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REVIEW ARTICLE

Clinical practice guidelines for the diagnosis and management of atopic dermatitis

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Abstract

Atopic dermatitis (AD), a chronic, relapsing dermatitis, is characterized by dry and pruritus skin in patients with a personal or family history of atopy. It affects up to 20% of children and 1-3% of adults in most countries worldwide, and leads to significant treatment costs and morbidity. These guidelines are developed in accordance with evidence-based publications and expert opinions. Following simple algorithms, the guidelines aim to assist adult and pediatric physicians in the better care of patients with AD. As with other diseases, there have been several diagnosis criteria proposed over time. Nonetheless, the classical Hanifin and Rajka criterion with no pathognomonic laboratory biomarkers is still the most widely used worldwide for the diagnosis of AD. The management of AD must be considered case by case to provide suitable care for each patient. Basic therapy is focused on avoiding specific/unspecific provoking factors and hydrating skin. Topical anti-inflammatory treatments such as glucocorticoids and calcineurin inhibitors are suggested for disease flare, and proactive therapy is best for long-term control. Other therapies, including antimicrobial agents, systemic antihistamines, systemic anti-inflammatory agents, immunotherapy, phototherapy, and psychotherapy, are reviewed in these guidelines. Crisaborole, a new topical phosphodiesterase 4 inhibitor, can be used twice daily in AD patients over three months old. Dupilumab, a biological drug for patients with moderate-to-severe AD, may be considered in patients with no improvement from other systemic treatments.

Key words: atopic dermatitis, Thai, guidelines, diagnosis, management

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Abbreviations

AD	atopic dermatitis
AH	antihistamines
ASIT	allergen-specific immunotherapy
CDLQI	Children's Dermatology Life Quality Index
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
FDA	Food and Drug Administration
IgE	immunoglobulin E
RCT	randomized controlled trial
SCORAD	Scoring of Atopic Dermatitis
SPT	skin prick test
S. aureus	*Staphylococcus aureus*
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
UV	ultraviolet

Introduction

These clinical practice guidelines were a joint project among the Dermatological Society of Thailand; the Allergy, Asthma, and Immunology Association of Thailand; and the Pediatric Dermatological Society of Thailand. This collaboration aimed to develop guidelines that would provide effective practical advice to general practitioners and physicians in different specialties for caring patients with atopic dermatitis.

Definition

Atopic dermatitis (AD), also called atopic eczema, is a chronic, relapsing-remitting skin disease commonly found in childhood. Intense itching is the predominant symptom, while excessive scratching can cause excoriation and lichenification of the skin.[1] The personal and family history regarding allergies such as allergic rhinitis, and/or asthma is related to AD.

Despite several proposed criteria, the classic Hanifin and Rajka criterion with no pathognomonic laboratory biomarkers is still the most commonly used set for the diagnosis of AD.[2,3] AD can be classified as intrinsic" (non-immunoglobulin E-associated) and "extrinsic" (immunoglobulin E-associated) AD. The latter is associated with an elevated level of total or allergen-specific immunoglobulin (Ig) E in serum or an IgE-mediated sensitization from skin prick test (SPT). Some patients with extrinsic AD also have a personal or family history of allergies such as allergic rhinitis, and/or asthma.[4]

Epidemiology

According to reports by the International Study of Asthma and Allergies in Childhood, phases I and III, allergic diseases are very common in Thailand.[5] The prevalence of eczema symptoms in children aged 6-7 and 13-14 in this country has been 16.7% and 9.6%, respectively.[5] A cross-sectional, multi centers survey was carried out in Bangkok in 2017 and 2018 by the Global Asthma Network. This study showed that the cumulative and 12-month-period prevalence rates of eczema among all children in Bangkok were 15.8% and 14.2%, respectively.[6]

Regarding the prevalence of eczema in adult patients, studies in 1975 and 1997 reported a prevalence of 15.2% and 9.4%, respectively, among university students in Bangkok.[7,8] In 2003, a study conducted at Naresuan University in the north of Thailand revealed an eczema prevalence of 15% among the students at that school.[9] In East Asia, adult-onset AD was reported to be 21.4% among eczema patients.[10] To date, there has been no study reporting the prevalence of adult-onset AD in Thailand.

Clinical features of atopic dermatitis

The clinical phenotype of AD is distinct and it changes with age during the course of the disease. The eczematous lesions can be manifested in acute (oozing, crusted, eroded vesicles, or papules on erythematous plaques), subacute (scaly erythematous papules or plaques), and chronic (lichenified, slightly pigmented, or excoriated plaques) features, with pruritus as a hallmark. There are three clinically distinct stages of AD - infancy, childhood, and adolescence/adulthood.

Diagnostic approaches to atopic dermatitis

The diagnosis of AD is based on one's history and clinical manifestations, such as morphology and the distribution of skin lesions. In 1980, major and minor criteria for a diagnosis of AD were proposed by Hanifin and Rajka (**Table 1**).[11] Three of four major criteria and three of 23 minor criteria are required for a diagnosis of AD. However, a large number of criteria are widely used in clinical practice.

