

CONSENSUS GUIDELINE

Consensus Guidelines for the Treatment of Atopic Dermatitis in Korea (Part I): General Management and Topical Treatment

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Background: Since the treatment guidelines for atopic dermatitis (AD) were released by the Korean Atopic Dermatitis Association (KADA) work group in 2006, there have been several advances in AD management. **Objective:** We aimed to establish updated evidence- and experience-based treatment guidelines for Korean AD. **Methods:** We collected a database of references from relevant systematic AD reviews and guidelines regarding general AD management such as bathing and skin care, avoidance of exacerbating factors, education and psychosocial support, and the use of moisturizers and topical anti-inflammatory and antipruritic drugs.

Evidence for each statement was graded and the strength of the recommendation for each statement classified. Thirty-nine KADA council members participated in three rounds of voting to establish an expert consensus of recommendations. **Results:** Basic AD treatment includes proper bathing and skin care, avoidance of exacerbating factors, proper education and psychosocial support, and use of moisturizers. The regular use of moisturizer has a steroid-sparing effect and reduces relapse episodes. The short- and long-term use of topical corticosteroids and calcineurin inhibitors improves AD symptoms and should be encouraged to use in an active and proactive treatment. Wet-wrap therapy can be used for rapid recovery of acute exacerbation. Topical antipruritic drugs cannot be recommended for the treatment of AD. **Conclusion:** This report provides up-to-date evidence- and experience-based treatment guidelines for AD regarding general management and topical treatment. In addition, the average agreement scores obtained by a panel of experts based on the Korean healthcare system and patient adherence are presented. (*Ann Dermatol* 27(5) 563 ~ 577, 2015)

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-Keywords-

Administration, topical, Guideline, Therapeutics

INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disorder caused by an individual's combined genetic, environmental, and immunologic background¹. Several therapeutic guidelines for AD treatment from work groups in various countries have been published²⁻⁵. To provide individualized and long-term AD treatment, various factors must be considered, including age, provocative and socioeconomic factors, patient adherence, and psychological status. The health care system and cultural background of a country can also affect the treatment decisions of both physicians and patients.

The Korean Atopic Dermatitis Association (KADA) convened the Korean AD Treatment Guideline Task Force group to develop updated evidence-based and practical AD treatment guidelines based on the Korean health care system and patient adherence. These revised treatment guidelines provide up-to-date, evidence-based treatment recommendations and the average agreement scores of expert panel members are presented for each key statement.

Recommendations for AD treatment are divided into two parts: nonsystemic treatment, including AD skin management and topical treatment, and systemic treatment. This report is the first of two parts in a guidelines series and includes information on AD management, such as bathing and skin care, avoidance of exacerbating factors, education and psychosocial support, and the use of moisturizers and topical anti-inflammatory drugs, antibiotics, and antipruritic drugs. Clinical questions are focused on therapeutic effects, detailed plans of action, side effects, cost-effectiveness, and measures to enhance patient compliance for each treatment.

MATERIALS AND METHODS

In developing the Korean guidelines for managing AD, KADA convened a working group of 12 dermatologists representing AD experts nationwide. The panel followed the methodology for developing guidelines detailed in the 2011 Guidance for the Development of Clinical Practice Guidelines from the National Evidence-based Healthcare Collaborating Agency⁶.

Database and literature research

The 12 members of the working group each conducted separate comprehensive computerized database searches of MEDLINE (accessed by PubMed) and Embase from January 1, 2005, to December 31, 2014, using combinations of the search terms "atopic eczema", "atopic dermatitis", "bathing", "cleanser", "triggering factor", "environ-

ment", "avoidance", "clothing", "food", "education", "psychosocial support", "topical agents", "emollient", "moisturizer", "wet wrap treatment", "topical" "topical corticosteroid", "calcineurin inhibitor", "pimecrolimus", "tacrolimus", "antibiotics", "antimicrobials" "topical anesthetics", "topical antihistamine", "capsaicin", "tiacrilast", and "phosphodiesterase inhibitors". These searches were supplemented by hand-searching references from related systematic reviews and guidelines of other groups. The members collected all the relevant statements on managing AD from the identified references.

Evaluation of the literature

The members of the working group graded the evidence of each statement and then classified the strength of the recommendation for each statement. The evidence of each statement was graded as follows: level 1, systematic review of randomized controlled trials (RCTs) and individual RCTs; level 2, systematic review of cohort studies and individual cohort study (including low-quality RCTs); level 3, systematic review of case-control studies and individual case-control studies; level 4, case series (and poor-quality cohort and case-control studies); and level 5, expert opinion. The strength of each recommendation was classified as A (level 1), B (levels 2 and 3), C (level 4), or D (level 5) (Table 1)⁷.

