed interest.

An evidence-based approach was used and evidence was obtained using a systematic search of PubMed, the Cochrane Library, and the Global Resources for Eczema Trials[2] databases from November 2003 through November 2012 for clinical questions addressed in the previous version of this guideline published in 2004,[1] and 1964 through 2012 for all newly identified clinical questions. Searches were prospectively limited to publications in the English language. Medical subject headings (MeSH) terms used in various combinations in the literature search included: "atopic dermatitis," "atopic eczema," "topical agents," "topicals," "nonpharmacologic," "barrier," "emollient," "moisturizer," "bathing," "oil," "topical corticosteroid," "hydrocortisone," "calcineurin inhibitor," "tacrolimus," "pimecrolimus," "coal tar," "phosphodiesterase inhibitors," "antimicrobial," "antiseptic," "retapamulin," "triclosan," "chlorhexidine," "beta-thujaplicin," "mupirocin," "triclocarban," "antibacterial soap," "topical antibiotic," "pseudomonic acid," and "potassium permanganate."

A total of 1789 abstracts were initially assessed for possible inclusion. After removal of duplicate data, 246 were retained for final review based on relevancy and the highest level of available evidence for the outlined clinical questions. Evidence tables were generated for these studies and used by the work group in developing recommendations. The American Academy of Dermatology's (AAD's) prior published guidelines on AD were also evaluated, as were other current published guidelines on AD.[1,3-5]

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy developed by editors of the US family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ USA*).[6] Evidence was graded using a 3-point scale based

on the quality of study methodology (eg, randomized control trial [RCT], case-control, prospective/retrospective cohort, case series), and the overall focus of the study (ie, diagnosis, treatment/prevention/screening, or prognosis) as follows:

I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life).
II. Limited-quality patient-oriented evidence.
III. Other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed based on the best available evidence tabled in the guideline. These are ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence.
B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

In those situations where documented evidence-based data were not available, expert opinion was used to generate clinical recommendations.

This guideline has been developed in accordance with the AAD/AAD Association *Administrative Regulations for Evidence-based Clinical Practice Guidelines* (version approved May 2010), which includes the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.[7] This guideline will be considered current for a period of 5 years from the date of publication, unless reaffirmed, updated, or retired at or before that time.

DEFINITION

AD is a chronic, pruritic inflammatory skin disease that occurs most frequently in children, but also affects many adults. It follows a relapsing course. AD is often associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of type I allergies, allergic rhinitis, and asthma. Atopic eczema is synonymous with AD.

INTRODUCTION

Topical agents are the mainstay of AD therapy. Even in more severe cases needing systemic or phototherapy, they are often used in conjunction with these modalities. Although discussed in separate subsections, topical agents from several classes are frequently used in combination, in part because they address different aspects of AD pathogenesis. Each class of treatment is discussed in regards to its mode of action and main use in therapy, and where possible, suggestions on dosing and monitoring are given based on available evidence.

NONPHARMACOLOGIC INTERVENTIONS

Moisturizers

Xerosis is one of the cardinal clinical features of AD and results from a dysfunctional epidermal barrier. Topical moisturizers are used to combat xerosis and transepidermal water loss, with traditional agents containing varying amounts of emollient, occlusive, and/or humectant ingredients. Although they often include water as well, this only delivers a transient effect, whereas the other components provide the main benefits.[8] Emollients (eg, glycol and glyceryl stearate, soy sterols) lubricate and soften the skin, occlusive agents (eg, petrolatum, dimethicone, mineral oil) form a layer to retard evaporation of water, whereas humectants (eg, glycerol, lactic acid, urea) attract and hold water.

The application of moisturizers increases hydration of the skin, as measured subjectively by patients and objectively by assessment of capacitance or conductance and with microscopy.[8-10] In addition, a number of clinical trials have shown that they lessen symptoms and signs of AD, including pruritus, erythema, fissuring, and lichenification.[9-13] Thus, moisturizers can themselves give some reduction in inflammation and AD severity. Furthermore, their use decreases the amount of prescription anti-inflammatory treatments required for disease control, as demonstrated in 3 RCTs.[13-15] Moisturizers can be the main primary treatment for mild disease and should be part of the regimen for moderate and severe disease.[16] They are also an important component of maintenance treatment and prevention of flares (further discussed in part 4 of these guidelines). Moisturizers are therefore a cornerstone of AD therapy and should be included in management plans (recommendations summarized in Table II and level of evidence summarized in Table III).

There is a lack of systematic studies to define an optimal amount or frequency of application of moisturizers.[17] It is generally thought that liberal and frequent reapplication is necessary such that xerosis is minimal. Traditional moisturizers are formulated into a variety of delivery systems, including creams, ointments, oils, gels, and lotions. Although most ointments have the advantage of not containing preservatives, which may cause stinging when applied to inflamed skin, they may be too greasy for some patients with AD. Lotions have a

Table II. Recommendations for nonpharmacologic interventions for the treatment of atopic dermatitis

The application of moisturizers should be an integral part of the treatment of patients with AD as there is strong evidence that their use can reduce disease severity and the need for pharmacologic intervention.
Bathing is suggested for patients with AD as part of treatment and maintenance; however, there is no standard for the frequency or duration of bathing appropriate for those with AD.
Moisturizers should be applied soon after bathing to improve skin hydration in patients with AD.
Limited use of nonsoap cleansers (that are neutral to low pH, hypoallergenic, and fragrance free) is recommended.
For the treatment of patients with AD, the addition of oils, emollients, and most other additives to bath water and the use of acidic spring water cannot be recommended at this time, because of insufficient evidence.
Use of wet-wrap therapy with or without a topical corticosteroid can be recommended for patients with moderate to severe AD to decrease disease severity and water loss during flares.

