Taiwanese Dermatological Association consensus for the management of atopic dermatitis

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Abstract
Background/Objective: This report describes the 2014 consensus of the Taiwanese Dermatological Association (TDA) regarding the treatment of atopic dermatitis (AD). The TDA consensus is distributed to practices throughout Taiwan to provide recommendations for therapeutic approaches for AD patients to improve their quality of life.

Methods: The information in the consensus was agreed upon by a panel of national experts at TDA AD consensus meetings held on March 16, May 4, and June 29, 2014. The consensus was in part based on the 2013 Asia-Pacific AD guidelines and the guidelines of the American Academy of Dermatology, with modification to reflect the clinical practice in Taiwan.

Results: The amendments were drafted after scientific discussions focused on the quality of evidence, risk, and benefits; all the consensus contents were voted on by the participating dermatologists, with approval by at least 75% for inclusion.

Conclusion: The consensus provides a comprehensive overview of treatment for AD, with some local and cultural considerations for practitioners in Taiwan, especially the use of wet dressings/wraps, systemic immunomodulatory agents, and complementary therapies.

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Introduction
Atopic dermatitis (AD) is a common inflammatory disease that appears to have increased in prevalence over the past few decades.2,3 The prevalence of AD in Taiwan is estimated to be approximately 6.7% based on the National Health Insurance database for 2000–2007.3 More specifically, the prevalence ranged from 1.7% to 3.35% in 2002,4,5 but has roughly doubled since then.3,6 From the investigation of The International Study of Asthma and...
Allergies in Childhood, the prevalence of AD in Taiwan in the 6–7 year age group was increased from 3.5% in phase I to 6.7% in phase II; in the 13–14 year age group, the prevalence increased from 1.4% in phase I to 4.1% in phase II.28 The increase of prevalence is especially prominent in teenagers. Although AD is common in childhood, it may also occur in adulthood. Adult-onset AD is defined by the first appearance of AD symptoms after the age of 20 years.27 Adult-onset AD differs from classical AD by preferentially affecting the face, hands, and flexural areas and frequently presents as a prurigo-like pattern. Early and/or current exposure to cigarette smoking may contribute cumulatively to the development of adult-onset AD.27 AD is a chronic relapsing disease that may last for several months or years. Family aggregation is commonly associated with AD,27 and the disease has physiological, psychological, and social impacts. AD requires a holistic assessment by healthcare practitioners, and a multidisciplinary, team-based approach involving dermatologists, general practitioners, pediatricians, respiratory specialists, allergologists, nurses, psychologists, nutritionists and social workers to provide proper care. Physicians should focus on the current treatment plan while aiming to improve overall safety and quality of life.

In Taiwan, the prevalence and impact of atopic dermatitis are dependent to some extent on various socioeconomic conditions, varying climates, and patient access to available therapies.3–6 With those factors in mind, the current treatment consensus has been developed to provide up-to-date and concise evidence- and experience-based recommendations directed towards general practitioners and general dermatologists in Taiwan regarding the management of pediatric and adult AD. The information in the consensus was agreed upon by a panel of national experts who convened at Taiwanese Dermatological Association (TDA) AD consensus meetings held on March 16, May 4, and June 29, 2014, with all of the specific aspects of the content requiring approval by at least 75% of the experts in attendance.

Materials and methods

Consensus panel

A total of 14 dermatologists recommended by their respective teaching hospitals across Taiwan and also by the TDA were invited to serve as the TDA Consensus Panel. The 2013 Asia–Pacific guidelines and the 2014 American Academy of Dermatology (AAD) guidelines for the management of AD were provided for the Consensus Panel,5,11,12 and then a variety of amendments made specifically for practitioners in Taiwan were included after discussion during the first two of the three consensus meetings. For each of these amendments, scientific discussions were conducted on the quality of evidence (including transparency and clear criteria) supporting the given amendment, as well as on the risks and benefits of the recommended practices. Following these discussions, the Consensus Panel proposed a draft of the TDA consensus for the treatment of AD, and then invited another 17 dermatologists recommended by 28 teaching hospitals in Taiwan to attend a third consensus meeting to vote on the final version of the consensus. A total of 27 dermatologists ultimately attended the third meeting.