Consensus process

A total of 39 of 54 KADA council members participated in the vote on the draft guideline statements. Each statement was given along with its grade of evidence and recommendation strength. Each participant had one vote per statement. Participants scored their level of agreement with each draft statement on a scale of 1~9, where 1 represented strong disagreement and 9 represented strong

Table 1. Level of evidence and strength of the recommendations

Strength of recommendation	Level of evidence	
A	1a	Systematic review of RCTs
	1b	Individual RCTs
B	2a	Systematic review of cohort studies
	2b	Individual cohort study(including low quality RCT)
	3a	Systematic review of case-control studies
C	3b	Individual case-control study
	4	Case series (and poor-quality cohort and case-control studies)
D	5	Expert opinion

RCT: randomized controlled trial.

agreement. Each voting score was assigned to one of three groups: disagreement (1~3), neutrality (4~6), and agreement (7~9). Consensus was defined as $\geq 75\%$ of participants scoring within the 7~9 range (agreement).

A second vote was performed after disclosing the additional information of previous voting results, including the mean score and proportion of agreement.

RESULTS

Bathing and basic skin care

Basic skin care, including bathing, represents a first strategy to maintain a good skin barrier and prevent and eliminate more severe infections, ultimately resulting in the normalization of immunologic responses and inflammation¹. Bathing can provide hydration of the skin and removal of scale, crust, and irritants such as sweat and allergens. The application of moisturizer soon after bathing is crucial for the further maintenance of hydration, because water easily evaporates from the skin, resulting in a higher transepidermal water loss⁸.

The recommendations for bathing are summarized in Table 2^{2,4,9-13}. Generally, a maximum bathing frequency of once per day is recommended². Strongly scrubbing with a towel is not recommended⁹. The proper duration of bathing is a short period of time (e.g., 5~10 min)^{2,10}, as some experimental studies have revealed that significantly longer exposure to water can disrupt the structural integrity of the skin barrier¹⁴⁻¹⁶. Warm or lukewarm water (27°C to 30°C) is recommended as the avoidance of temperature extremes is established in the management of AD¹⁷. There are very limited data about the usefulness of bathwater additives in the treatment of AD.

AD skin is vulnerable to increased skin surface pH, which has various effects on barrier function, desquamation of corneocytes, induction of inflammation, secretion of lamellar bodies, and antimicrobial defense¹⁸⁻²¹. Nonsoap cleansers (e.g., syndets, aqueous solutions), which have a neutral or low pH and are less allergenic, nonirritating, and

fragrance-free, are recommended. Soap-based cleansers, which have a high pH and contain surfactants, should be avoided, because they can cause dry skin, irritation, and contact dermatitis¹¹⁻¹³. Antiseptic-containing cleansers are not recommended due to the limited duration of action of antiseptics and limited clinical data regarding their effectiveness³. Although one RCT provided evidence for the effectiveness of a bleach bath to control moderate to severe AD infections (2b, B)²²⁻²⁶, the use of a bleach bath in the treatment of AD failed to achieve a consensus among Korean experts. Elimination of the belief that natural ingredients in cleansers or emollients are better is necessary. "Natural" does not mean "safe"; sometimes, these natural ingredients may have a higher risk of producing contact dermatitis.

Gentle drying after bathing (a soft-pat dry with a towel and the avoidance of rubbing) is recommended²⁷. After bathing and soft-pat drying, the application of moisturizer is recommended.

Avoidance of exacerbating factors

Recognition of exacerbating or triggering factors is an indispensable component of the personalized avoidance strategies in patients with AD, and these recommendations are summarized in Table 3^{4,5,28-37}. Such factors may differ according to age, environment, and individual social and daily lifestyles. In addition to climate and pollution, other known AD-exacerbating factors include clothing, the presence of house dust mites (HDMs) in the home, cosmetics, certain foods, dietary changes, physiological stressors (infections, sweat, etc.), and emotional stress³⁸. One recent multicenter, cross-sectional, epidemiologic study including 125 adults and 116 children with moderate to severe AD found that the factors most commonly perceived by patients as triggers of AD flares were perfumes and personal hygiene products (44% of adults, 34.5% of children), followed by articles of clothing, presence of HDMs, sudden changes in temperature, and stress. The foods most frequently perceived as triggers were sweets (3.88%), sea-

Table 2. Expert consensus recommendations for bathing and basic skin care

Recommendation	Level of evidence	Recommendation strength	Mean agreement score (range)	% of respondents (agreement score ≥ 7) (n=39)	Reference
Bathing with warm or lukewarm water (27°C~30°C) for a short period of time (e.g., 5~10 min) is recommended.	3b	B	7.5 (1~9)	92.3%	2, 4, 9, 10
Strong scrubbing with a towel is not recommended.	4	C	8.6 (5~9)	100%	9
Non-soap cleansers (syndets, aqueous solutions) that are neutral to acidic pH, hypoallergenic, non-irritant and fragrance-free are recommended.	4	C	7.8 (5~9)	92.3%	11~13