Table 1. Features to be considered in the diagnosis of patients with atopic dermatitis by Hanifin & Rajka (1980)

Major features (3 of 4 required)
1. Pruritus
2. Typical morphology and distribution
2.1 Flexural lichenification or linearity in adults
2.2 Facial and extensor involvement in infants and children
3. Chronic or chronically-relapsing dermatitis
4. Personal or family history of atopy, such as asthma, allergic rhinitis, atopic dermatitis
Minor features (3 of 23 required)
1. Xerosis
2. Ichthyosis/palmar hyperlinearity/keratosis pilaris
3. Immediate (type 1) skin test reactivity
4. Elevated serum immunoglobulin E
5. Early age of onset
6. Tendency toward cutaneous infections (*S. aureus* and Herpes simplex virus)/impaired, cell-mediated immunity

Table 1. (Continued)

Minor features (3 of 23 required) (Continued)
7. Tendency toward non-specific hand or foot dermatitis
8. Nipple eczema
9. Chelitis
10. Recurrent conjunctivitis
11. Dennie-Morgan infraorbital fold
12. Keratoconus
13. Anterior subcapsular cataract
14. Orbital darkening
15. Facial pallor/facial erythema
16. Pityriasis alba
17. Anterior neck fold
18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Course influence by environmental/emotional factors
23. White dermographism/delayed blanch

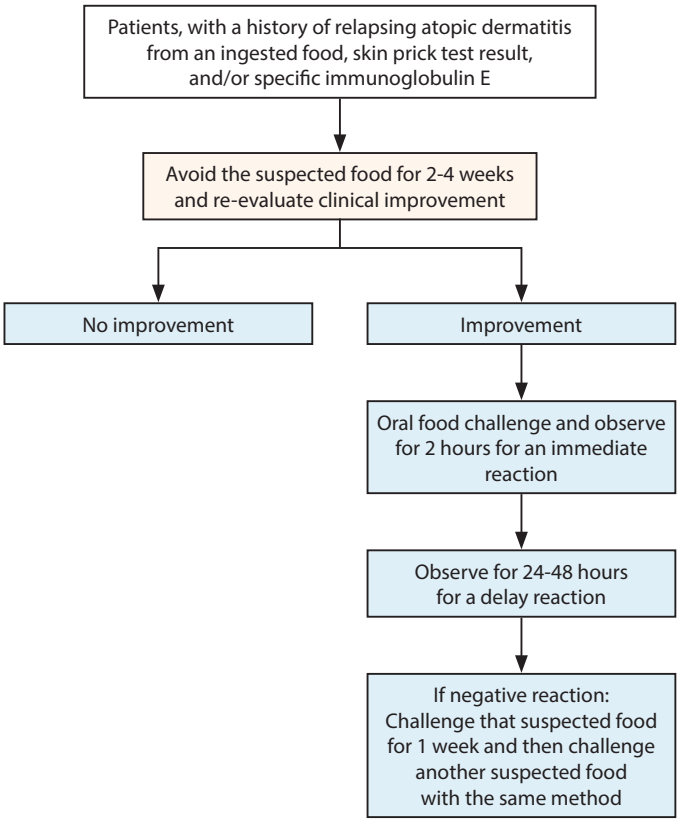

Figure 1. Diagnostic algorithm of oral food challenge test in patients with atopic dermatitis

AD is diagnosed according to its clinical presentation, rather than from the results of diagnostic testing. However, the use of percutaneous skin or *in vitro* tests, ranging from SPT to specific IgE to relevant allergens, can be used to identify potentially allergic triggering factors.[2,12] Similarly, patch testing may be used as a screening tool in patients with AD who have recalcitrant disease or those with suspected allergic contact dermatitis.[13]

Clinicians have to be aware that food allergies relating to AD is commonly found in children under five years of age. The Food Allergy Expert Panel suggests that a food allergy test may be considered in children with moderate-to-severe AD who do not respond well after proper treatment.[12] It should be noted that one-third of children with AD who test positive for food allergies do not have clinical symptoms after sensitization. Thus, an oral food challenge test (elimination and re-challenge) should be performed on children to confirm the diagnosis of food-induced eczema in patients with AD in order to avoid unnecessary food avoidance. **Figure 1** demonstrates diagnostic algorithm for food allergy with oral food challenge test in patients with persistent moderate to severe AD.[14]

Guidelines for the management of patients with AD (Figure 2, 3, and Table 2)[3,15-21]

The aims of AD treatment are to reduce symptoms (pruritus and dermatitis), prevent exacerbations, and optimize treatment to prevent therapeutic risks.