AD, Atopic dermatitis.

Table III. Strength of recommendations for the use of topical therapies in the treatment of atopic dermatitis

Recommendation	Strength of recommendation	Level of evidence	References
Use of moisturizers	A	I	9-16,18-21,126
Bathing and bathing practices	C	III	23,24,26,28,30
Application of moisturizers after bathing	B	II	24,25
Limited use of nonsoap cleansers	C	III	27-30
Against use of bath additives, acidic spring water	C	III	31,32,127
Wet-wrap therapy	B	II	34-41
Use of TCS	A	I	42-46
Consideration of a variety of factors in TCS selection	C	III	49,128,129
Frequency of application	B	II	51-53
Proactive use of TCS for maintenance	B	II	54-56
Need for consideration of side effects with use	A	I	57,58,66
Need for monitoring for cutaneous side effects with potent TCS	B	III	57,58,66
Specific routine monitoring for systemic side effects with TCS not needed	C	III	57,58,62,66
Addressing fears with use	B	III	67-69
Use of TCI	A	I	70,76,81
Use as steroid-sparing agents	A	I	82,83
Off-label use of TCI in those age <2 y	A	I	76,89
Counseling on local reactions with TCI and the preceding use of TCS	B	II	81,85,96
Proactive use of TCI for maintenance	A	I	54,93-95
Concomitant TCS and TCI use	B	II	82,83,106-109
Informing patients regarding theoretical risk of cutaneous viral infections with use	C	III	82,98
Awareness of black-box warning of TCI	C	III	98-101
Routine monitoring of TCI blood levels not needed	A	I	102,103
Against routine use of topical antistaphylococcal treatments	A	I	110-112
Bleach baths and intranasal mupirocin for those with moderate to severe AD and clinical infection	B	II	113
Against use of topical antihistamines	B	II	42,115-117

AD, Atopic dermatitis; *TCI*, topical calcineurin inhibitors; *TCS*, topical corticosteroids.

higher water content that can evaporate and may be less ideal in those with significant xerosis.

Prescription emollient devices (PEDs) are a newer class of topical agents designed to target specific defects in skin barrier function observed in AD. They include preparations having distinct ratios of lipids that mimic endogenous compositions and creams containing palmitoylethanolamide, glycyrrhetinic acid, or other hydrolipids. They are generally recommended for 2 or 3 times daily use depending on the specific agent. Although there is some evidence that PEDs also lessen symptoms and signs of AD, including xerosis and inflammation, they have only been tested in a small number of controlled studies.[16,18-20] They are approved as 510(k) medical devices based on the assertion that they serve a

structural role in skin barrier function and do not exert their effects by any chemical actions. This approval process requires less rigorous clinical efficacy data than that needed for Food and Drug Administration approval of drugs. In addition, these agents are more costly, although they are considered safe adjunctive treatments. There are now several moisturizers containing ceramides and/or filaggrin breakdown products that are available over the counter, though the compositions are not necessarily equivalent to those of the PEDs.

Head-to-head trials between specific moisturizing products are few in number, and those performed to date have not demonstrated one to be superior to others, including the PEDs. One study of 39 subjects with mild to moderate AD found no difference in efficacy among glycyrrhetinic acid–containing hydrolipid cream, 3:1:1 ceramide:cholesterol:free fatty acids cream, and an over-the-counter petroleum-based skin protectant moisturizer when used for 3 weeks.[21] Another study showed similar parity for an over-the-counter oil-based moisturizing cream and a palmitoylethanolamide-containing PED during a 4-week application period.[16] Therefore, the choice of moisturizing agent is highly dependent on individual preference. The ideal agent should be safe, effective, inexpensive, and free of additives, fragrances, perfumes, and other potentially sensitizing agents. But regardless of the particular product used, moisturizing to address the defective barrier is an important therapeutic concept given our current understanding of AD pathogenesis. Trials are also underway to test if skin barrier protection and moisturizer use from birth reduces the likelihood of development of AD in genetically predisposed infants.[22]

Bathing practices, including additives

Bathing can have differing effects on the skin depending on the manner in which it is carried out. Bathing with water can hydrate the skin and remove scale, crust, irritants, and allergens, which can be helpful for patients with AD.[23] However, if the water is left to evaporate from the skin, greater transepidermal water loss occurs.[24] Therefore, application of moisturizers soon after bathing is necessary to maintain good hydration status.[24,25]

There are few objective data from which to determine best bathing practices, and most recommendations stem from expert consensus and personal experience. The recommendations of the current work group are summarized in Table II (level of evidence in Table III). Although 1 survey[26] of children found that more patients with AD shower as opposed to bathe in a tub, over 80% of subjects were older than 5 years, likely influencing the results, and there are no comparative studies to suggest one particular form of bathing as better. There is also no clear frequency or duration of bathing that is optimal for those with AD. However, it is generally recommended that up to once-daily bathing be performed to remove serous crust, as long as moisturizers follow as above; the duration should be limited to short periods of time (eg, 5-10 minutes) with use of warm water. If there are areas of significantly inflamed skin, soaking in plain water for 20 minutes followed by the immediate application of pharmacologic anti-inflammatory therapies (eg, topical corticosteroids [TCS]) to these sites, without toweling dry, is a helpful treatment measure. This "soak and smear" technique can improve response in cases where the topical anti-inflammatory alone is inadequate.[23]