Table 3. Expert consensus recommendations for avoidance of exacerbating factors

Recommendation	Level of evidence	Recommendation strength	Mean agreement score (range)	% of respondents (agreement score ≥ 7) (n = 39)	Reference
Controlling the environment and daily vacuuming of mattresses over time significantly reduces house dust mite allergens.	2b	B	7.6 (1~9)	87.2%	28~35
The proper diagnosis of contact dermatitis using a patch test and other tools to confirm true immunoglobulin E-mediated allergies must be undertaken to avoid the specific contact allergen.	5	D	7.8 (6~9)	92.3%	4, 5
A specific-food-free diet (especially for infants or toddlers) should only be considered when allergy to the specific food trigger is identified based on proper procedures, including a food diary and allergy test by a specialist.	2b	B	7.9 (7~9)	92.3%	4, 5, 36, 37
Smooth clothing and avoidance of irritating fabrics and fibers and tightening garments are preferred.	5	D	8.2 (5~9)	94.9%	4, 5
Clothes which induce perspiration must be avoided, for the reason that sweating is an important source and triggering factor for atopic dermatitis.	5	D	8.3 (5~9)	97.4%	4, 5
Nail trimming is helpful for the prevention of viscous cycles.	5	D	8.2 (4~9)	92.3%	4, 5
Maintaining the proper temperature and humidity in an indoor environment is important to prevent sweating or excess dryness.	5	D	8.4 (7~9)	100%	4, 5
The avoidance of perfumes and personal hygiene and cosmetic products containing solvents, such as formaldehyde, and preservatives, such as paraben can be recommended particular to the individuals.	5	D	7.6 (2~9)	84.6%	4, 5

food (2.33%), and eggs (2.33%) among adults and eggs (7.63%) and fish (3.05%) among children.

In the second half of childhood and in adulthood, the most common airborne allergens exacerbating AD are derived from HDM species. In more than 90% of Korean homes, the level of exposure to HDMs is clinically remarkable. More than 40% of patients with AD are sensitized to HDMs³⁹. The severity of AD is related to indoor concentrations of HDMs in children without sensitization to HDM, and this concentration likely acts as a nonspecific irritant as well as an allergen⁴⁰. Avoidance of HDMs is an effective method that can be used to control AD exacerbation^{28-32,41}. At 25°C and 75% relative humidity, HDMs can grow well and their antigen concentrations can accumulate^{33,34}. Controlling the environment and vacuuming mattresses daily can significantly decrease one's level of exposure to HDMs³⁵.

Allergens should be determined by assessing clinical symptoms and laboratory test results. The proper diagnosis of contact dermatitis using patch testing and other tools to confirm true immunoglobulin E (IgE)-mediated allergies must be undertaken to avoid specific contact with the al-

lergen^{3-5,38}.

To diagnose a food allergy, clinical symptoms or signs after suspected food allergen intake or exposure must be reproducible, as broad-panel allergy testing unrelated to a clinical history of a reaction to certain foods should be avoided. The National Institute of Allergy and Infectious Diseases Food Allergy Expert Panel advocates food allergy testing only in cases of children younger than 5 years of age with moderate to severe AD and treatment resistance despite proper management and topical therapy and/or consistent episodes of an immediate allergic reaction after eating a specific food^{36,37}. Food diaries are useful for this purpose. If IgE-mediated food allergy is suspected, a diet eliminating the candidate food allergen for 4~6 weeks is recommended. If patients responded to the elimination diet, an oral food challenge should be done to confirm the causal relationship of food intake and AD lesions. Consultation with a dietitian is recommended for advice on suitable avoidance and alternatives^{3,27}.

Wearing soft-textured clothing and avoiding rough-textured fabrics and tight garments are preferred⁴². Although wearing silk fabric may be helpful, it is not clear whether

silk is superior to cotton^{43,44}. One recent meta-analysis failed to show the effectiveness of the use of functional textiles in AD treatment⁴⁵. Another study indicated that residual laundry detergent in clothes is an aggravating factor of winter xerosis⁴⁶. Water softening using an ion-exchange method provided no additional benefit to usual care⁴⁷. There is a paucity of well-controlled studies about the effects of environmental modification on AD. General consensus recommendations include the avoidance of mechanical and chemical irritants (such as wool, acids, and bleaches) and organic solvents (such as formaldehyde and toluene).

Education and psychosocial support

Aggravation due to mental stress can be easily identified in AD patients, and minimizing such stress can be helpful in controlling the disease^{28,48-50}. Psychotherapeutic approaches and behavior therapy can be considered to manage individual emotional factors that trigger AD, such as viscous itch-scratch cycles, comorbidity with anxiety and depression, and low quality of life^{4,51}.

Patient and parent education is effective in the management of AD⁵²⁻⁵⁵ and should aim to provide information about the clinical characteristics of AD (etiology, clinical manifestations, and disease course in layperson language), aggravating and relieving factors, self-management, and improving coping skills. Psychological and psychosomatic interventions are necessary and important tools of educational programs.