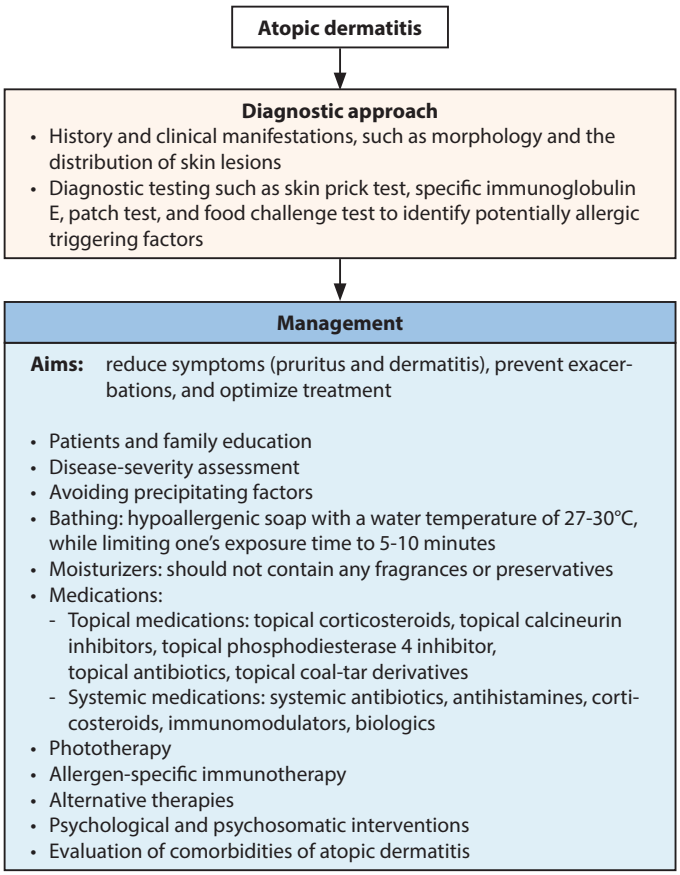

Figure 2. Diagnostic approach and management of atopic dermatitis

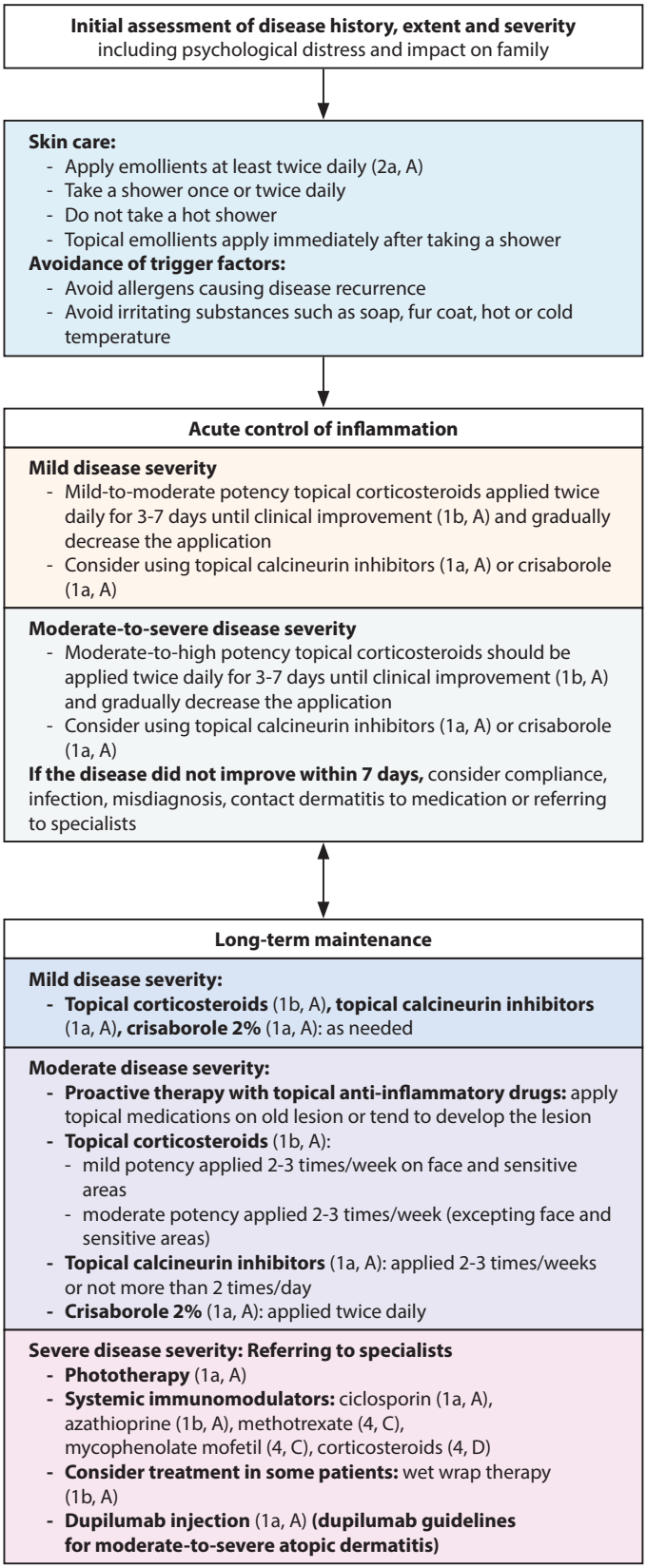

Figure 3. Algorithm for the treatment of atopic dermatitis

Table 2. Level of evidence and strength of recommendation of treatments.

