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Original Article

Taiwanese Dermatological Association consensus for the management of atopic dermatitis: A 2020 update

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Background/Purpose: Atopic dermatitis (AD) is a chronic inflammatory disease commonly seen in children and increasingly recognized in adults. With recent advances in the therapeutic development for AD, the Taiwanese Dermatological Association (TDA) established a committee to update the consensus for AD management in Taiwan. This report describes the 2020 updated consensus for the management of AD.

Methods: A panel of 11 core members was convened to review and discuss aspects of AD management and draft recommendation during the first two meetings. The 2015 TDA consensus and the 2017 European guideline, along with recent peer-reviewed articles, serve as the foundation for the update. In the third meeting, AD expert dermatologists selected on a national scale were invited to vote on the final statements. A total of 27 dermatologists attended the final meeting. The consensus was achieved when ratings of 7–9 (out of a total score of 9) accounted for $\geq$ 75% of the total votes.

Abbreviations: NB-UVB, narrow-band ultraviolet B; UVA, ultraviolet A.

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Results: Consensus was achieved on the therapeutic options for AD by lines of treatment. A treatment algorithm was presented to illustrate the place of each modality in terms of basic care, acute disease control, and maintenance therapy. Special considerations for the pediatric population, as well as for women during pregnancy and lactation, are discussed.
Conclusion: Topical corticosteroids with long-term emollient-based therapies remain the cornerstone of AD treatment. Systemic treatments are indicated when topical therapies and phototherapy fail to control the disease. The recent approval of dupilumab and emerging targeted therapies are expected to bring significant clinical benefit for patients whose disease is inadequately managed by existing options.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder with increasing prevalence in Taiwan and many other regions in the world.[1,2] Based on data obtained from both local and international investigations, the prevalence of AD symptoms in Taiwan has increased significantly in the past few decades, ranging from 4.1% to 6.7% among selected cohorts.[1] Although commonly known as a childhood disease, about 1 in 4 adults with AD reported symptom onset during adulthood. Different from childhood AD, adult-onset AD is associated with higher rates of dermatitis involving the face, hands, and the feet but lower rates of that involving flexural lesions and other AD phenotypes.[3] Food allergy and exposure to cigarette smoking are known to be associated with the risk of adult-onset AD.[4,5] Besides the signs and symptoms of the disease, AD is associated with considerable comorbidities, spanning from allergic rhinitis/asthma to non-atopic conditions, including psychiatric, immune-related, and cardio-metabolic diseases.[2] AD is the leading cause of non-fatal disease burden of skin conditions and has a significant impact on physical, emotional, social and economic levels.[2]

The etiology of AD is likely multifactorial, involving complex interactions between genetic susceptibility and environmental risk factors.[6] Over the past decades, studies have highlighted the primary pathogenic role of immune dysregulation and skin barrier deficiency in AD.[2,7] Cutaneous inflammation, either primary or secondary, further attenuates skin barrier proteins which results in a positive feed-forward and feedback loop between the epithelium and the immune system that perpetually drives AD pathology.[8] Altogether, AD is likely driven by barrier dysfunction (increased trans-epidermal water loss [TEWL] and decreased barrier lipids), together with abnormal immune activation of type 2 T helper cells (Th2) and varying degrees of Th22, Th1, and possibly Th17 cells among different disease subtypes and ethnic groups.[7,9,10]

The diagnosis of AD remains clinical and relies on features listed in the diagnostic criteria such as the Hanifin and Rajka criteria and the American Academy of Dermatology Consensus Criteria.[11,12] Currently, no standardized scoring system exists for AD severity assessment. Eczema Area and Severity Index (EASI) and SCORing AD (SCORAD) are validated and used as outcome measures in clinical trials, with EASI being the preferred method.[13] For clinical practice, Investigator Global Assessment (IGA), Patient-Oriented Eczema Measure (POEM), and itch intensity may be more feasible.[13] Cutpoints of severity strata were proposed for EASI: 1 for clear/almost clear and mild, 6—7 for mild and moderate, 21—23 for moderate and severe.[13] In addition, clinical features for considering moderate-to-severe AD were proposed by US experts, including body surface area $\geq$10%, individual lesions with moderate-to-severe features, areas that are highly visible or functionally important, and significantly impaired quality-of-life (QoL).[14]

In 2015, the Taiwanese Dermatological Association (TDA) published its consensus for the management of AD.[1] Following recent advances in disease knowledge and therapeutic development,[6] there is a need to update the consensus to provide optimal quality of care for patients with AD in Taiwan. Three consensus meetings were held on April 28th, July 14th, and October 5th of 2019. This paper presented the updated consensus for the management of AD in Taiwan. Special considerations for the management in the pediatric population, as well as women during pregnancy and lactation, were also discussed.

Methods

Consensus panel

The core committee consisted of 11 dermatologists with expertise in the management of AD. The 2015 TDA consensus and the 2017 European guidelines for AD management served as the basis of the updated version.[1,15,16] Recent peer-reviewed articles and clinical experience were also taken into account in revising the recommendations. During the first two meetings, the core committee drafted, discussed, and approved the updated statements. For the third meeting, additional 19 dermatologists recommended by established institutions across Taiwan were invited to vote on the final statements. A total of 27 dermatologists attended the final meeting.

Consensus voting system

The experts who convened at the third consensus meeting cast their votes for each proposed recommendations by

rating their approval on the 9-point scale, with 9 being strongly agreed. Items with ratings of 7–9 accounted for ≥75% of the total votes were regarded as achieving consensus. If any item were not approved, potential amendments were proposed and voted in a *Yes-No* manner, and the amendment was regarded as approved if > 50% voted *Yes*. The amended item was then voted on the 9-point scale for final consensus. If the amended item was not approved (>50% voted *No*) or the final consensus was not achieved (ratings of 7–9 accounted for < 75% of the total votes), a different amendment was proposed and voted upon until final consensus was achieved.