A multidisciplinary team (e.g., doctors, nurses, psychologists, and dieticians) approach is recommended (1a, A)⁵⁶. There is evidence that a systematic educational program considering the factor of age substantially improves AD severity scores⁵³. Workshops and educational sessions led by a doctor, nurse, or other health care professional⁵⁷, as well as live video or practicing interventions, can be beneficial to patients by improving their knowledge of AD and

the use of bathing, skin clearing, and moisturizers and other topical treatments (2b, B)⁴. Recommendations are summarized in Table 4^{28,48-50,52-55}.

Moisturizer

AD patients have very dry skin and defective skin barrier function. Regular use of moisturizer is a basic therapy for the management of AD. Recommendations for moisturizer use are summarized in Table 5^{4,5,9,58-67}. Mild AD can be improved by the appropriate use of moisturizer. Moisturizer application should also be maintained in patients with moderate to severe AD, which also requires topical or systemic anti-inflammatory treatment during acute flares to induce remission^{58,59}. Data from RCTs show that moisturizers have a long- and short-term steroid-sparing effect in mild to moderate AD and in preventing AD flares⁶⁰⁻⁶³. The antipruritic effect of certain moisturizers in the treatment of AD has also been proven in RCTs⁶⁴. Some moisturizers have been found to restore a defective skin barrier while decreasing exposure to irritants and showing anti-inflammatory and antimicrobial effects^{62,65,66}. The Barrier Enhancement for Eczema Prevention trial, a large-scale RCT on the effectiveness of intensive moisturizer therapy in early life to prevent AD and/or allergic reactions or reduce disease severity, is underway with encouraging results in a pilot study^{68,69}.

Although no clinical trials have studied the proper amount or frequency of moisturizer use in AD patients, moisturizer should be used at least twice daily, and more frequently during acute flare-ups. Adult patients with AD should use approximately 250 g or more of moisturizer per week^{4,67} and apply it to their whole body, regardless of the presence of lesions, since barrier defects and subclinical inflammation may also be present on lesion-free skin. The recommendation is to use moisturizer after taking a bath while the skin is still moist (within 3 min). During acute flare-ups, moisturizer should be used more

Table 4. Expert consensus recommendations for education and psychosocial support

Recommendation	Level of evidence	Recommendation strength	Mean agreement score (range)	% of respondents (agreement score ≥ 7) (n = 39)	Reference
Aggravation due to mental stress can be easily identified in patients, and attempts to minimize stress can be helpful to control AD.	3b	B	7.5 (5~9)	84.6%	28, 48~50
Parental education leads to more effective AD management.	2a, 2b	B	8.1 (5~9)	94.9%	53, 54
Psychological and psychosomatic interventions are an essential and helpful part of educational programs.	1a	A	7.3 (3~9)	79.5%	52~55

AD: atopic dermatitis.

Table 5. Expert consensus recommendations for moisturizer use

Recommendation	Level of evidence	Recommendation strength	Mean agreement score (range)	% of respondents (agreementscore ≥ 7) (n = 39)	Reference
Moisturizer should be used at least twice a day and should be more frequently used during acute flare-ups.	5	D	7.7 (4~9)	89.70%	4, 5, 9
AD adults should use a minimum of 250 g moisturizer per week.	4	C	7.4 (3~9)	82.10%	4, 67
Active treatment with topical corticosteroids is required first, and emollients should be steadily applied as a basic treatment regardless of flare-up status.	1b	A	8.1 (4~9)	94.90%	58, 59
The regular use of moisturizer has short- and long-term steroid-sparing effects and reduces the frequency of acute episodes.	1b	A	8.3 (6~9)	94.90%	60~63
Some moisturizers improve skin barrier function, decrease exposure to irritants, and have anti-inflammatory and antimicrobial effects.	4	C	7.6 (3~9)	82.10%	60~66
Moisturizers are effective in the relief of AD pruritus.	1a	A	7.6 (4~9)	84.60%	64

AD: atopic dermatitis.

Table 6. Expert consensus recommendations for TCSs

Recommendation	Level of evidence	Recommendation strength	Mean agreement score (range)	% of respondents (agreementscore ≥ 7) (n = 39)	Reference
1 FTU generally covers the surface area of two palms.	5	D	7.6 (5~9)	87.9%	77
TCS applications should be tapered if signs of inflammation disappear.	5	D	8.1 (6~9)	94.9%	4, 5
Proactive treatment with intermittent TCS therapy during long-term follow-up is helpful to reduce acute flares.	1a	A	7.8 (2~9)	92.3%	73, 74~79
TCSs can effectively relieve AD pruritus.	1a	A	7.6 (3~9)	89.7%	64
Education of children and their parents about the side effects of TCS and signs and symptoms of worsening eczema will lead to increased compliance.	5	D	7.8 (3~9)	97.4%	4