Treatment	Level of evidence	Strength of recommendation
Moisturizer		
- A regular use of emollients should be helpful for treatment.	2a	A
Topical corticosteroids		
- Topical corticosteroids, with an improved risk/benefit ratio, are recommended in AD.	1b	A
- Diluted topical corticosteroids may be used under wet wrap for a short-term period in acute AD to increase their efficacy.	1b	A
- Proactive therapy, e.g. twice-weekly application in the long-term follow-up, may help to reduce relapses.	1b	A
Topical calcineurin inhibitors		
- Topical calcineurin inhibitors have a significant effect, compared to vehicles in short-term and long-term treatment of AD.	1a	A
- Topical calcineurin inhibitors are especially suitable for sensitive skin areas (the face, intertriginous areas, and anogenital area).	1a	A
- Proactive therapy with twice-weekly application of topical calcineurin inhibitors may reduce relapses.	1a	A
- Topical calcineurin inhibitors (tacrolimus and pimecrolimus) have been shown to be safe and effective for children under two years of age.	1b	A
Topical phosphodiesterase 4 inhibitor		
- Topical phosphodiesterase 4 inhibitor has been shown to be effective for children over three months of age.	1a	A
Antimicrobial therapy		
- A short-term treatment with systemic antibiotics may be beneficial if the skin is obviously superinfected with bacteria.	2b	B
Antihistamines		
- There is not enough evidence to support the general use of both first- and second-generation H_1-AH for pruritus in AD.	1b	A
- The first generation of the sedative AH may allow for a better sleep in acute situations with exacerbations of eczema.	4	D

Table 2. (Continued)

Treatment	Level of evidence	Strength of recommendation
Systemic corticosteroids		
- Short-term (up to two weeks) treatment with systemic corticosteroids may be an option in treating an acute flare in exceptional cases of AD. The daily dose should be adjusted to and should not exceed 0.5-1 mg/kg/day	4	D
Systemic immunomodulators		
- Azathioprine	1b	A
- Ciclosporin		
- Ciclosporin may be used in chronic, severe cases of AD in adults.	1a	A
- Ciclosporin may be used in children and adolescent patients showing a refractory or severe course of disease.	2b	B
- Methotrexate	4	C
- Mycophenolate mofetil	4	C
Biologic agents		
- Dupilumab	1a	A
- Omalizumab, rituximab, alefacept	4	C
Phototherapy		
- Narrowband ultraviolet B is a more effective treatment than broadband ultraviolet B.	1a	A
- Ultraviolet A1 is effective in the acute phase.	1a	A
Allergen-specific immunotherapy	1a	A
Psychological and psychosomatic interventions	1a	A

1. Patients and family education

Patients and their family should be educated in order to understand the course of the disease and to know how to properly manage themselves to control their symptoms and prevent an exacerbation of the disease. Interdisciplinary educational programs by dermatologists, allergists, pediatricians, psychologists, and nursing staff help to significantly improve their patients' quality of life.

2. Disease-severity assessment

The Eczema Area and Severity Index (EASI); the Rajka and Lengeland: Grading of severity of atopic dermatitis; and the Scoring of Atopic Dermatitis (SCORAD) are the most common scales for assessing disease severity in AD patients. These scales identify condition as mild, moderate, or severe. As regards the psychological impact, the Thai Dermatology Life Quality Index (DLQI)[22] and the Thai Children's Dermatology Life Quality Index (CDLQI)[23] can be used. A disease-severity assessment is crucial in terms of treatment planning and further investigations.

3. Avoiding precipitating factors

Many factors can contribute to the exacerbation of AD, such as infections, temperature, humidity, irritants, emotional stress, food allergens, and aeroallergens. Physicians should identify those aggravating factors and then advise patients to avoid them. Wisuthsarewong et al.[24] reported the most common aggravating factors in 560 patients with AD aged less than 15 years were dry skin, seasonal change (especially summer and winter), dust, foods, furry pets, emotional change, furry toys, cigarette smoke, and skin infection, respectively.

In vitro testing for IgE antibodies or SPT can be used to identify potential allergens. However, as mentioned previously, specific IgE and SPT can produce a false positive result. In patients who are suspected of having a food allergy, relying on the results of specific IgE or SPT to food allergens may cause an unnecessary food avoidance. Food avoidance without a prior test can lead to malnutrition in children and a poorer quality of life and lower immunity. Thus, food allergy should be confirmed by doing an oral food challenge test before giving the patient any advice.[12] Anaphylaxis has been reported in some patients with AD who stopped eating a particular food and then returned to it. The mechanism was believed to be a loss of desensitization.

4. Management of AD

4.1 General recommendations for patients with AD

Patients should avoid aggravating factors and substances such as rough cloth textures, heavy sun exposure, hot temperatures, steam and hot vapors, body scrubbing, and scratching. Patients are encouraged to wear loose clothing and to keep their nails short and clean.