Results

The consensus recommendations for the management of AD in lines of treatment were approved (ratings 7–9) by 96% of the participants (Table 1). The degree of approval for each treatment modality and their respective recommendations were presented in the order listed in Table 1: emollients (100%, Table 2), topical corticosteroids (TCSs, 96.2%, Table 3), antihistamines (96.2%, Table 4), therapeutic patient education (100%, Table 5), topical calcineurin inhibitors (TCIs, 96.2%, Table 6), burst use of systemic corticosteroids (96.2%, Table 7), phototherapy (96%, Table 8), topical/systemic antibiotics (96.3%, Table 9), systemic immunomodulatory agents (100%, Table 10), antiseptics (92%, Table 11), and alternative medicine (88.5%, Table 12). The treatment algorithm is presented in Fig. 1 (100%).

Discussion

Emollients

AD is characterized by impaired skin barrier function resulting from the interplay between genetic and environmental factors. Emollients are essential in the management of AD (Table 2). They can provide hydration to the stratum corneum (humectants) and slow water evaporation (occlusives).[1] A 2017 Cochrane review found that emollients reduce the number of flares, prolong the time to flare, and decrease the need for TCSs. But no convincing evidence suggests one product is superior to another.[17] Recent randomized controlled trials (RCTs) also demonstrated regular use of emollient reduced disease severity, flares, and the need for TCS in children with mild-to-moderate AD.[18,19] Different preparations might be indicated based on the skin and environmental conditions, e.g., emollients containing higher lipids are suitable for dry skin in winter.[1,15] Patients should be advised on the adequate and appropriate use of emollients, as well as avoidance of potential irritants in some products. Wet wrap can be used along with topical therapies, and it will be addressed later in *Considerations in pediatric populations*.

Cleansing and bathing remove crust and bacteria while increase skin hydration. Classic soaps can cause skin dryness and irritation due to anionic surfactants and alkaline pH.[20] Instead, nonsoap-based cleansers containing synthetic detergents or surfactants provide mild cleansing and are better tolerated by patients with AD.[21] Emollients should be applied directly after bathing to prevent TEWL.[1,15] The temperature and duration of bathing are not standardized, but warm water for 5–10 min is generally acceptable.[15,22] Use of emollient bath additives was not shown to provide meaningful benefit for children with AD beyond standard care.[23] Another recent study showed steroid-sparing and skin microbiome improving effects of an investigational lipid-containing body wash compared with the synthetic bar, but found no significant difference in AD severity improvement between groups.[24] Hydrotherapy with some thermal spring water, as revealed from some cohort studies, may have some benefit for patients with mild-to-moderate AD,[16,25] and their therapeutic effects on the skin microbial diversity and immune regulation have been reported.[25,26]

Topical corticosteroids

TCSs remain the first-line anti-inflammatory treatment for moderate-to-severe AD, and their efficacy has been well-established in adults and children (Table 3).[1,15] As a maintenance strategy, proactive application (e.g., intermittent or twice-weekly dosing) of TCSs plus emollient significantly reduced the risk of relapse for as long as 20 weeks.[1,15,27]

Numerous TCSs are available in a variety of potencies and galenic formulations.[1,15] Different bases are recommended depending on the skin condition, i.e., cream base for weepy/inflamed skin, ointment base for dry/lichenified skin, and lotion base for hair-bearing areas.[1] Patients should be instructed on the quantity and duration of the treatment (e.g., 1–2 weeks for acute flare) and appropriate tapering strategies after a substantial reduction in pruritus has been noted.[15] TCSs can be applied to active lesions, and prolong used under physician's supervision is also permitted. Retreatment may be required when relapses occur.

Potential side effects of TCSs include a variety of skin changes (i.e., atrophy, telangiectasias, striae, steroid acne, and rosacea), systemic absorption, and hypothalamic-pituitary-adrenal suppression. However, evidence suggested appropriate use of fluticasone propionate is not associated with changes in skin thickness and in serum cortisol.[1] Very potent TCSs (e.g., clobetasol propionate) may induce adrenal suppression even with just one application.[15] Skin infection with TCSs is less concerning, as evidence suggested eczema herpeticum was associated with untreated AD, and TCSs reduce *Staphylococcus aureus (S. aureus)* colonization in AD.[1,16] In adults, the development of cataracts or glaucoma was documented with systemic corticosteroid but not with TCSs.[15] Potent TCSs should be avoided on the face, and particularly on the eyelids, flexures, and genital area.[1]

Nonadherence to TCSs is associated with concern/fear of their side effects (TCS phobia or corticophobia).[28] In a large international study evaluating levels of corticophobia by the validated Topical Corticosteroid Phobia (TOPICOP) score, Taiwan is among the top three counties with the highest levels of corticophobia.[29] Recognizing this phenomenon and providing accurate information are necessary for improving medication adherence and treatment outcome.

Table 1 General overview of the Taiwanese Dermatological Association consensus in lines of treatment for atopic dermatitis (AD).