TCS: topical corticosteroid, FTU: fingertip unit, AD: atopic dermatitis.

frequently in conjunction with anti-inflammatory treatment and continued as maintenance therapy^{4,5,9}. Moisturizer treatment without the use of anti-inflammatory agents during acute flares may increase one's susceptibility to bacterial or viral infection⁷⁰. Conventional moisturizers contain occlusives, humectants, and emulsions. Newer classes of emollients designed to restore skin barrier defects include distinct ratios of lipids that resemble physiological compositions, such as ceramides:cholesterol:essential fatty acids in the ratios of 3:1:1 or 1:1:1. Although these new moisturizers are used worldwide as prescribed devices for the treatment of AD, only a few studies have demonstrated the effects of moisturizer on skin barrier function recovery and symptoms and signs of AD in a randomized and controlled manner^{59,62,65}.

A few moisturizer-containing substances with nonsteroidal

anti-inflammatory effects such as *N*-palmitoylethanolamine and sunflower seed oil have been developed, and some of them have been shown to lessen pruritus, xerosis, and inflammation and have steroid-sparing effects in a small number of controlled studies⁶⁰⁻⁶⁶.

Various types of moisturizer are available as creams, ointments, oils, gels, or lotions. Ointment or oily cream-type moisturizers, rather than lotions, are suitable for AD patients. However, some patients may not like these formulas because they feel greasy. At bedtime, lotion or aqueous cream-type moisturizers are desirable. In winter, higher lipid contents are preferable.

Because moisturizers including proteinaceous antigens or haptens may induce an allergic reaction, it is not desirable to use them in children younger than 2 years⁷¹.

An over-the-counter moisturizer with a petrolatum-base

was proven to be as effective as prescribed moisturizers in the treatment of children with mild to moderate AD in an RCT⁷², which suggests the cost-effectiveness of moisturizer treatment is a factor in selecting a moisturizer. Because adherence to moisturizer usage is key to the successful treatment of AD, patient preferences and tolerances should be considered when selecting a moisturizer to enhance adherence to the therapy.

Topical corticosteroids

Topical corticosteroids (TCSs) are important anti-inflammatory drugs for managing AD, especially during acute

Table 7. The potency of topical corticosteroids

Potency	Generic name
Class 1 (superpotent)	Clobetasol propionate 0.05%
	Halobetasol propionate 0.05%
	Diflorasone diacetate 0.05%
	Diflucortolone valerate 0.3%
Class 2 (potent)	Betamethasone dipropionate 0.05%
	Mometasone furoate 0.1%
	Halcinonide 0.1%
	Fluocinonide 0.05%
Class 3 (potent, upper/ midstrength)	Desoximetasone 0.25%, 0.05%
	Amcinonide 0.1%
	Betamethasone dipropionate 0.05%
	Betamethasone valerate 0.1%
Class 4 (midstrength)	Difluprednate 0.05%
	Desoximetasone 0.25%
	Mometasone furoate 0.1%
	Methylprednisolone aceponate 0.1%
Class 5 (lower midstrength)	Triamcinolone acetonide 0.1%
	Fluocinolone acetonide 0.025%
	Budesonide 0.025%
	Desoximetasone 0.05%
	Fluticasone propionate 0.05%
	Hydrocortisone butyrate 0.1%
	Hydrocortisone valerate 0.2%
Class 6 (mild strength)	Fluocinolone acetonide 0.025%
	Betamethasone valerate 0.05%
	Prednicarbate 0.25%
	Clobetasol butyrate 0.05%
Class 7 (least potent)	Prednisolone valeoroacetate 0.3%
	Alclometasone dipropionate 0.05%
Class 7 (least potent)	Desonide 0.05%
	Hydrocortisone 2.5%, 1%
	Dexamethasone 0.1%
	Flumethasone pivalate 0.02%
	Flucortin butylester 0.75%
	Prednisolone acetate
Prednisolone valeroacetate	
Hydrocortisone butyrate propionate	

Modified from Ference and Last (Am Fam Physician 2009;79:135-140)⁷⁶.

flares. TCS recommendations are summarized in Table 6^{4,5,64,73-79}. TCSs significantly improve AD lesions compared to placebo^{73,74}. Data from a meta-analysis of RCTs showed that TCSs are effective in the relief of AD pruritus⁶³ (relative risk = 0.66, $p < 0.001$) and have a significant effect in reducing *Staphylococcus* colonization⁷⁵.

TCSs are classified according to their potency (Table 7)⁷⁶. Most TCSs are enough strong to be used only once daily⁷⁷. The fingertip unit (FTU) is commonly suggested, as it has been found that the amount of TCS from the distal skin crease to the tip of an adult patient's index finger is equivalent to approximately 0.5 g TCS. Using 1 FTU of TCS, applying the amount on the surface area of the two palms of the patient is appropriate (Fig. 1)⁷⁸.