Consensus voting system

The 27 dermatologist experts attending the third consensus meeting cast their votes for individual content items by rating their approval of each item on a scale from 1 to 9, with 1 representing highly disagreed and 9 representing highly agreed. Statements with ratings of 7–9 by ≥ 75% of the total votes were listed as achieving consensus. In the event that the original version of an item was not approved—i.e., when ratings of 7–9 accounted for < 75% of all the votes—potential amendments to the item were drafted and then voted upon. Votes on these amendments were conducted on a yes/no basis, with an agreement rating of > 50% required for implementation. If an amendment to an item was approved, the amended item was then voted on again using the 1–9 scale, with approval again contingent upon ratings of 7–9 accounting for ≥ 75% of the votes. When ratings of 7–9 for an amended item accounted for < 75% of the votes, or when no votes for an amendment itself accounted for ≥ 50% of the votes, a different amendment to the item was voted upon. In this way, each item was either approved in its original form or in some amended form.

Results

The consensus recommendations stratified by different lines of treatments for AD were approved by the participants with ratings of 7–9 accounted for 84% of the total votes cast (Table 1). The first line treatments include emollients, topical corticosteroids (TCGs), antihistamines and therapeutic patient education; the second line treatments include topical calcineurin inhibitors (TCIs), burst use of systemic corticosteroids, phototherapy, and topical/systemic antibiotics, while the third line treatments include systemic immunomodulatory agents, antiseptics, and alternative medicine. The use of emollients and TCSs both obtained 100% of the participants rating 7–9 (Tables 2 and 3), antihistamines were agreed by 96% of the participants (Table 4), and therapeutic patient education was approved by 100% of the experts (Table 5). Among the second line treatments, the percentages of rating 7–9 by the participated experts were TCIs 100% (Table 6), burst use of systemic corticosteroids 96% (Table 7), phototherapy 100% (Table 8), and topical/systemic antibiotics 100% (Table 9). The consensus recommendations of systemic immunomodulatory treatments for AD were approved by the 95.6% of participants (ratings of 7–9; Table 10), while the consensus recommendations of antiseptics and alternative medicine treatments for AD were approved by 100% and 95.6% of the experts, respectively (Tables 11 and 12). After confirming these three lines of treatment, the committee proposed an algorithm of treatment stratified by three steps in real practice (Figure 1). The initial assessment should include a detailed history and extent/severity of AD, followed by the first step of treatment with emollients, therapeutic patient education and avoidance of irritants/allergens. When the disease activity flares acutely, immediate control of pruritus and inflammation by antihistamines and TCSs is recommended. If the symptoms improve, the Step 2 maintenance therapy such as TCIs, proactive or intermittent treatment with TCSs could be used. If the symptoms aggravate after Step 1 treatment, burst use of systemic corticosteroids, phototherapy, or control of infections might be needed. If these intensive treatments still do not work, the third step treatments such as systemic immunomodulatory agents, potent TCs, aggressive phototherapy, alternative medicine or psychotherapeutic approach might be helpful. All the patients may shift to maintenance therapy once the AD symptoms are controlled after Step 3 treatment or intensive treatment, and they may further change to Step 1 basic care if the AD lesions achieve complete remission (Figure 1).

Discussion

Emollients

As a barrier between the host and the environment, skin not only prevents water loss from within, but also protects against external insults from the environment. Skin barrier function is impaired in patients with AD, both in the lesional skin and normal looking skin,
as demonstrated by increased transepidermal water loss and decreased water content. In particular, filaggrin is important for the functional integrity of the skin barrier. Alterations in the filaggrin gene, which result in a weakening of the skin barrier, have been identified in eczema, and evidence indicates that a greater variety of filaggrin gene mutations are present in Asia. Filaggrin gene mutations as predisposing factors for AD have been reported in Japanese patients, and evidence indicates that FLG P478S polymorphism may confer susceptibility to the development of AD among Taiwanese people.

Emollients are crucial to restore skin barrier and the successful management of AD. Emollients may contain both occlusives, which provide a layer of lipid on the surface of the skin to slow water loss and increase moisture content in the skin, and humectants, which are substances introduced into the stratum corneum to increase its moisture retaining capacity. It is commonly believed that emollients could restore the impaired skin barrier function that is characteristic of AD. However, there have only been a few well designed studies evaluating the efficacy of emollient therapy. The consensus recommendations for emollients are listed in Table 2.

In a randomized, controlled trial involving 30 adults with mild-to-moderate AD, 5 weeks of treatment with hydrophilic cream significantly reduced the total body area affected, the itch score and the Eczema Area and Severity Index score compared to vehicle only treatment.