First Line Treatment
• Emollients
• Topical corticosteroids
• Antihistamines
• Therapeutic patient education
Second Line Treatment
• Topical calcineurin inhibitors
• Burst use of systemic corticosteroids
• Phototherapy
• Topical and systemic antibiotics
Third Line Treatment
• Systemic immunomodulatory agents
• Antiseptics
• Alternative medicine

Antihistamines

Antihistamines (H1 antagonists) have long been used for the management of pruritus associated with AD (Table 4). However, no convincing evidence to date supports the use of antihistamines for AD treatment.[30] Antihistamines may benefit AD patients with urticarial features or food-induced urticaria.[1,15] Physicians may use sedating antihistamines to help sleep in AD patients while recognizing the lack of high-level evidence and considering potential risks.[31] Non-sedating antihistamines (i.e., cetirizine, fexofenadine, or loratadine) generally have no or weak effects on pruritus, although they have a good long-term safety profile.[30] Cetirizine has been shown to reduce the duration of moderate-to-potent TCSs use in a subgroup of infants with severe AD.[1,16] Higher doses of cetirizine (20—40 mg) has an effect on pruritus attributed to sedation.[15] The use of topical antihistamines for the treatment of patients with AD is not recommended based on current clinical evidence, although animal studies have shown favorable effects of topical antihistamines on inflammation and barrier function.[32] The recent discovery of the role of H4-mediated inflammation and the clinically meaningful improvement of skin lesions of an H4 receptor antagonist in AD has shed light on the therapeutic potential of antihistamine treatment.[33]

Therapeutic patient education

Patient education has therapeutic effectiveness and is recommended for the management of AD.[1,16] The principles and components of the education are depicted in Table 5, and it should be delivered in layperson language.[1] Together with the patients and/or caregivers, the physician should set and review short- and long-term goals and discuss how to apply each treatment modality accordingly.

There are a variety of education delivery models, and age-related structured educational programs have the most evidence-based benefit in both children and adults.[1,16] A comprehensive patient education program can improve disease severity, help patients and caregivers to better cope with the disease and treatments.[1,16] Many tools are used in the education programs, but no evidence supports one tool is better than another.[16] Verbal and written information with practical demonstration could facilitate the learning process and lead to greater patient empowerment.[1] Treatment adherence is affected by corticophobia, adverse effects of topical treatments, children's lack of cooperation, and the time-consuming nature of the treatments. Addressing these factors could optimize treatment outcome and improve QoL.[1]

Table 2 Consensus recommendations for emollients.

1. Regular emollient therapy is an essential component in the management strategy of AD.
2. Emollients should be applied at least twice daily or as frequently as the skin gets dry depending on the climate, moisture, or the use of air conditioning.
3. Ensure adequate quantities are used.
4. Emollients may be used during active disease flares in conjunction with topical anti-inflammatory agents, and also as maintenance therapy.
5. Fragrances and preservatives in emollient may act as possible irritants.
6. The application of moisturizers should be an essential and 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.
7. 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.
8. Moisturizers should be applied soon after bathing to improve skin hydration while the skin is still moist in patients with AD.
9. If cleansers are required, limited use of nonsoap cleansers (that are neutral to low pH, hypoallergenic, and fragrance-free) is recommended.
10. 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 body of evidence.
11. Wet-wrap therapy with or without a topical corticosteroid may be used for patients with moderate-to-severe AD to decrease disease severity and water loss during flares.

Table 3 Consensus recommendations for topical corticosteroids (TCSs).

1. TCSs are recommended for AD-affected individuals who have failed to respond to good skin care and regular use of emollients alone. TCSs are effective and safe when used appropriately and under adequate supervision. TCSs should be used until skin flares are under control.
2. A variety of factors should be considered when choosing a particular TCS for the treatment of AD, including patient age, the location, severity and chronicity of the eczema, 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.
3. Twice-daily application of TCSs is generally recommended for the treatment of AD; however, evidence suggests that once-daily application of some TCSs[a] may be sufficient.
4. Appropriate quantities of TCSs to be used should be discussed with the patient.
5. TCSs can be applied to areas of broken skin (e.g. skin with scratch wounds, acute inflamed eczema with oozing or chronic eczema with fissures).
6. TCSs are not contraindicated in the presence of infection but the infection should be treated.
7. Proactive, intermittent use of TCSs as maintenance therapy (1 or 2 times/wk) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone.
8. 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 TCSs are used. Monitoring by physical examination for cutaneous side effects during long-term, potent TCSs use is recommended.
9. No specific monitoring for systemic side effects is routinely recommended for patients with AD.
10. Patient fear of side effects associated with the use of TCSs for AD should be recognized and addressed to improve adherence and avoid undertreatment.

[a] Fluticasone propionate 0.05% cream; mometasone furoate 0.1% cream.

Table 4 Consensus recommendations for antihistamines.

1. A subset of patients with a mixture of AD and dermographism, allergic rhinitis, and bronchial asthma may benefit from antihistamines.
2. Sedating antihistamines may be used short term, under supervision where itch of eczema causes sleep disturbance.
3. There is insufficient evidence to recommend the general use of antihistamines as part of the treatment of AD.
4. Short-term, intermittent use of sedating antihistamines may be beneficial in the setting of sleep loss secondary to itch, but should not be substituted for management of AD with topical therapies.
5. Nonsedating antihistamines are not recommended as a routine treatment for AD in the absence of urticaria or other atopic conditions such as rhinoconjunctivitis.
6. The use of topical antihistamines for the treatment of patients with AD is not recommended because of the risk of absorption and of contact dermatitis.

Table 5 Consensus recommendations for therapeutic patient education.

1. Disease nature.
2. Avoidance of irritants and allergens, including dietary recommendations for childhood AD.[15]
3. Treatment adherence should be emphasized at each consultation and should encompass the following:
   - Appropriate treatment doses.
   - Treatment application frequency.
   - How to step up or step down treatment.
   - Management of infected eczema.
   - Information should be tailored to suit patients' cultural practices regarding skin care and bathing.
   - Patients and caregivers should be informed that in patients with more pigmented skin, AD may temporarily cause the skin to lighten or darken.