Application of TCSs should be tapered if signs of inflammation disappear⁷⁹. Proactive treatment with TCS therapy (e.g., once- or twice-weekly application) to areas known to commonly relapse in the maintenance period may help to reduce acute flares^{73,74,80}. Schmitt et al.⁸⁰ concluded in their systematic review that long-term (40-week) proactive therapy with TCS did not result in skin atrophy and telangiectasia or systemic side effects, such as adrenal suppression, and can be safely used during the AD maintenance period.

On skin with coexistent infections, TCSs have been widely used along with systemic or topical antibiotics. However, a review by Cochrane did not find any additional benefit from the concomitant use of antibiotics and TCS com-

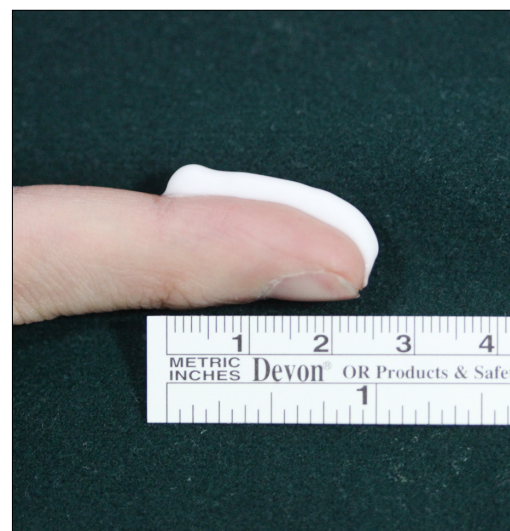


Fig. 1. The fingertip unit (FTU) method is used in to determine the amount of topical corticosteroids (TCS) or calcineurin inhibitors to apply. The amount from the distal skin crease to the tip of an adult patient's index finger is equivalent to approximately 0.5 g TCS. 1 FTU generally covers the surface area of two palms.

pared to the use of TCS alone for AD treatment⁸¹. Combination therapy with a topical calcineurin inhibitor (TCI) did not have a synergistic effect in one study⁸², but it did in others^{83,84}.

Local side effects of TCS include steroid acne, flushing, skin atrophy, hypertrichosis, striae, telangiectasia, and allergic contact dermatitis, which may occur occasionally in the treated area⁸⁵; however, these side effects can be resolved with discontinuation or appropriate treatment. The risk of cataract or glaucoma development when TCS is applied to the periorbital area is uncertain. Systemic side effects are extremely rare, but they have been reported. Children have a greater chance of developing adrenal suppression, since they have a relatively greater body surface area-to-weight ratio and a higher systemic absorption. Routine screening tests for systemic side effects of TCSs are not required.

Potent TCSs can be used in the following amounts to avoid systemic and local side effects: 15 g/month in infants, 30 g/month in children, and 60~90 g/month in adults⁴. For infants and children, the elderly, or pregnant woman, mild to moderate TCSs can be used instead of more potent varieties of TCSs⁸⁶.

For pregnant women, potent or very potent TCSs should be chosen as a second-line option for as short a time as possible, and relevant obstetric care is needed, as TCSs increase the possibility of fetal growth restriction. It has been proven that the use of ≤200 g TCSs during the pregnancy period is not associated with fetal growth restriction⁸⁶.

A meta-analysis of RCTs recommended that superpotent TCSs be used only once daily, because this is as beneficial as twice-daily application⁸⁷.

Steroid phobia is widespread and can cause treatment failure among AD patients. To increase treatment compliance, it is important to educate children and their parents about the side effects of TCSs and signs and symptoms of worsening eczema^{4,5,9}.

Wet-wrap therapy

Wet-wrap therapy (WWT) can be helpful to quickly reduce AD severity, and it is often useful for acute flares and/or recalcitrant disease⁸⁸⁻⁹⁷. For better results and to reduce the risk of infection, WWT use must be based on proper education and can be administered on an outpatient or inpatient basis^{88,94}. A recent RCT demonstrated that a 4-week proactive schedule of WWT with diluted TCSs was superior to WWT with moisturizer in children with severe AD⁸⁹. The first step of WWT is to apply topical agents to the lesion. Next, the skin is covered with a wet inner layer of tubular bandages followed by a dry outer layer. Gauze or a cotton suit can be used as an alternative. The WWT can be maintained from several hours to a day at a time (an illustration of how to use WWT can be found online at http://www.atopy.re.kr/academy/news_02.asp). Further RCTs and clinical studies are needed to determine the ideal topical agents to use as well as duration, covering agent, and frequency. WWT recommendations are summarized in Table 8^{87,88,93,94}.