Limited use of nonsoap cleansers that are neutral to low pH, hypoallergenic, and fragrance free is recommended. Soaps consist of surfactants that interact with stratum corneum proteins and lipids, but in a manner that causes damage, dry skin, and irritation.[27,28] Most soaps are alkaline in pH, whereas the skin's normal pH is 4 to 5.5. Instead, nonsoap-based surfactants and synthetic detergents (syndets) are often recommended for better tolerance, although this is based on only a few supportive clinical studies.[29,30]

With the exception of bleach, which is discussed in detail below, data are limited on the addition of oils, emollients, and other related additives to bath water and their benefits for AD.[26,31] The quantity of emollient deposited on the skin via a bath additive is likely to be lower than that from direct application. No published RCTs have tested the clinical benefit of combining bath emollients with directly applied emollients after bathing. Thus, at this time, the routine use of bath additives cannot be recommended. Use of acidic spring water for bathing (balneotherapy) also has limited supporting evidence.[32] The use of water-softening devices has also not been shown to have benefits over the use of normal water.[33]

Wet-wrap therapy

Wet-wrap therapy (WWT) is one method to quickly reduce AD severity, and is often used in the setting of significant flares and/or recalcitrant disease. It may be performed on an ambulatory or inpatient basis.[34,35] Most use a technique of a topical agent that is covered by a wetted first layer of tubular bandages, gauze, or a cotton suit, followed by a dry second/outside layer. For more generalized disease, 2 layers of nonirritating

Table IV. Recommendations for the use of topical corticosteroids for the treatment of atopic dermatitis

Topical corticosteroids are recommended for AD-affected individuals who have failed to respond to good skin care and regular use of emollients alone.
A variety of factors should be considered when choosing a particular topical corticosteroid for the treatment of AD, including patient age, areas of the body to which the medication will be applied, and other patient factors such as degree of xerosis, patient preference, and cost of medication.
Twice-daily application of corticosteroids is generally recommended for the treatment of AD; however, evidence suggests that once-daily application of some corticosteroids may be sufficient.
Proactive, intermittent use of topical corticosteroids as maintenance therapy (1-2 times/wk) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone.
The potential for both topical and systemic side effects, including possible hypothalamic-pituitary-adrenal axis suppression, should be considered, particularly in children with AD in whom corticosteroids are used.
Monitoring by physical examination for cutaneous side effects during long-term, potent steroid use is recommended.
No specific monitoring for systemic side effects is routinely recommended for patients with AD.
Patient fears of side effects associated with the use of topical corticosteroids for AD should be recognized and addressed to improve adherence and avoid undertreatment.

AD, Atopic dermatitis.

clothing can be similarly prepared. WWT appears to help via occluding the topical agent for increased penetration, decreasing water loss, and providing a physical barrier against scratching. The wrap can be worn from several hours to 24 hours at a time, depending on patient tolerance. Most suggest several days of use, although a few studies continued WWT for up to 2 weeks.[35]

In 2 comparative trials, the application of TCS with wet wraps was more efficacious than using only moisturizers with the wraps.[36,37] Care should be taken, however, when mid- to higher-potency corticosteroids are applied under the wraps, as absorption is increased and may cause hypothalamic-pituitary-adrenal axis suppression, especially if used widely on the skin. Temporary decreases in early morning serum cortisol levels have been reported, although short courses of use have not been associated with prolonged adrenal suppression.[38,39] Two studies showed that this risk could be decreased by limiting to once-daily application or by diluting the potent TCS to 10% or even 5% of their original strength.[37,40] Some prefer to use low- to medium-potency TCS instead of dilution. The potential for increased risk of infection has been raised with the use of mid- to higher-potency topical steroids in WWT, although the data are sparse and conflicting regarding its actual occurrence.[35,36,41]

TOPICAL CORTICOSTEROIDS

TCS are used in the management of AD in both adults and children and are the mainstay of anti-inflammatory therapy. They act on a variety of immune cells, including T lymphocytes, monocytes, macrophages, and dendritic cells, interfering with antigen processing and suppressing the release of proinflammatory cytokines. They are typically introduced into the treatment regimen after failure of lesions to respond to good skin care and regular use of moisturizers alone.

Efficacy

TCS have been used to treat AD for more than 60 years. Their efficacy has been demonstrated with a wide variety of preparations and strengths, with more than 110 different RCTs performed to date.[42] They are generally the standard to which other topical anti-inflammatory therapies are compared. In addition to decreasing acute and chronic signs of AD, multiple trials have shown decreased pruritus with their application.[43-46] TCS are used for both active inflammatory disease and for prevention of relapses. Comparative trials are limited in duration and scope (ie, they mainly involve 2, and occasionally 3, agents), and as a result, there are no data to support 1 or a few specific agents as being more efficacious than others. Patient vehicle preference, along with cost and availability, often determine their selection. A summary of recommendations on TCS use is in Table IV, with the level of evidence in Table III.