4.*2 Bathing*

To avoid epidermal dehydration from bathing, it's best to use a hypoallergenic soap and a water temperature of 27-30°C, while limiting one's exposure time to 5-10 minutes. After gently drying the skin, topical emollients should be applied immediately to slightly humid skin.[3] Bathing with antiseptic soaps or solutions should be avoided, as they can cause skin irritation.

Some soaps have added food ingredients such as hydrolyzed wheat protein, rice starch, and rice bran, which aim to improve the skin-barrier function.[25] These soaps should be used with caution in patients with AD, as several reports suggest that exposure to highly environmental food allergens increase the risk of epicutaneous food sensitization, particularly in patients with a skin-barrier dysfunction.[26]

Some studies have reported the benefits of body washes containing diluted sodium hypochlorite (0.006%). They indicate that bathing the skin lesions with sodium hypochlorite 0.006% for 5-10 minutes two to three times a week and then washing them with water can reduce the disease severity and the need for topical corticosteroids (TCS) or antibiotics,

especially in patients with a recurrent skin infection.[27,28] However, a systematic review and meta-analysis showed no significant differences compared to using a water bath alone. Therefore, such body washes should be performed under a physician's recommendation and care.[29]

4.3 Moisturizers (2a, A)

Using a skin moisturizer is a first step and can be an effective treatment. It can keep the skin hydrated for 2-6 hours, depending on the type of moisturizer. The amount that should be used on newborns, infants, young children, and adults ranges from 100, 150-200, to 250 g/week, respectively.[30] Moisturizers for patients with AD should not contain any fragrance or preservatives. It is recommended to use plain moisturizers such as cold cream, cream base, 3-10% urea, or petrolatum twice daily. Regularly using a moisturizer can decrease the use of TCS and thus prevent an exacerbation of the disease.

The frequent use of prescribed and over-the-counter preparations containing peanut[31] and oatmeal[32] have been reported to potentially cause sensitization in children and to lead to food allergies.[21]

Whether an emollient should be applied before or after a topical drug depends on factors such as skin status, the vehicle types of moisturizers, the patient's convenience, and the physician's opinion. Generally, moisturizers (in a preparation of cream or lotion) should be applied first, followed by topical drugs on the inflamed skin. On the other hand, if a moisturizer is an ointment, the ointment should be applied after a topical drug on the inflamed skin. A certain period of time should lapse before applying one after another.[2]

4.4 Topical corticosteroids (TCS) (1b, A)

Corticosteroids are the mainstay and effective treatment for patients with AD. A mild-to-moderate potency of TCS should be applied twice daily on the inflamed skin during acute exacerbation, and then discontinued during disease remission. A proactive therapy is a long-term, intermittent application of anti-inflammatory agents to the previously affected skin, along with an ongoing emollient treatment of the unaffected skin. Studies have shown that the use of fluticasone propionate cream,[33] methylprednisolone aceponate cream,[33] and mometasone fuorate cream[34] twice weekly on the previously affected skin significantly decreased the risk of AD relapses, compared to using a placebo in a proactive strategy. Another technique that can increase the efficacy of TCS is an occlusion. Wet-wrap therapy has been reported to be safe and effective in children with severe or refractory AD.[35,36]

TCS can be associated with significant adverse effects when used chronically. The local side effects of TCS are mainly skin changes such as skin atrophy, telangiectasias, purpura, hypopigmentation, acne, rosacea, striae distensae, and hypertrichosis. Systemic side effects may occur from extensive-area use or from the long-term use of TCS. These include glaucoma, cataract, adrenal insufficiency, Cushing's syndrome, and growth retardation.[3]

4.*5 Topical calcineurin inhibitors (TCI) (1a, A)*

TCI, as a second-line therapy in treating AD, can be used over TCS in sensitive skin areas such as the face and intertriginous and anogenital sites, especially for topical long-term use.[3] It is an effective treatment for the prevention, maintenance, and reduction of AD exacerbation. Typically, a twice-daily application is recommended during AD flares, followed by once daily during improvement, and then it should be discontinued during remission. However, a proactive strategy, such as applying TCI twice weekly on the previously inflamed skin, can also reduce disease exacerbation and improve the quality of life in such patients.[37]

a. Tacrolimus

Tacrolimus can be used for any severity of AD. Tacrolimus 0.03% ointment is recommended in children aged 2-16, while tacrolimus 0.1% ointment is recommended in patients aged over 16 years. Tacrolimus 0.1% showed no difference in potency when compared with moderate-to-potent TCS,[38] but it was more potent than tacrolimus 0.03% and pimecrolimus 1%. Tacrolimus 0.03% was superior to mild corticosteroids and pimecrolimus 1%.[38] The efficacy and safety of tacrolimus ointment have also been reported in children under aged two years,[38] as have the intermittent or continuous long-term use as a monotherapy for up to four years.[38]

b. Pimecrolimus

Pimecrolimus 1% is effective for mild-to-moderate AD on the face and other sensitive skin areas.[39] Pimecrolimus 1% had similar efficacy to low-to-medium potent TCS.[39] In Thailand, it is recommended to use on infants over three months old. The safety of the long-term use of pimecrolimus as a monotherapy up to five years has been reported.