Topical calcineurin inhibitors

TCIs exert anti-inflammatory effects by blocking calcineurin-dependent T-cell activation, which leads to the release of proinflammatory cytokines and mediators of AD². TCIs used to treat AD include pimecrolimus cream (1%) and tacrolimus ointment (0.03% in children and 0.1% in adults), which have been proven to help improve and control AD in both children and adults^{5,98,99}. Recommendations for TCI use are summarized in Table 9^{4,98-105}.

A meta-analysis showed that tacrolimus 0.1% and mid-potency TCS hydrocortisone butyrate 0.1% are comparable in the efficacy, whereas the efficacy of tacrolimus 0.03% is inferior to hydrocortisone butyrate 0.1% but superior to low-potency TCS hydrocortisone acetate 1%⁹⁸. Pimecrolimus cream has been considered less efficacious than mid-to high-potency TCS, although there are no studies comparing pimecrolimus and TCS³. Tacrolimus is approved for

Table 8. Expert consensus recommendations for WWT

Recommendation	Level of evidence	Recommendation strength	Mean agreement score (range)	% of respondents (agreementscore ≥7) (n=39)	Reference
For lesions with exudates, WWT can increase the efficacy of topical corticosteroids.	1b	A	7.9 (6~9)	92.3%	88, 89
WWT with diluted corticosteroids or emollient with moderate to severe AD without risk of infection can be used for the quick reduction of AD severity.	2b	B	7.2 (5~9)	75.8%	93, 94

WWT: wet wrap therapy, AD: atopic dermatitis.

Table 9. Expert consensus recommendations for TCIs

Recommendation	Level of evidence	Recommendation strength	Mean agreement score (range)	% of respondents (agreement score ≥ 7) (n = 39)	Reference
TCIs have a significant effect in the short-term and long-term treatment of AD.	1b	A	8.1 (3~9)	97.4%	98~100
Proactive therapy with tacrolimus ointment is effective to reduce the occurrence of flares.	1b	A	7.7 (3~9)	89.7%	4, 99~101
Long-term use of TCIs does not increase the risk of malignancy.	2a	B	7.5 (3~9)	89.7%	105
None of the TCI induces skin atrophy.	1a	A	8.3 (6~9)	100%	103, 104

TCl: topical calcineurin inhibitor, AD: atopic dermatitis.

the treatment of moderate to severe AD, and pimecrolimus is approved for mild to moderate AD^{5,99}.

Korean dermatologists strongly recommend the use of TCIs for both active and proactive treatment of AD. The 2012 European guidelines recommend TCIs as a first-line therapy in the short- and long-term treatment of AD⁵. Proactive therapy with tacrolimus ointment could reduce the frequency of relapse⁴. The 2013 Asian-Pacific guidelines recommend TCIs as a second-line therapy for both acute AD and long-term proactive treatment. The 2014 American guidelines also recommend the use of TCIs for the active and proactive treatment of AD².

In a proactive regimen, TCI application 2 to 3 times a week on frequent recurrent sites can effectively reduce relapses⁴. After the acute flare is controlled, long-term management with topical tacrolimus significantly decreased the number of episodes compared with vehicle and increased the time to relapse and number of flare-free days^{100,101}. The efficacy and safety of topical tacrolimus 0.1% use for 6 months to 5 years is well documented in children with moderate to severe AD⁵. In adults with mild to moderate AD, pimecrolimus cream 1.0% also reduced the occurrence of flares¹⁰².

TCl has no risk of cutaneous atrophy, and it has few harmful effects on collagen synthesis^{103,104}. This favors the use of TCIs over TCS in thin-skinned areas such as the eyelid, perioral region, genitalia, axillary area, or inguinal fold, as well as for long-term management. TCl has steroid-sparing effects and that can be maintained during long-term use (up to 12 months)^{2,106}.

The most common local side effects of TCIs are stinging and burning sensations. Irritation is seen more frequently with TCIs than with TCSs but tends to decrease with repeated applications or when patients are shortly pretreated with TCSs^{107,108}. Physicians should provide this information to patients when TCIs are first prescribed to prevent premature discontinuation of TCIs. Infections with vi-

rus such as herpes simplex, eczema herpeticum, or molluscum contagiosum have been reported during TCI use¹⁰⁹⁻¹¹¹, but these studies failed to prove a causal relationship^{106,112}.

Topical tacrolimus and pimecrolimus have been approved for adults and children older than 2 years^{5,109}. However, topical tacrolimus 0.03% and pimecrolimus can be safely used in children younger than 2 years, even in infants¹⁰⁵. There are several case reports of lymphoma and skin cancer in patients treated with TCIs. However, there is currently no scientific evidence of an increased risk of malignancy due to TCI use¹¹³.

Routine blood monitoring of tacrolimus or pimecrolimus levels is not needed in AD patients, as systemic absorption after topical application of both TCIs is negligible^{114,115}.

Topical antipruritic agents

1) Topical anesthetics

Local anesthetics are sometimes used to achieve a temporary antipruritic effect. The antipruritic effect of local anesthetics was reported in patients with AD¹¹⁶; however, controlled clinical studies are lacking (4, C).