Dosage

TCS are grouped into 7 classes, from very low/lowest potency (VII) to very high potency (I), based on vasoconstriction assays. Table V provides some

Table V. Relative potencies of topical corticosteroids

Class	Drug	Dosage form(s)	Strength (%)
I. Very high potency	Augmented betamethasone dipropionate	Ointment	0.05
	Clobetasol propionate	Cream, foam, ointment	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
II. High potency	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream	0.05
	Betamethasone dipropionate	Cream, foam, ointment, solution	0.05
	Desoximetasone	Cream, ointment	0.25
	Desoximetasone	Gel	0.05
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, gel, ointment, solution	0.05
	Halcinonide	Cream, ointment	0.1
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream, ointment	0.5
III-IV. Medium potency	Betamethasone valerate	Cream, foam, lotion, ointment	0.1
	Clocortolone pivalate	Cream	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream, ointment	0.025
	Flurandrenolide	Cream, ointment	0.05
	Fluticasone propionate	Cream	0.05
	Fluticasone propionate	Ointment	0.005
	Mometasone furoate	Cream	0.1
	Triamcinolone acetonide	Cream, ointment	0.1
V. Lower-medium potency	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
	Prednicarbate	Cream	0.1
VI. Low potency	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinolone acetonide	Cream, solution	0.01
VII. Lowest potency	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, lotion, ointment, solution	0.25, 0.5, 1
	Hydrocortisone acetate	Cream, ointment	0.5-1

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Includes representative examples and not all available agents.

representative examples of available agents in each class. There is a paucity of studies that examine a range of TCS doses in large numbers of patients and with the lack of an established optimum, great variability in dosing exists. Some use a short burst of a high-potency TCS to rapidly control active disease, followed by a quick taper in potency, whereas others use the lowest-potency agent thought to be needed and adjust upward only if this fails.

No universal standard exists for quantity of application, although suggested methods include use of the adult fingertip unit (the amount from the distal interphalangeal joint to the fingertip, or approximately 0.5 g, being applied over an area equal to 2 adult palms), following the rule of 9's that measures the percent affected area, and use of charts that propose amounts based on patient age and body site.[47,48]

Children have a proportionately greater body surface area to weight ratio, and as a result, have a higher degree of absorption for the same amount applied. But during significant acute flares, the use of mid- or higher-potency TCS for short courses may be appropriate to gain rapid control of symptoms, even in children.[49,50] However, for long-term management, the least-potent corticosteroid that is effective should be used to minimize the risk of adverse effects. Greater caution regarding TCS potency is also needed when treating thin skin sites (ie, face, neck, and other skin folds), where there is greater penetration and higher likelihood for systemic absorption. It is important to monitor quantities of TCS used over time, which may impact efficacy and safety.

Frequency of application

Most studies on the efficacy of TCS in AD management involve twice-daily application. This is the most common clinical practice and also the generally recommended frequency. However, there is evidence to suggest that once-daily application of some potent corticosteroids may be as effective as twice-daily application.[51] Some newer formulations also use once-daily application.[52,53]

For acute flares, use of TCS is recommended every day until the inflammatory lesions are significantly improved and less thick, for up to several weeks at a time. After obtaining control of an outbreak, the goal is to prolong the period until the next flare. Previously, TCS use was stopped on improvement of symptoms and signs of disease, switching to the use of moisturizers alone and reinstituting the TCS only with subsequent relapses. However, in recent years, a more proactive approach to maintenance has been advocated for those patients who experience frequent, repeated outbreaks at the same body sites.[54-56] This entails the scheduled application of a TCS once to twice weekly at these particular locations, a method that has reduced rates of relapse and increased time to first flare relative to the use of moisturizers alone (to be discussed further in part 4 of these guidelines).

Adverse effects and monitoring

The incidence of reported side effects from TCS use is low; however, most studies fail to follow up patients long term for potential complications.[57] Cutaneous side effects include purpura, telangiectasia, striae, focal hypertrichosis, and acneiform or rosacea-like eruptions. Of greatest concern is skin atrophy, which can be induced by any TCS, though higher-potency agents, occlusion, use on thinner skin, and older patient age increase this risk.[57,58] Many of these side effects will resolve after discontinuing TCS use, but may take months. Sites of treatment should be assessed regularly for these adverse effects, particularly with use of more potent agents. Continuous application of TCS for long periods of time should be avoided, to limit the occurrence of negative changes. Proactive, once to twice weekly application of mid-potency TCS for up to 40 weeks has not demonstrated these adverse events in clinical trials.[54]

TCS application on AD lesions does reduce *Staphylococcus aureus* bacterial load, likely via decreasing the inflammatory cytokines that inhibit antimicrobial peptide production.[59,60] There is some worry that TCS may impair the process of wound healing and re-epithelialization, although excoriated and fissured lesions should be included in treatment given that the underlying inflammation and pruritus lead to these secondary changes. Allergic contact dermatitis/type IV hypersensitivity can develop to TCS or other ingredients in their formulations, such as propylene glycol and preservatives. This should be considered if lesions fail to respond as expected or worsen with application. Patch testing is needed to determine if the allergen is the steroid compound itself or a component of the vehicle.[61] Development of tachyphylaxis is of concern for some practitioners, where the efficacy is thought to decrease with repeated use of the same agent, although data are lacking to suggest that this is a significant clinical problem. Although there is documented risk with systemic corticosteroid use, an association between topical steroid use and the development of cataracts or glaucoma is not as clear.[57] Nonetheless, minimizing use at periocular sites may be prudent.