Topical calcineurin inhibitors

Two TCIs, tacrolimus ointment and pimecrolimus cream, have been shown to have anti-inflammatory and immunomodulatory effects in AD treatment.[1,15] Both TCIs are approved for patients aged $\geq$2 years, and their efficacy have been demonstrated in clinical trials for short-term and long-term use (Table 6).[1,15] Twice-weekly application of tacrolimus ointment as proactive therapy has also been shown to prevent, delay and reduce disease relapse over 1 year.[1,15] While a previous meta-analysis indicated that application of the TCS, fluticasone propionate, might be more efficacious to prevent flare of AD than TCI (tacrolimus), a Cochrane systematic review found exactly the

Table 6 Consensus recommendations for topical calcineurin inhibitors (TCIs).

1. TCIs (tacrolimus and pimecrolimus) are recommended and effective for acute and chronic treatment, along with maintenance, in patients with AD, and are particularly useful in selected clinical situations, such as recalcitrance to steroids, sensitive areas (e.g., face, anogenital, and skin folds), steroid-induced atrophy, or long-term uninterrupted topical steroid used areas.
2. Do not use TCIs under occlusion as this may enhance percutaneous absorption and increase risk of immunosuppression, unless under physician's direction.
3. Proactive, intermittent use of tacrolimus ointment as maintenance therapy 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.
4. TCIs 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 TCIs application site reactions. Patients with AD should be counseled about the possibility of these reactions.
5. Routine blood monitoring of TCIs levels in patients with AD who are applying these agents is not recommended at this time.

Table 7 Consensus recommendations for burst use of systemic corticosteroids.

1. Although systemic steroids are used by some providers to treat AD because they rapidly improve clinical symptoms, caution is warranted to ensure their administration is time-limited and judicious.
2. Rebound flare and increased disease severity is a commonly observed phenomenon upon discontinuation of systemic steroids.
3. Systemic steroids may be considered for short-term (3—7 days) use in individual cases whereas other systemic or phototherapy regimens are being initiated and/or optimized.
4. Burst systemic steroids may be considered for individuals with acute flare-ups to achieve rapid and effective symptomatic control.
5. Long term systemic steroids should generally be avoided in patients with AD because the potential short- and long-term adverse effects largely outweigh the benefits.

Table 8 Consensus recommendations for phototherapy.

1. Phototherapy treatment of all forms should be under the guidance and ongoing supervision of a physician knowledgeable in phototherapy techniques.
2. The light modality chosen should be guided by factors such as availability, cost, patient skin type, skin cancer history, and patient use of photosensitizing medications.
3. Phototherapy can be used as maintenance therapy in patients with chronic disease.
4. Narrowband-UVB and UVA1 are the most frequently used efficacious regimens in patients with AD. Phototherapy with medium-dose UVA1 might be used to control acute flares while narrowband-UVB in the management of chronic AD.
5. Caution should be exercised in the treatment of patients with fair skin phenotype, and with prior personal or family history of cutaneous malignancy.

Table 9 Consensus recommendations for topical and systemic antibiotics.

1. Secondary infection should be suspected in patients with moderate-to-severe AD who have weeping dermatitis, folliculitis and overt clinical signs of infection, or who are not responding to first-line topical therapy.
2. Topical antibiotic therapy may be appropriate for localized areas of infection.
3. Systemic antibiotics are appropriate and can be recommended for use in patients with clinical evidence of bacterial infections in addition to standard and appropriate treatments for AD disease itself (which may include the concurrent use of topical corticosteroids). The use of systemic antibiotics in the treatment of non-infected AD is not recommended.
4. 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.

opposite, that "tacrolimus 0.1% ointment was better in its efficacy than low-potency TCSs, pimecrolimus 1%, and tacrolimus 0.03%.[34,35] Unlike corticosteroids, TCIs do not cause skin atrophy, and therefore are more suitable for long-term use and for applying in thin and sensitive skin regions such as the face, intertriginous sites, and anogenital area.[1,15,34]

The most common side effects of TCIs are transient burning and pruritus at the application sites during the first few days of application, particularly in patients with acute

Table 10 Consensus recommendations for systemic immunomodulatory agents.

1. Short-term systemic corticosteroids may be used to treat AD because they rapidly improve clinical symptoms. Caution is warranted to ensure their administration is time-limited and judicious.
2. Systemic immunomodulatory agents are indicated for the subset of AD patients in whom optimized topical regimens and/or phototherapy do not adequately control the signs and symptoms of disease, or in whom these treatment modalities are contraindicated. Systemic immunomodulatory agents may be indicated in patients who are corticosteroid dependent.
3. All immunomodulatory agents should be adjusted to the minimal effective dose once response is attained and sustained. Adjunctive therapies should be continued to use the lowest dose and duration of systemic agent possible.
4. Potential adverse effects are well documented for each immunomodulatory agent. Thus, patients receiving these systemic immunomodulatory agents should be monitored for such potential consequences.
5. Cyclosporine is effective and recommended as a treatment option for patients with AD refractory to conventional topical treatment.
6. Azathioprine is recommended as a systemic agent for the treatment of refractory AD.
7. Methotrexate is recommended as a systemic agent for the treatment of refractory AD. Folate supplementation is recommended during treatment with methotrexate.
8. Mycophenolate mofetil may be considered as an alternative, variably effective therapy for refractory AD.
9. Dupilumab is a TFDA approved biological agent for moderate-to-severe AD. It is recommended for whom topical treatment is not sufficient and other systemic treatment is not advisable.

Table 11 Consensus recommendations for antiseptics.

1. Topical antiseptics (e.g. triclosan, benzalkonium chloride, chlorhexidine) in bath emollients are popular choices, particularly for children, and can reduce staphylococcal colonization.
2. Bleach baths may be helpful particularly for maintenance in cases of moderate-to-severe AD with frequent bacterial infections.
3. There is less concern about the development of bacterial resistance with the use of dilute bleach relative to the use of topical and systemic antibiotics.
4. Topical hypochlorous acid is also available as an alternative to dilute bleach baths.
5. Antiseptic bath products may aggravate AD due to irritant or allergic contact dermatitis and removal of normal commensal organisms.
6. Antiseptic textiles may decrease skin colonization by *S. aureus*, but may not show better clinical benefits than standard treatment.