The routine use of topical anesthetics in AD is not recommended as an antipruritic therapy⁴.

2) Topical cannabinoid receptor agonists

Topical cannabinoid receptor agonists have been reported to have antipruritic and analgesic effects (4, C)¹¹⁷. However, further studies are needed to recommend their routine use.

3) Topical capsaicin

Capsaicin is the major constituent of hot chili peppers and has an antipruritic effect in various dermatoses. Some previous studies reported a reduction of itching in AD patients after use of topical capsaicin (4, C)^{118,119}. However,

no controlled study has been performed to date, and further studies are needed.

4) Topical doxepin

A controlled study documented that an antipruritic effect of doxepin 5% cream in AD patients (2b, B)¹²⁰. However, RCTs on the use of doxepin in AD are lacking.

5) Topical mast cell stabilizers

Tryptase and histamine, released by mast cells, lead to the induction of pruritus in AD. Some studies have reported the usefulness of mast cell stabilizers in AD (2b, B)¹²¹. However, further controlled trials are needed.

Other topical anti-inflammatory agents

1) Phosphodiesterase inhibitors

Phosphodiesterase-4 (PDE4) inhibitors produce anti-inflammatory effects by inhibiting the secretion of various cytokines from inflammatory cells such as lymphocytes and monocytes. Roflumilast, an oral PDE4 inhibitor, is used to treat moderate chronic obstructive pulmonary disease, and apremilast, which has a relatively low incidence of adverse effects, is approved by the US Food and Drug Administration in the treatment of active psoriatic arthritis¹²². However, systemic side effects such as nausea and vomiting are relatively common with these drugs. Studies on the development of topical PDE4 inhibitors are underway, although thorough study and experimentation will be required before clinical use^{123,124}. Nevertheless, recent studies have demonstrated the clinical efficacy and safety of topical PDE4 inhibitors, which will likely be used as topical anti-inflammatory agents in the treatment of AD.

DISCUSSION

Because AD chronically relapses, the active participation of patients in basic skin care, avoidance of aggravating factors, and appropriate application of topical medicines is important to achieve an effective treatment outcome²⁻⁵. Patient education and psychological intervention are closely related to the prevention of recurrence and shortening of disease duration⁴⁸⁻⁵⁵.

This report provides the level of evidence, recommendation strength, and average agreement scores of an AD expert panel regarding the general management and topical treatment of AD. Most recommendations regarding environmental control are based on both expert consensus and personal experience. The assessment of aggravating factors and their avoidance should be personalized. Indiscriminate food restriction is unnecessary and can lead to

malnutrition and growth problems in children with AD^{3-5,9}. Food allergies should be determined by elimination and challenge tests of suspected food while considering both medical history and results of laboratory tests.

Education can lead to greater improvement in AD management by increasing patient adherence to therapy^{53,54}. It is necessary to provide specific and individualized information, such as how to use moisturizer or anti-inflammatory agents and the adequate amount to apply, according to each patient's disease course. Moisturizer itself has steroid-sparing and antipruritic effects. The regular use of moisturizer lowers the number of relapse episodes⁶⁰⁻⁶⁶. However, moisturizer cannot replace topical anti-inflammatory treatment. During flare-ups, active topical anti-inflammatory treatment should be primarily considered. "1 FTU" is a useful tool that can be used to explain to AD patients the adequate amount of topical anti-inflammatory agent to apply⁷⁸. Even after the AD lesions disappear, patients with frequent relapsing disease courses require proactive treatment with TCSs or TCIs^{3-5,9}.

Steroid phobia is widespread due to the inconsistency of information regarding its usage¹²⁵. If a caregiver has mistrust about TCS use, this can lead to a missed opportunity of timely anti-inflammatory intervention and increased flare-ups that require more intensive treatment. Many patients tend stop using TCSs because they confuse the side effects of TCS use with signs and symptoms of worsening AD, which leads to treatment failure. Specific education is needed regarding effective and safe long-term TCS usage, TCS side effects, and signs and symptoms of worsening eczema to increase patient adherence to TCS therapy and achieve successful AD management^{4,5,9}. Education and psychosocial support is essential, especially for AD patients with frequent relapse episodes^{4,51}.

WWT can increase the efficacy of TCSs or moisturizer and facilitate a faster recovery of AD lesions⁸⁸⁻⁹⁷. To achieve better results and reduce the risk of infection, WWT use must be based on proper education on an ambulatory or inpatient basis.

Evidence supporting the routine use of topical antipruritic drugs is lacking in the treatment of AD. However, in patients with refractory pruritus, the use of topical antipruritic agents can be considered.

This report might require supplementary statements or a revision of recommendations based on upcoming publications and results of the many ongoing clinical studies of AD. These guidelines provided evidence- and experience-based recommendations and will be helpful for physicians and AD patients in improving treatment outcome and quality of life.

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