Topically applied corticosteroids, particularly high- and very high–potency agents, can be absorbed at a degree sufficient to cause systemic side effects. The risk of hypothalamic-pituitary-adrenal axis suppression is low but increases with prolonged continuous use, especially in individuals receiving corticosteroids concurrently in other forms (inhaled, intranasal, or oral).[62] As discussed above, children are more susceptible as a result of a greater body surface to weight ratio. There is also some concern for negative effects on linear growth, although reports have given mixed conclusions.[63-65] Hyperglycemia and hypertension have rarely been reported.[57,66]

A systematic review concluded that TCS overall have a good safety profile.[57,66] No specific monitoring for systemic side effects is recommended for patients with AD at this time. However, if hypothalamic-pituitary-adrenal axis suppression is a concern, this can be assessed by performing a cortisol stimulation test to check for appropriate adrenal response. As discussed in part 1 of these guidelines, some children with AD are underweight as a result of severe disease, although further decline in growth should prompt consideration for investigation.

Addressing concerns with TCS use

Although judicious use of TCS is certainly warranted, recognition of undertreatment as a result of steroid phobia is also important. One survey of 200 dermatology outpatients with AD found that 72.5% were worried about use of TCS on their own or their child's skin, with 24% admitting noncompliance with therapy as a result of these concerns.[67] Other

Table VI. Recommendations for the use of topical calcineurin inhibitors for the treatment of atopic dermatitis

TCI are recommended and effective for acute and chronic treatment, along with maintenance, in both adults and children with AD, and are particularly useful in selected clinical situations (Box 1).
TCI are recommended for use on actively affected areas as a steroid-sparing agent for the treatment of AD.
For patients with AD <2 years of age with mild to severe disease, off-label use of 0.03% tacrolimus or 1% pimecrolimus ointment can be recommended.
Pimecrolimus cream and tacrolimus ointment may cause skin burning and pruritus, especially when applied to acutely inflamed skin. Initial treatment of patients with AD using topical corticosteroids should be considered to minimize TCI application site reactions. Patients with AD should be counseled about the possibility of these reactions.
Proactive, intermittent use of TCI as maintenance therapy (2-3 times per week) on areas that commonly flare is recommended to help prevent relapses while reducing the need for topical corticosteroids, and is more effective than the use of emollients alone.
The concomitant use of a topical corticosteroid with a TCI may be recommended for the treatment of AD.
No consistent increases in the prevalence of cutaneous viral infections have been seen with continuous or intermittent use of TCI for up to 5 years; however, physicians should inform their patients of these theoretical cutaneous risks, given the lack of safety data for longer periods of time.
Clinicians should be aware of the black-box warning on the use of TCI for patients with AD and discuss as warranted.
Routine blood monitoring of tacrolimus and pimecrolimus levels in patients with AD who are applying these agents is not recommended at this time.

AD, Atopic dermatitis; *TCI*, topical calcineurin inhibitor.

studies have shown that patient knowledge of steroid class potencies is poor and leads to inappropriate use.[68,69] Thus, to achieve good response, it is important to address such fears and incorrect beliefs. The risks associated with TCS use do appear to be low with appropriate application and choice of potency, combined with periods of nonuse.[57] A higher strength of recommendation (than actual level of evidence) is therefore placed on counseling, because the benefits outweigh the risks.

TOPICAL CALCINEURIN INHIBITORS

Topical calcineurin inhibitors (TCI) are a second class of anti-inflammatory therapy introduced in 2000. They are naturally produced by *Streptomyces* bacteria and inhibit calcineurin-dependent T-cell activation, blocking the production of proinflammatory cytokines and mediators of the AD inflammatory reaction. They have also been demonstrated to affect mast cell activation, and tacrolimus decreases both the number and costimulatory ability of epidermal dendritic cells.[70]

Efficacy

Two TCI are available, topical tacrolimus ointment (0.03% and 0.1% strengths) and pimecrolimus cream (1% strength). Both agents have been shown to be more effective than vehicle in short-term (3-12 weeks) and long-term (up to 12 months) studies in adults and children with active disease.[71-76] Physician global evaluation scores showed decline, as did the percent body surface area involved and patient evaluation of symptoms and signs of disease. Tacrolimus is approved for moderate to severe disease, whereas pimecrolimus is indicated for mild to moderate AD, and 6-week comparative studies support a greater effect for tacrolimus over this time period for all AD severities.[77-80]

A meta-analysis of 25 RCTs found tacrolimus 0.1% to be as effective as the mid-potency TCS hydrocortisone butyrate 0.1%, whereas tacrolimus 0.03% is less effective than hydrocortisone butyrate 0.1% but more effective than the low-potency TCS hydrocortisone acetate 1%.[81] Pimecrolimus cream has not been directly compared with low-potency TCS, but is less efficacious than mid- and high-potency TCS.[76,81] A summary of recommendations on TCI use is in Table VI, with the level of evidence in Table III.