Table 12 Consensus recommendations for alternative medicine.

1. Patients and parents should be advised that complementary therapies have not undergone sufficient evaluation of efficacy or safety.
2. Clinicians should enquire about and encourage patients to share information about any complementary therapies that are being used.
3. Probiotics, prebiotics, or synbiotics may provide some benefits but are currently not recommended because of insufficient evidence of effectiveness.
4. The use of fish oils, zinc, vitamins (D, E, B6, and B12), and melatonin for AD treatment lacks sufficient evidence.
5. Patients should be warned of possible contamination of so-called natural therapies with steroid medication.
6. While traditional Chinese herbal medicine may be effective in the treatment of AD, to date, there is limited supporting evidence from well-designed studies.
7. Acupuncture is in lack of sufficient evidence to support its usage in the treatment of AD.

presentations.[15,34] These local symptoms are mild-to-moderate and more frequently seen with tacrolimus than pimecrolimus.[34] It may be beneficial for patients' compliance to adequately inform them about the transient burning sensation after TCI application. In the acute phase of AD, initial treatment with TCSs should be considered to minimize side effects of TCIs.[1,15] Although viral skin infections have been reported during the treatment of TCIs, several clinical trials failed to demonstrate an increased frequency of infections with TCIs.[15,34] Physicians should acknowledge that the box warning issued by the US Food and Drug Administration (FDA) on TCIs is based on several case reports of lymphoma and skin cancer in patients treated with TCIs.[1] Much of the available data do not support the association of TCIs with increased risk of lymphoma, non-melanoma skin cancer, other malignancies or photocarcinogenicity.[15] A recent European cohort study found a low absolute risk of lymphoma and skin cancer associated with TCIs use, but the results could be affected by residual confounding such as severe AD and reverse

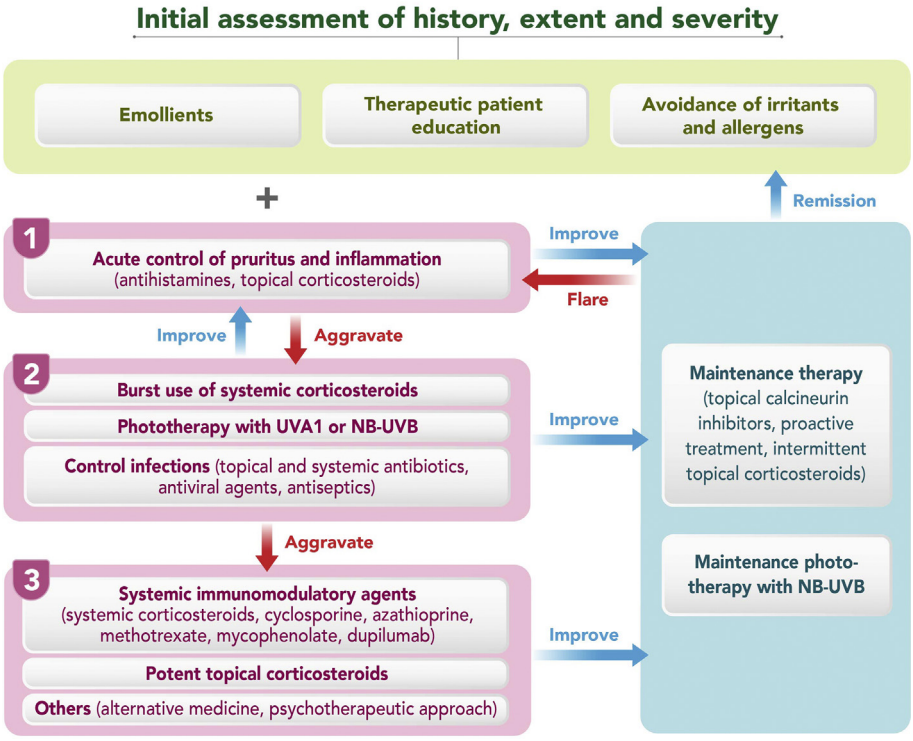

Figure 1 Atopic dermatitis treatment algorithm. A 3-step treatment algorithm is proposed. The initial assessment should include detailed history and the extent and severity of AD, followed by delivering basic care with emollients, therapeutic patient education and avoidance of irritants/allergens. If the patient presented with acute signs and symptoms, Step 1 treatment is to provide immediate control of pruritus and inflammation by antihistamines and TCSs. If the symptoms aggravate, Step 2 treatment options such as burst use of systemic corticosteroids, phototherapy, or control of infections might be considered. If these treatments fail to provide sufficient disease control, Step 3 treatment options such as systemic immunomodulatory agents, potent TCSs, alternative medicine or psychotherapeutic approach might be helpful. All patients may be switched to maintenance therapy once the disease is under control, and they may return to continuing basic care if the lesions achieve complete remission.

causation.[36] Combination therapy of phototherapy and TCIs is not advisable due to the lack of additive effect, potential increased immunosuppression, and theoretical cancer risk.[1,15,37] Effective sun protection may also be advised in patients treated with TCI.