4.6 Topical phosphodiesterase 4 inhibitor (1a, A)

Crisaborole 2% ointment has been approved by the EU and US FDA for patients with mild-to-moderate AD. It acts by inhibiting phosphodiesterase 4 and reducing inflammatory cytokines, resulting in a significant decrease in inflammatory skin and pruritic symptoms. It can be used twice daily in mild-to-moderate AD patients aged over three months. Pain, burning, and stinging sensations have been reported regarding application sites in some patients.[40,41] Currently, it is not available in Thailand. It is expected to be available in 2021.

4.7 Antimicrobial therapy (2b, B)

Antimicrobial therapy can be used in AD patients with a superimposed bacterial infection. Suitable topical or systemic antibiotics should act against *Staphylococcus aureus* (*S. aureus*) and *Streptococcus pyogenes*. The optimal duration of treatment is 1-2 weeks. Adding topical antibiotics to topical steroids can decrease the amount of *S. aureus* from the skin.[42] The prolonged use of antibiotics is not recommended. The 2010 Cochrane review of randomized controlled trials (RCTs) reported a lack of quality trials to support the use of antimicrobial and antiseptic preparations for AD treatment. Antibiotics are not recommended for the treatment of AD that does not have superimposed bacterial infection.[43]

4.8 Topical coal-tar derivatives

Currently, there is no adequate data to support the clinical efficacy of coal tar in patients with AD.[17] However, it can control an exacerbation of AD in some patients.

4.9 Systemic antihistamines

Although there is no adequate data to prove the efficacy of systemic antihistamines (AHs) in patients with AD, such drugs are widely used in acute flares against pruritus. Sedating AHs may be helpful for the reduction of itches and sleepiness during disease flares.[21] It should be noted that topical AHs are not recommended because there are no adequate evidences of topical AHs to control AD symptoms. Moreover, topical AHs can cause allergic or photoallergic contact dermatitis.[17]

4.10 Systemic corticosteroids (4, D)

For patients with an uncontrolled disease with TCS, oral prednisolone or intramuscular injections of triamcinolone can be administered as a short-term treatment. Oral prednisolone at a dose of 0.5-1 mg/kg/day for up to maximum 2 weeks can be given. Long-term use, especially in children, is not recommended, due to side effects such as growth restriction and hormonal suppression.[21]

4.11 Systemic immunomodulators

a. Ciclosporin (1a, A)

Ciclosporin is suggested as a first-line, short-term treatment for moderate-to-severe AD.[44] A higher dosage of 5 mg/kg/day yields a better response and is more efficacious than a lower dosage.[45] Nonetheless, the lowest dose that can control the disease is recommended to minimize its side effects. Major concerned side effects are hypertension and renal impairment. Thus, treatment should be started with a dosage of 3 mg/kg/day, and then slightly decreased at a dose of 0.5-1 mg/kg/day every two weeks.[15] In addition, a combination of ciclosporin with ultraviolet (UV) therapy is not recommended. UV protection is strongly suggested during ciclosporin use.[15]

b. Azathioprine (1b, A)

Azathioprine is recommended as a second-line treatment for moderate-to-severe AD patients who are unresponsive or who develop adverse effects from ciclosporin.[45] The suggested initial dose is 50 mg/day in adult, and this dosage should be titrated according to the clinical response and its possible side effects. The recommended dosages of azathioprine in adults and children are 1-3 mg/kg/day and 1-2 mg/kg/day, respectively. It should not be used in combination with UV therapy.[15]

c. Methotrexate (4, C)

Methotrexate is recommended as a third-line treatment for adults with severe AD. The starting doses are 5-15 mg/week in adults and 10-15 mg/m^2/week in children. The dosage should be increased weekly in steps of 2.5-5 mg/week, not exceeding 25 mg/week.[15] As methotrexate is teratogenic, men and women of childbearing potential must use effective contraception during therapy.[45]

d. Mycophenolate mofetil (4, C)

There are some reports on the efficacy of mycophenolate mofetil in patients with refractory AD who are unresponsive or develop adverse effects to ciclosporin. The recommended dosages in children are 600-1200 mg/m^2/day, divided twice daily, and not exceeding 2 g/day in adult.[15]

4.12 Biologics

a. Dupilumab (1a, A)

Dupilumab is a fully human monoclonal antibody that blocks the common α-chain of interleukin-4 and interleukin-13 receptors. It has been approved as a first-line treatment by the EU and US FDA in 2017 for patients aged over six years with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when systemic therapies are not advisable.[15]

For the treatment of Thai patients aged 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. It can be used with or without TCS. The algorithm of dupilumab treatment is illustrated in **Figure 4**.