Dosing

In the United States, the TCI are approved as second-line therapy for the short-term and noncontinuous chronic treatment of AD in nonimmunocompromised individuals who have failed to respond adequately to other topical prescription treatments for AD, or when those treatments are not advisable. TCI have the benefit of not carrying risk for cutaneous atrophy, with little negative effect on collagen synthesis and skin thickness. TCI can therefore be used as steroid-sparing agents and long-term studies

Box 1. Clinical situations in which topical calcineurin inhibitors may be preferable to topical steroids

Recalcitrance to steroids
Sensitive areas (eg, face, anogenital, skin folds)
Steroid-induced atrophy
Long-term uninterrupted topical steroid use

to 12 months have shown that they do reduce the need for TCS use.[82,83] They have also been demonstrated to be more effective in reversing skin atrophy than vehicle.[84]

TCI have particular use at sensitive skin sites, such as the face and skin folds, where there is a greater adverse risk profile with TCS. Three studies of pimecrolimus noted greater improvement at the face and neck compared with other body sites and in 1 RCT, more subjects achieved clearance of eyelid dermatitis using pimecrolimus compared with vehicle (45% vs 19%).[84-87] In a 3-week RCT of tacrolimus 0.1% ointment compared with fluticasone 0.005% ointment in adults with moderate to severe facial AD in which conventional treatment was ineffective or poorly tolerated, tacrolimus gave greater improvement in the modified severity score.[88] Fewer patients opted to switch from tacrolimus to fluticasone than vice versa. Box 1 lists situations in which TCI may be preferable to topical steroids.

Tacrolimus 0.03% ointment and pimecrolimus cream are indicated for use in individuals age 2 years and older, whereas tacrolimus 0.1% strength is only approved in those older than 15 years. However, evidence from clinical trials supports the safe and effective use of topical tacrolimus 0.03% and pimecrolimus in children younger than 2 years, including in infants.[76] The indications for tacrolimus were based on early studies that suggested that the 0.03% and 0.1% strengths were equally effective and safe in children, although the 0.1% strength showed superiority in adults.[89,90] Subsequent clinical experience with the off-label use of tacrolimus 0.1% in children has led many to believe it is more effective than the 0.03% formulation, but there is a need for additional formal comparative studies.

Frequency of application

Twice-daily application of the tacrolimus ointments and pimecrolimus cream are significantly more effective at decreasing signs of inflammation, affected body surface area, and associated pruritus of lesional areas on the head/neck and nonhead/neck locations than vehicle or once-daily application in adults, children, and infants.[91,92]

Proactive, intermittent application of TCI 2 to 3 times weekly to recurrent sites of disease has also been shown to be effective in reducing relapses. After gaining control of acute disease, topical tacrolimus (0.03% in children and 0.1% in adults) significantly reduced the number of exacerbations compared with vehicle, and increased the time to first exacerbation and the number of flare-free days.[93-95] It has been used for up to 1 year using this strategy, without significant adverse events noted.

Adverse effects

The most common side effects seen are local reactions such as stinging and burning. These symptoms are more frequent than that seen with TCS, but tend to lessen after several applications or when first preceded by a short period of topical steroid use.[96] Patients should be advised of these adverse effects to avoid premature discontinuation of treatment. There are scattered reports of allergic contact dermatitis and a rosacea-like granulomatous reaction caused by TCI.

Patients with flaring and/or severe AD are at risk for secondary infections as a result of the skin disease (discussed further below in "Topical Antimicrobials and Antiseptics"). The effect of continuation of TCI treatment on infected lesions has not been studied, but the prescribing information advocates against their use during acute infection. As with TCS, topical tacrolimus applied to noninfected lesions has been associated with reduced *Staphylococcus aureus* colonization, also likely a result of reduced inflammation and barrier dysfunction.[97] No consistent increases in the prevalence of cutaneous viral infections have been demonstrated with continuous or intermittent use of TCI for up to 5 years.[82,83,98] However, physicians should inform their patients of these theoretical risks given the lack of long-term safety data.

TCI boxed warning should be discussed with patients before use. Rare cases of malignancy (eg, skin cancer and lymphoma) have been reported in patients treated with these agents, although a causal relationship has not been established. This warning was added in response to widespread off-label use in children younger than 2 years, and based on a theoretical risk from the use of high-dose oral calcineurin inhibitor therapy in patients post-transplantation and from animal studies with exposures 25- to nearly 50-fold the maximum recommended human dose.[99] Interim analyses of ongoing, 10-year surveillance studies to address these concerns have not found evidence of increased malignancy rates relative to that expected in the

general pediatric population.[98,99] Several studies, including a large case-control study of 293,253 patients, have noted an increased risk of lymphoma that correlates with AD severity, but not with TCI use.[100,101] Overall, the TCI have demonstrated a good safety profile to date when used as recommended, but continued assessment is needed. Proactive guidance on the content of the black-box warning can reduce anxiety on the part of patients and parents.

There is no evidence to suggest a need for routine blood monitoring of tacrolimus or pimecrolimus levels in patients with AD. Both TCI have shown consistently low to negligible systemic absorption after topical application, without any notable sequelae.[102,103] Use in conditions with a much more severely impaired skin barrier that would give increased absorption, such as with Netherton syndrome, may warrant such monitoring.[104,105]

Use with TCS

TCI may be combined with TCS use in a number of ways. Often topical steroids are used first for control of a flare, given greater potency and to reduce occurrence of some of the local symptoms associated with TCI. TCI can then be used both to spare topical steroid use and to prevent relapse. Only a few comparative trials have formally tested the TCS plus TCI combination, which may be used sequentially or concomitantly. In 1 study, 4 weeks of topical betamethasone butyrate propionate and tacrolimus sequential therapy improved lichenification and chronic papules to a greater degree than betamethasone butyrate propionate and emollient sequential therapy.[106] Tacrolimus 0.1% ointment used concomitantly with desoximetasone ointment was superior to tacrolimus and vehicle and the combination of clocortolone 0.1% cream with tacrolimus 0.1% ointment was also superior to either topical agent alone.[107,108] However, 1 study of pimecrolimus cream added to fluticasone 0.05% cream did not appear to offer any significant advantage in the treatment of AD flares.[109]