Systemic corticosteroids

Systemic corticosteroids are the most frequently used systemic treatment for moderate-to-severe AD, particularly as a short-term (<1 week) therapy for acute flares, but could be used up to 1–2 weeks.[1,16,38] The suggested dosage of oral corticosteroids is up to 0.5 mg/kg/day.[16] Due to their rapid-onset clinical effects, oral corticosteroids may be used as a bridge to other systemic treatments or phototherapy.[1,38] However, several well-documented side effects including rebound flares upon discontinuation significantly limit their use to short-term control of acute symptoms (Tables 7 and 10).[1,16,38]

Phototherapy

Phototherapy is a well-established treatment modality for moderate-to-severe AD and is used more frequently for adults than children (Table 8).[1,15] Previous studies have indicated the effects of ultraviolet (UV) on the skin, including immunosuppression, anti-inflammation, immunomodulation, and antipruritic function.[1,15] In addition, UV has an antimicrobial effect against *S. aureus* due to improvement of inflammation and skin barrier.[15] Common modes of phototherapy include broadband UVB, narrow-band UVB (NB-UVB), UVA1, and photochemotherapy (e.g., psoralen and UVA, [PUVA]). Medium-does (i.e., 50 J/cm^2) UVA1 (MD-UVA1) and NB-UVB have been demonstrated to have similar efficacies and are currently the mainstay modalities in phototherapy.[1,15,39] Both MD-UVA1 and NB-UVB are typically used as second-line treatments for AD. MD-UVA1 is generally used to control acute flares, whereas NB-UVB is used in the management of chronic AD. In addition, other UV light sources may serve as alternative options if warranted.[1,37]

Potential long-term risks exist for all UV irradiation, such as increased non-melanoma skin cancer and photoaging, and are best-known with the use of PUVA in psoriasis.[15] The long-term risk of melanoma also seems to be higher in adults treated with PUVA than with UVB.[1] For this reason, long-term safety and carcinogenic risk of photochemotherapy (e.g., PUVA) must be considered, especially for children and those receiving systemic immunomodulatory agents and TCIs.[15,37,40] Other limitations of phototherapy include the availability of equipment, accessibility

of treatment, cost, and limited efficacy in difficult-to-treat areas (e.g., hairy skin and skin folds).[15,37] Physicians should consider these limitations along with patient-specific factors and the duration of treatment for the decision-making in daily practice.[1,37]

Topical and systemic antibiotics

Patients with AD are susceptible to secondary skin infections with a variety of microorganisms, including *Staphylococcus*, *Streptococcus*, herpes simplex virus, molluscum contagiosum virus, human papillomavirus, and *Malassezia* species (Table 9).[1] *S. aureus* colonization is the most common cause of skin infection in patients with AD compared with healthy individuals.[1,2] Overgrowth of *S. aureus* with reduced cutaneous microbial diversity has been implicated in AD pathogenesis.[2,16] Superantigens produced by *S. aureus* can contribute to persistent inflammation, disease exacerbation, and resistance to TCSs.[1,2,16] Topical antibiotic therapy may be effective for treating localized infection as they reduce *S. aureus* colonization, but clinical evidence is limited.[41] However, long-term use of topical antibiotics is not recommended due to the increased risk of resistances and sensitizations.[16,42,43] Instead, it should be noted that TCSs, TCIs, and phototherapy are able to reduce *S. aureus* colonization in AD.[16]

Flucloxacillin (dicloxacillin) is considered the first-line choice for bacterial infections in pediatric AD, though cephalexin may be preferred in clinical use.[1,16,44] Systemic antibiotics can be used for AD with clinical signs of bacterial infection.[1,16] Although high-level evidence supporting the use of systemic antibiotics is lacking, clinical experience has indicated low-dose antibiotics may be effective for long-term management of recalcitrant AD.[1] Physicians should be familiar with local resistance patterns when prescribing antibiotics. A previous study in Taiwan found a high prevalence of methicillin-resistant *S. aureus* and multi-drug resistance from colonizing and infecting *S. aureus* in children with AD, and suggested that trimethoprim-sulfamethoxazole, rifampin, fusidic acid, and mupirocin are suitable for *S. aureus* decolonization.[45]

Systemic immunomodulatory agents

For patients with severe or refractory AD that substantially impacts their QoL and social activities, systemic treatment is often required. Corticosteroids, cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil are available non-biologic drugs; and dupilumab is the first biologic agent approved for AD (Table 10).

Systemic corticosteroids are frequently used for acute flares and not for long-term use due to unfavorable risk/benefit ratio and rebound flares. Clinical trials have shown cyclosporine effective for adult and pediatric populations.[1,16] Cyclosporine, licensed in many European countries, is currently recommended as the first-line short-term conventional systemic treatment option for moderate-to-severe AD by a systematic review of 34 RCTs.[46] The time to reach the expected full response for cyclosporine is about 2 weeks at doses of 2.5—5 mg/kg/day.[16] Short-term use with the lowest effective dose is recommended because of short-term (e.g., nausea and paresthesia) and long-term (e.g., hypertension, renal impairment, and skin changes) side effects and rebound flares. Combining cyclosporine with phototherapy is not recommended due to the risk for skin cancer, although the cancer risk is lower in Asians. Case reports and observational studies suggest that mycophenolate mofetil may be effective, but gastrointestinal side effects are commonly seen at initiation.[1,16] The time to response is 8—12 weeks at doses of 1—3 g/day for adults.[16]

Both methotrexate (5—25 mg/week) and azathioprine (2—3 mg/kg/day) are comparably effective for severe AD.[1,16] The time to response for both agents is 8—12 weeks, and they can be used long-term with proper monitoring of side effects and liver enzymes.[16] While both agents were well-tolerated in the short-term treatment, hematological abnormalities were more common with azathioprine.[1,16]

Dupilumab, an IL-4Rα monoclonal antibody that inhibits IL-4/IL-13 signaling, has been approved for adults with moderate-to-severe AD in Taiwan in May 2018. It is administered subcutaneously with an initial 600 mg loading dose followed by 300 mg injections every other week. The time to response is 4—6 weeks.[16] Phase III clinical trials have demonstrated significant improvements in skin lesions and QoL, as well as reduced flares up to 52 weeks in adults treated by dupilumab with or without topical therapies.[6] Efficacy of dupilumab has also been shown in adults with difficult-to-treat AD who failed cyclosporine.[6] It remains to be investigated the time to relapse following dupilumab discontinuation after successful treatment; nonetheless, clinical experience suggests >8 weeks is possible.[16]