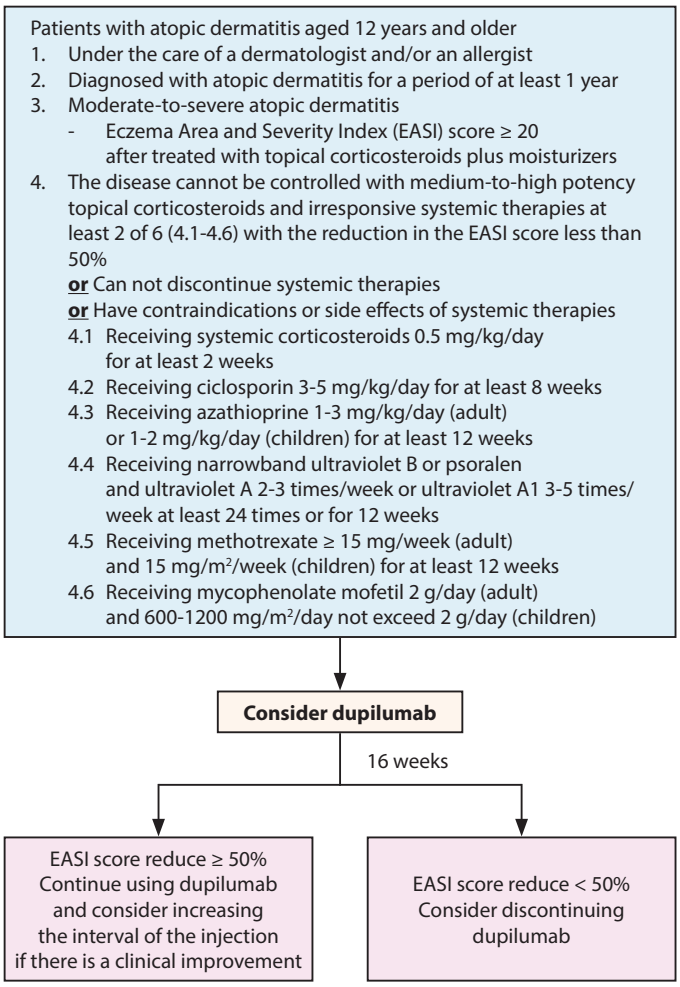

Figure 4. Dupilumab guidelines for moderate-to-severe atopic dermatitis

b. Omalizumab, rituximab or ustekinumab (4, C)

No adequate evidence is available to support the injection of omalizumab, rituximab, or ustekinumab.[15] They are not approved by the US FDA for patients with moderate-to-severe AD. These agents may be considered in patients who are unresponsive to other therapies.

4.***13 Phototherapy (1b, A)***

Phototherapy is an option for adult patients and children aged 12 and older.[16]

4.14 Allergen-specific immunotherapy (ASIT) (1a, A)

ASIT is a potentially effective treatment modality for IgE-mediated AD. A subcutaneous administration using house-dust mites is most commonly employed for ASIT in AD.[46-48] A study by Chu et al.[49] reported that patients with AD can benefit from ASIT with cat and/or dog dander, as confirmed in allergic asthma and allergic rhinitis. It can be administered sublingually or subcutaneously. Some studies have shown that ASIT can reduce the disease's severity and improve the quality of life of patients with AD.[50] ASIT therapy should be conducted under specialists' care.

4.15 Alternative therapies

Vitamin supplements may play an effective role in the treatment of AD. Vitamin D supplementation, especially in AD patients with a low level of serum vitamin D, can reduce AD symptoms. Nevertheless, the best therapeutic dose of vitamin D supplement in AD remains unknown.[51] Benefits from other supplements, such as hempseed probiotics, selenium, pyridoxine, fish oil, docosahexaenoic acid, zinc, and evening primrose oil, are uncertain.[52] Thus, vitamin supplementation is not routinely recommended for use in AD patients.[15]

4.16 Quality of life and emotional stress (1a, A)

AD has a significant effect on the quality of life of patients and their families. Stress and emotional factors can exacerbate the disease.[12] Psychosomatic counseling, psychotherapeutic approaches, behavioral-therapy techniques, autogenetic training, and relaxation techniques are beneficial in the management of patients with AD.[15]

5. Prevention

5.1 Primary prevention

There is evidence that exclusive breastfeeding for three to four months reduces the risk of developing AD in children up to two years old.[53] Apart from breastfeeding, feeding high-risk infants (with a positive family history of atopy) with a hydrolyzed cow's milk formula either in extensive or partial forms, rather than cow's milk formula, may reduce the risk of AD.[54-57] For high-risk infants whose mother has insufficient breast milk, the use of partially hydrolyzed whey formulas and extensively hydrolyzed casein formulas, rather than cow's milk, may reduce the risk of developing AD in children from infancy to aged six years.[57] There is no evidence that dietary avoidance during pregnancy and breast-feeding in high-risk mothers can reduce the risk to children of developing AD. Moreover, diet restrictions in pregnant women can lead to maternal or fetal nutritional deficiencies, or both.[58]

Probiotic supplementation to prevent the risk of developing AD in children has been intensively studied. A systematic review and meta-analysis of 28 studies (27 RCTs and one non-RCT) has demonstrated that probiotic supplementation during the prenatal and/or postnatal (early-life) period can reduce the risk of developing AD in infants and older children.[59] Other studies have indicated that probiotic supplementation can decrease the risk of AD, but it did not reduce the risk of developing wheezing and/or asthma.[60] Although probiotic supplementation has been intensively studied, how to supplement it (the types and quantities of microorganisms, the dose, and the duration) still needs to be investigated. Thus, to date, there is still no agreed-upon recommendation regarding supplementing probiotics to reduce the risk of AD in children.