Other studies have examined the use of continuous, daily TCI therapy between flares, particularly with topical pimecrolimus. Pimecrolimus application led to more days without flare, a decreased number of days needing TCS rescue, and an increased median time to first flare, compared with vehicle.[82,83]

TOPICAL ANTIMICROBIALS AND ANTISEPTICS

Atopic individuals are predisposed to skin infections because of a compromised physical barrier, coupled with diminished immune recognition and impaired antimicrobial peptide production. *Staphylococcus aureus*, in particular, is a frequent culprit and colonizer of the skin in AD. Its presence, even without overt infection, appears to trigger multiple inflammatory cascades, via toxins that act as superantigens and exogenous protease inhibitors that further damage the epidermal barrier and potentiate allergen penetration.

Table VII. Recommendations for the use of topical antimicrobials and antiseptics for the treatment of atopic dermatitis

Except for bleach baths with intranasal mupirocin, no topical antistaphylococcal treatment has been shown to be clinically helpful in patients with AD, and is not routinely recommended.
In patients with moderate to severe AD and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity.

AD, Atopic dermatitis.

A 2010 Cochrane review of RCTs found a lack of quality trials to support the use of antimicrobial and antiseptic preparations to treat AD (further discussed in part 3 of these guidelines).[110] The review also did not find any clear benefit for topical antibiotics/antiseptics, antibacterial soaps, or antibacterial bath additives in either the setting of clinical infection or uninfected AD, noting that even positive findings in studies often had poor reporting of details. Although the addition of a topical antibiotic to a topical steroid reduces the amount of *Staphylococcus aureus* isolated from the skin, the combination has not been found to improve either global outcomes or disease severity compared with the steroid alone.[59,111,112] Thus, topical antimicrobial preparations are not generally recommended in the treatment of AD (recommendation in Table VII, level of evidence in Table III). They can be associated with contact dermatitis, and there is also concern that their use could promote wider antimicrobial drug resistance.

An exception to the above antimicrobial agents is the use of bleach baths with intranasal topical mupirocin. In 1 RCT of 31 children with moderate to severe AD, treatment of an infectious episode with oral cephalexin for 2 weeks followed by the addition of household bleach to bathwater plus intranasal application of mupirocin for 3 months led to a greater improvement in disease severity than simple bathing alone.[113] Enhanced clinical improvement was noted only in the skin submerged in the bath (not the head/face). Bleach baths may therefore be helpful in cases of moderate to severe disease with

frequent bacterial infections, and particularly for maintenance, as cultures did not show clearance of the bacteria in the majority of patients. There is less concern about the development of bacterial resistance with use of dilute bleach relative to the use of topical and systemic antibiotics. Topical hypochlorite products are also available as an alternative to dilute bleach baths, but at higher cost and without any RCTs published to date.

In children and adults with clinically uninfected AD, the use of underwear made of silver impregnated textile did not reduce the severity of the AD compared with cotton underwear.[114] Use of silk fabric with a durable antimicrobial finish has limited positive data, and needs further investigation.

TOPICAL ANTIHISTAMINES

Topical antihistamines have been tried for the treatment of AD but unfortunately have demonstrated little utility and are not recommended (see Table VIII, level of evidence in Table III). Studies investigating topical doxepin have demonstrated a short-term decrease in pruritus in some cases, but with no significant reduction in disease severity or control. Treatment has local side effects, particularly stinging and burning, and can also cause sedation.[115,116] There are multiple reports of allergic contact dermatitis secondary to the use of topical doxepin; however, the specific incidence of this outcome cannot be established with certainty based on the available data.[117] There are no controlled studies on the use of topical diphenhydramine for AD. It may also cause allergic or photoallergic contact dermatitis.[118] Widespread application, use on broken skin, and/or combined use with oral diphenhydramine are not advised because of risk for systemic toxicities such as toxic psychosis (eg, hallucinations, delirium), particularly in children.[119,120]

OTHER TOPICAL AGENTS

Topical coal tar derivatives have been used for many years in the treatment of inflammatory skin diseases, particularly psoriasis. There are, however, very few trials of coal tar preparations and their efficacy in the treatment of AD.[121] Munkvad[122] investigated a preparation designed to be more cosmetically acceptable than traditional formulations and found it to be as effective as 1% hydrocortisone acetate cream on left/right paired comparison for mild to moderate disease. But given only a 4-week study and 5 of 30 patients reported itching and soreness, there are not adequate data to make a recommendation regarding the use of coal tar topical agents. A recent study of organotypic skin models from patients with AD and control subjects did find that coal tar activates the aryl hydrocarbon receptor signaling pathway, resulting in enhanced epidermal differentiation, increased levels of filaggrin, and inhibition of a major AD cytokine pathway (interleukin-4/signal transducer and activator of transcription (STAT)-6).[123]

Table VIII. Recommendations for the use of topical antihistamines for the treatment of atopic dermatitis

The use of topical antihistamines for the treatment of patients with atopic dermatitis is not recommended because of the risk of absorption and of contact dermatitis.