In clinical trials, mild-to-moderate conjunctivitis was more frequent in patients with AD who received dupilumab than placebo, and it was associated with AD severity and history of conjunctivitis.[47] As for infection risk, a pooled analysis of clinical trials showed dupilumab does not increase overall infection rates and is associated with reduced risk of serious/severe infections and non-herpetic skin infections in moderate-to-severe AD when compared with placebo.[48] In a phase III open-label extension study, the long-term safety and efficacy of dupilumab were sustained in patients with moderate-to-severe AD for up to 76 weeks.[49]

These is no comparison of the efficacy of different immunosuppressive agents and suggestions of treatment priorities. A network meta-analysis may provide a more reliable result in terms of treatment priorities, yet is far beyond the scale of this current consensus.

Antiseptics

Topical antiseptics can reduce staphylococcal colonization; however, their role in the management of AD is limited, as evidence suggests no clear benefit to antiseptics in non-infected AD (Table 11).[1,16] Antiseptics may potentially trigger disease aggravation, as cases of irritation or allergic contact dermatitis caused by antiseptic products have been reported, even in very young children.[1,50,51]

Bleach (sodium hypochlorite, NaOCl) bath has been used in the management of AD for its well-known antimicrobial effect. Studies have shown diluted bleach baths (0.005%),

analogous to swimming in a chlorinated pool, decrease the clinical severity of atopic eczema in patients with clinical signs of secondary bacterial infection.[52,53] Additionally, it has been shown to have anti-inflammatory, antipruritic effects without disrupting epidermal barrier function.[54] Bleach baths are effective in reducing the severity of AD, but a meta-analysis revealed that the efficacy might be largely attributed to water bath alone within 4 weeks of intervention.[55] As an alternative to bleach bath, bleach body wash was shown effective for moderate-to-severe *S. aureus*-colonized AD without significant reduction in staphylococcal colonization in a 6-week, prospective, open-labeled study.[56]

Antimicrobial textiles have the potential to benefit patients with infected AD, as they can decrease staphylococcal colonization.[16] Silver-coated textiles have shown improvements in localized lesions, while AEGIS-coated silk textiles did not provide additional benefit to standard care.[16] Of note, *in vitro* analysis of these functional textiles has raised concern about the loss of antimicrobial activity after laundering.[57]

Alternative medicine

Complementary and alternative medicine (CAM) has received growing interest and utilization as an adjunctive approach in AD treatment.[1,16] A recent study found CAM users were characterized by having longer disease duration and a significant disease burden, which may indicate an unmet need in disease management.[58] Evidence suggests that some of the CAM modalities may have a role in the management of AD, but high-quality studies are needed to indicate efficacy and to recommend their use in clinical practice (Table 12).[1,16,59,60] Probiotics and related preparations are gaining popularity, but data are conflicting for their use in AD.[15,60] Recent research has shown the important role of the skin microbiome in AD development, and emerging data suggest manipulating the microbiome with topical commensal organisms may have potential for expanding AD treatments.[61] Melatonin supplementation in Taiwanese children with AD showed reduced sleep-onset latency and improved disease severity in a small RCT.[62] Further studies are needed to validate the results and evaluate the optimal treatment conditions in children and even in adults.

Traditional Chinese medicine (TCM) is a commonly practiced CAM system in Taiwan. A national survey found over 30% of Taiwanese patients with AD have used TCM, and it may help reduce hospitalization rate.[63] Chinese herbal formula may be effective for AD; however, systematic reviews found no conclusive evidence, and reports of possible liver and cardiac toxicities warrant further caution.[1,16] Acupuncture seems effective for treating itch in AD, but more robust evidence is needed before recommendations could be made.[16,64] A recent meta-analysis also call for more higher-quality evidence on TCM and related treatments.[65]

Psychotherapeutic approaches such as counseling, relaxation methods, and behavioral techniques may be used for AD management as they could help improve itch-scratch behavior, sleep disturbances, treatment adherence, and mental health comorbidities.[16] Psychological interventions are essential for AD management both in educational programs and in a personalized, integrative multidisciplinary program.[16,66]

Upcoming and emerging therapies

Crisaborole, a topical phosphodiesterase 4 inhibitor for mild-to-moderate AD in patients aged $\geq$2 years, is available in the US but not yet approved in Taiwan. The efficacy is better than the vehicle, but its place in therapy remains to be determined.[15] There are also systemic agents targeting different AD pathways currently in phase III clinical trials. The Janus kinase inhibitors (e.g., baricitinib, upadacitinib, abrocitinib) may hold great promise for future treatments. The anti-IL-31Rα nemolizumab has shown a significant antipruritic effect. Other potential agents include the anti-IL-13 tralokinumab and the neurokinin 1 antagonist tradipitant.

Considerations in pediatric populations

The principle of AD treatment is similar between adult and pediatric populations. However, aspects of AD management that are worth considering in pediatric patients are discussed below.