There has been recent evidence that applying moisturizers as soon as possible after birth (within a maximum of three weeks) and continuing this until aged six months can reduce the risk of developing AD at aged six months.[61] Applying moisturizers on a regular basis during the first six months of life seems to be a cost-effective strategy to prevent AD.[62] One RCT demonstrated that applying ceramide-dominant emollient on a regular basis (two times/day) from the first week of life up to 26 and 32 weeks resulting in a significant reduction in food sensitization in children aged one year old.[63]

On the other hand, Cochrane Database showed that applying moisturizers during the first year of life in healthy infant and infant with high-risk AD was not effective in preventing eczema by one to two years of age, and probably increase risk of skin infection. However, there was a heterogeneity of those studies that affected the certainty of evidence.[64]

5.2 Secondary preventions

Secondary preventions are meant to avoid possible allergens and precipitating factors.

Specialists' referral

Consulting with AD specialists, such as allergists and dermatologists, is suggested for those with a doubtful diagnosis of AD, those with refractory to first-line therapy, a severity of AD with significant dysfunction, a suspicious immune deficiency, and/or food allergies or an allergy to other allergens.

Comorbidities of AD

AD is associated with atopic and non-atopic comorbidities. Atopic diseases, particularly allergic rhinitis, asthma, food allergy, and atopy-associated eye disorders, are not only the common comorbidities but one of the diagnostic criteria for AD. Non-atopic comorbidities involve cutaneous infection, sleep disturbance, anxiety, and depression. Mechanisms of interaction between AD and its comorbidities could be multidirectional. Therefore, worsening of which could have a negative impact on others. Thorough assessment and proper management of those comorbidities are crucial for improving overall treatment outcomes.[65]

Patients with AD have an increased risk of developing allergic rhinitis and asthma. A study of Thai children demonstrated that 40% of those with AD developed other allergic diseases. Ten percent of them developed asthma and 36% developed allergic rhinitis.[24]

Patients with AD had an increased prevalence of acute urticaria. One study reported that 16.2% of patients with AD had such hives.[66] Early-onset AD was also reported to be a risk factor in developing chronic spontaneous urticaria.[67] On the other hand, 50.2% of patients with acute urticaria were reported to have AD, asthma, or allergic rhinitis.[68]

Prognosis

AD is the first step in the atopic march, followed by allergic rhinitis and asthma. These problems will increase among patients who have a family history of atopy. Generally, the onset of AD is found during infancy. Fifty percent and 85% of patients will develop the disease during their first or their fifth year of life, respectively. A study focused on Thai children with AD showed that 73% of them developed the disease in their first two years, with a mild degree of severity (30.9%,) a moderate degree (51.8%), and a severe degree (17.3%). Factors that influenced the severity of the disease included an early age of onset, a history of cow's milk allergy, and a history of food allergy.[24]

Patients with age onset of AD during the first two years of life tend to have a higher rate of disease remission than those who develop the disease during adolescence or adulthood. Patients with a high degree of disease severity tend to have the disease persistently until adulthood.[69] A systematic review and meta-analysis have revealed that 80% of patients had disease remission at the age of eight, and fewer than 5% of patients continued to have the disease for 20 years after being diagnosed.[69]

A study of Thai children with AD showed that those with mild, moderate, and severe AD would experience disease remission at the median age of 3.4, 3.5, and 7.0 years, respectively. Two-thirds of patients with AD would have disease remission within their first five years.[70]

Conclusion

AD is a common chronic skin disease that can severely affect physical and psychological aspects of the patients. Patients and family education, disease assessment, identifying aggravating factors, treating comorbidities, and medicines optimization are all important to provide the suitable care for patients with AD. New systemic targeted therapies such as dupilumab are effective, safe, and licensed treatment option with potential ocular side effects. Other biologicals targeting key pathways in the atopic immune response and Janus kinase inhibitors are among emerging treatment options. Further studies with a long-term follow up are recommended to investigate the impact on AD-associated comorbidities, in addition to skin manifestations, and more targeted, or even personalized, treatment approaches for AD.

Conflict of interest disclosure

The authors declare that they have no conflicts of interest in this manuscript.

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Appendix I. Grades of evidence and strength of recommendations for these clinical practice guidelines

Grades of evidence	
1a	Meta-analysis of RCTs
1b	Single RCT
2a	Systematic review of cohort studies
2b	Single cohort study and RCTs of limited quality
3a	Systematic review of case-control studies
3b	Single case-control study
4	Case series, case-cohort series, or cohort studies of limited quality, expert committee opinions

Abbreviations: RCT, randomized controlled trial

Classification of strength of recommendation

Recommendation strength	Evidence grade
A	1a, 1b
B	2a, 2b, 3a, 3b
C	4
D	Expert committee opinion