Topical phosphodiesterase inhibitors are another new class of anti-inflammatory treatments,[124,125] but remain available only in clinical trials, also precluding any recommendations for or against their use at this time.

GAPS IN RESEARCH

In review of the currently available highest level of evidence, the expert work group acknowledges that although much is known about the use of nonpharmacologic and pharmacologic topical therapies for AD, much has yet to be learned. Significant gaps in research were identified, including but not limited to: RCTs to better determine optimal bathing techniques, including controlled studies on frequency, duration, and the effects of bathing and use of bath emollients; well-designed, large trials to better test the effects of topical antimicrobial agents and TCS-TCI in combination; and studies to provide additional long-term safety data on the use of TCI. It is hoped that such gaps are closed to further optimize the use of topical therapeutic options.

We thank Melinda Jen, MD, Michael Osofsky, MD, Kathleen Muldowney, MLS, Charniel McDaniels, MS, and Tammi Matillano for technical assistance in the development of this manuscript. We also thank the AAD Board of Directors, the Council on Science and Research, the Clinical Guidelines Committee, and all commenting Academy members for their thoughtful and excellent comments.

Dr Tom is supported by a National Institutes of Health (NIH)/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) research career development grant (K23AR060274). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIAMS or NIH.

Disclosures: The American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence

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Dr Eichenfield served as a consultant for Anacor, Bayer, and Leo Pharma receiving honoraria, and TopMD receiving stock options; was a consultant and speaker for Galderma receiving honoraria; served as a consultant, speaker, and member of the advisory board for Medicis/Valeant receiving honoraria; and was an investigator for Anacor, Astellas, Galderma, and Leo Pharma receiving no compensation. Dr Eichenfield was recused from discussions and voting on recommendations addressing moisturizers. Dr Tom served as an investigator for Anacor receiving no compensation. Dr Krol served as an investigator for Pierre-Fabre receiving grants. Dr Paller served as a consultant to Anacor, Galderma, Leo Pharma, Promius, Sanofi/Regeneron, and TopMD receiving honoraria, and was an investigator for Astellas, Galderma, Leo Pharma, and TopMD receiving no compensation. Dr Bergman served as a consultant for Pediapharm receiving honoraria. Dr Bergman was recused from discussions and voting on recommendations addressing moisturizers. Dr Chamlin served on the advisory boards for Galderma, Promius, and Valeant receiving honoraria. Dr Chamlin was recused from discussions and voting on recommendations addressing moisturizers. Dr Cohen served on the advisory boards and as a consultant for Ferndale Labs, Galderma, and Onset receiving honoraria; served on the board of directors and as a consultant for Brickell Biotechnology and Topica receiving honoraria, stock, and stock options; and was a consultant for Dermira and Dr Tattoff receiving honoraria and stock options. Dr Cohen was recused from discussions and voting on recommendations addressing moisturizers and topical steroids. Dr Cooper served as a consultant for Kimberly Clark receiving salary. Dr Cooper was recused from discussions and voting on recommendations addressing paper products. Dr Feldman served on the advisory boards for Amgen, Doak, Galderma, Pfizer, Pharmaderm, Skin Medica, and Stiefel receiving honoraria; was a consultant for Abbott, Astellas, Caremark, Coria, Gerson Lehrman, Kikaku, Leo Pharma, Medicis, Merck, Merz, Novan, Peplin, and Pfizer receiving honoraria, and Celgene, HanAll, and Novartis receiving other financial benefits; was a speaker for Abbott, Amgen, Astellas, Centocor, Dermatology Foundation, Galderma, Leo Pharma, Novartis, Pharmaderm, Sanofi-Aventis, Stiefel, and Taro receiving honoraria; served as a stockholder and founder for Causa Technologies and Medical Quality Enhancement Corporation receiving stock; served as an investigator for Abbott, Amgen, Anacor, Astellas, Basilea, Celgene, Centocor, Galderma, Medicis, Skin Medica, and Stiefel receiving grants, and Suncare Research receiving honoraria; and had other relationships with Informa, UptoDate, and Xlibris receiving royalty, and Medscape receiving honoraria. Dr Feldman was recused from discussions and voting on recommendations addressing moisturizers. Dr Hanifin served on the advisory board for Chugai Pharma USA receiving honoraria; was a consultant for GlaxoSmithKline, Merck Elocon Advisory Board, Pfizer, and Valeant Elidel Advisory Board receiving honoraria; and served as an investigator for Asubio, Dohme, and Merck Sharp receiving grants. Dr Margolis served as a principal investigator for a Valeant postmarketing study. All sponsored research income was paid directly to his employer. Dr Silverman served as a speaker for Galderma and Promius receiving honoraria. Dr Silverman was recused from discussions and voting on recommendations addressing moisturizers. Dr Simpson served as a consultant for Asubio, Brickell Biotech, Galderma, Medicis, Panmira Pharmaceuticals, and Regeneron, and a speaker for Centocor and Galderma receiving honoraria; and was an investigator for Amgen, Celgene, Galderma, and Regeneron receiving other financial benefits. Dr Simpson was recused from discussions and voting on recommendations addressing moisturizers. Dr Elmets served on a data safety monitoring board for Astellas receiving honoraria. Drs Berger, Schwarzenberger, Cordoro, Davis, Williams, and Sidbury, Ms Block, Mr Harrod, and Ms Smith Begolka have no conflicts of interest to declare.

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