TCSs. Different TCSs preparations with respective age limits have been approved by the FDA. Given the higher ratio of body surface area to weight in children than in adults, less potent TCSs should be used.[1] A systematic review reported less than 3% of mild adrenal suppression in children treated with TCSs and suggested close clinical monitoring of this very rare phenomenon is adequate.[67] The monthly dosages of TCSs are in the average of 15 g for infants, 30 g for children, and up to 90 g for adolescents (and adults).[15] As children are more susceptible to steroid-induced glaucoma and cataract, long-term use of TCSs around the eyelids and periorbital regions should be avoided in children with AD.[68,69]

TCIs. Both tacrolimus 0.03% ointment and pimecrolimus 0.1% cream are licensed for patients aged $\geq$2 years as second-line therapy for acute and maintenance phases. However, they can be used off-label in those $<$2 years, including in infants, as supported by clinical trial evidence.[70] Tacrolimus 0.1% ointment is indicated in adults and adolescents aged 16 years and above. TCIs may be useful in children requiring long-term topical treatment or frequent use of mild TCS for facial AD.[1]

Antihistamines. Although sedating antihistamines are used for sleep disturbance due to pruritus, it is not recommended for long-term use because they may affect children's quality of sleep.[16] A recent non-interventional study found that early use of antihistamines in children with AD was associated with increased symptoms of attention-deficit/hyperactivity disorder (ADHD).[71] However, the relationships among AD severity, sleeping problems, antihistamine use, and mental health problems are complex, and no adverse effects on behavior or learning processes were found in infants with AD using the second-generation antihistamine cetirizine. Whether antihistamine use contributes to the development of ADHD or acts as

a surrogate for AD severity and its comorbid sleeping problems remains to be investigated in the future.[71]

Phototherapy. Phototherapy is not contraindicated in children, but it is less used than in adults.[15] In general, the use of phototherapy in young children should be cautious as long-term safety remains unknown. NB-UVB has a good safety profile in children; however, caution must be exercised when considering other modalities, as their safety is less certain.[37]

Systemic immunomodulatory agents. Although systemic treatments may be used in pediatric AD, less clinical data are available.[16] The use of oral corticosteroid in pediatric population should be limited and even more cautious than in adults due to well-known side effects and high incidence of rebound flare upon discontinuation.[16,72] Some agents have different starting doses in children than in adults, e.g., 10–15 mg/m^2/week for methotrexate, and 20–50 mg/kg/day for mycophenolate mofetil.[16] Dupilumab has been approved for patients aged ≥12 years in the US in March 2019.

Others. Wet wrap is a useful technique along with other topical therapies, but is labor-intensive and not commonly practiced.[1,2] Also, evidence on the efficacy of wet wrap over standard care is of low-quality.[73] Wet wrap may enhance systemic absorption of TCSs/TCIs and potential side effects deserve attention.[1,15] Sleep disturbance is common in children with AD, and clinical trials suggested melatonin can safely improve disease severity and sleep quality.[62,74] Mental health disorders (e.g., anxiety, depression, ADHD, etc.) are comorbidities in children and adolescents with AD and may be exacerbated by poor sleep and disease severity.[2] Recently, involvement of pediatric psychologists in a personalized integrative multidisciplinary program has been shown valuable for difficult-to-treat pediatric AD, and psychological factors predicted long-term treatment success.[66] It is important for physicians to recognize these risks and provide necessary referrals for psychotherapeutic interventions.[16]

Considerations during pregnancy and lactation

Women with AD who required treatment during pregnancy and lactation deserve special consideration.[75] Physicians should note the prescribing information of each modality and exercise good clinical judgement when treating these patients.

TCSs. Overall, the use of TCSs in pregnancy, with the exception of fluticasone propionate, has been considered safe. Fluticasone propionate should be avoided because it is not metabolized by the placenta. Avoid using very potent TCSs since they may be associated with low birth weight, although rescue therapy for localized chronic/lichenified lesions may be acceptable. TCSs should be applied after breastfeeding, and the nipples should be cleaned before feeding.

TCIs. There are limited data on the use of TCIs during pregnancy and lactation. According to the prescribing labels in Taiwan, tacrolimus ointments should be used only if clearly needed during pregnancy and are not recommended during lactation despite low systemic absorption; pimecrolimus should be used with caution during pregnancy and should not be used on the breast during lactation. However, based on experience from oral calcineurin inhibitors and low systemic absorption of TCIs, along with favorable benefit/risk ratio of TCIs, off-label use of TCIs during pregnancy is recommended. Similar to TCSs, TCIs should be applied after breastfeeding, and the nipples should be cleaned before feeding.

Antihistamines. With their limited clinical efficacy, antihistamines may be used if indicated during pregnancy. Cetirizine and loratadine both have a good safety profile in pregnant women, and loratadine is preferred because of the large clinical experience. Physicians should use sedating antihistamines with strict indications and weigh the risk and benefit carefully.

Phototherapy. Both NB-UVB and UVA1 are recommended when clinically feasible, but psoralens should be avoided. UVB therapy decreases folic acid levels, and thus it should be supplemented preconceptually and during the first trimester. Care should be taken for pregnancy-induced hyperpigmentation (e.g., melasma) as phototherapy may exacerbate this condition.

Systemic immunomodulatory agents. The use of systemic corticosteroids as rescue therapy should be limited for short-term (<2–3 weeks) and up to 0.5 mg/kg/day during pregnancy and lactation, with prednisolone preferred over dexamethasone in pregnant patients. Cyclosporine may be used after careful evaluation as first-line systemic therapy for long-term control during pregnancy and lactation. The use of azathioprine is debated and generally not recommended, but it may be used if other alternatives are not available. Methotrexate and mycophenolate mofetil are absolutely contraindicated during pregnancy and lactation, and they must be discontinued for a period of up to 6 months prior to conception. Dupilumab is not recommended during pregnancy and lactation until more data and experience are available.

Summary

This paper presents the updated TDA consensus for the management of AD. TCS therapy with long-term emollient-based therapies remains the cornerstone of treatment. Systemic treatments are indicated when topical therapies and phototherapy failed to control the disease. Recommendations of each treatment modality are provided, and the treatment algorithm outlines their place in therapy. Treatment considerations for the pediatric population and for women during pregnancy and lactation are discussed. The recent approval of dupilumab, as well as emerging targeted therapies, are expected to bring significant clinical benefit for patients whose disease is inadequately managed by existing options. The TDA will continuously update the content when new information on the disease and therapies becomes available.

Declaration of Competing Interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

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