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

<table>
<thead>
<tr>
<th>First line treatment</th>
<th>Second line treatment</th>
<th>Third line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emollients</td>
<td>Topical calcineurin inhibitors</td>
<td>Systemic immunomodulatory agents</td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>Burst use of systemic corticosteroids</td>
<td>Antihistamines</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Phototherapy</td>
<td>Alternative medicine</td>
</tr>
<tr>
<td>Therapeutic patient education</td>
<td>Topical and systemic antibiotics</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Consensus recommendations for emollients for atopic dermatitis (AD).

- Regular emollient therapy is an essential component in the management strategy of AD.
- Emollients should be applied at least 2 times daily or as frequently as the skin gets dry depending on the climate, moisture, or the use of air conditioning.
- Emollients may be used in conjunction with topical anti-inflammatory agents, and also as maintenance therapy. Apply after swimming or bathing while the skin is still moist.
- Fragrances and preservatives in emollient may act as possible irritants.
- The application of moisturizers should be an integral part of the treatment of patients with AD as there is strong evidence that their use can reduce disease severity and the need for pharmacologic intervention.
- Bathing is suggested for patients with AD as part of treatment and maintenance; however, there is no standard for the frequency or duration of bathing appropriate for those with AD.
- Moisturizers should be applied soon after bathing to improve skin hydration in patients with AD.
- Limited use of nonsoap cleansers (that are neutral to low pH, hypoallergenic, and fragrance free) is recommended.
- For the treatment of patients with AD, the addition of oils, emollients, and most other additives to bath water and the use of acidic spring water cannot be recommended at this time, because of insufficient evidence.
- Use of wet-wrap therapy with or without a topical corticosteroid can be recommended for patients with moderate to severe AD to decrease disease severity and water loss during flares.

Table 3. Consensus recommendations for topical corticosteroids (TCSs).

- 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.
- 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.
- Twice-daily application of corticosteroids is generally recommended for the treatment of AD; however, evidence suggests that once-daily application of some corticosteroids may be sufficient.
- Appropriate quantities of TCSs to be used should be discussed with the patient.
- 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).
- TCSs are not contraindicated in the presence of infection but the infection should be treated.
- 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.
- The potential for both topical and systemic side effects, including possible hypothalamic–pituitary–adrenal axis suppression, should be considered, particularly in children with AD in whom corticosteroids are used. Monitoring by physical examination for cutaneous side effects during long-term, potent steroid use is recommended.
- No specific monitoring for systemic side effects is routinely recommended for patients with AD.
- Patient fears of side effects associated with the use of TCSs for AD should be recognized and addressed to improve adherence and avoid undertreatment.

AD – atopic dermatitis.

Table 4. Consensus recommendations for antihistamines.

- A subset of patients with a mixture of AD and dermographism, allergic rhinitis, and bronchial asthma may benefit from antihistamines.
- Sedating antihistamines may be used short term, under supervision where itch of eczema causes sleep disturbance.
- There is insufficient evidence to recommend the general use of antihistamines as part of the treatment of atopic dermatitis.
- 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 atopic dermatitis with topical therapies.
- Non-sedating antihistamines are not recommended as a routine treatment for atopic dermatitis in the absence of urticaria or other atopic conditions such as rhinoconjunctivitis.
- The use of topical antihistamines for the treatment of patients with atopic dermatitis is not recommended because of the risk of absorption and of contact dermatitis.
control patients. Ceramide-based emollient therapy applied twice daily for 3 weeks reduced pruritus and successfully improved AD according to investigator global assessment in 58% of children aged 3 months to 16 years in an open-label community-based trial. Randomized and controlled trials are required to determine the optimal quantity and frequency of emollient therapy. The use of an emollient as an adjunct to TCS therapy provides a steroid-sparing alternative to single-agent TCS while minimizing the likelihood of flares. Patients should be advised on the quality, quantity and frequency of moisturizers use required for maintaining skin barrier function. Based on the skin characteristics and seasonal changes, different galenic preparations of emollient might be indicated, including ointments, creams, and lotions. For example, greasy emollients are suitable for very dry skin in winter, while creamy emollients are more suitable for dry skin in summer.

Emollient therapy also includes the avoidance of irritating cleansers, and using appropriate soap substitutes and/or emollient additives when bathing or showering. Fragrances and preservatives included in emollients may act as possible irritants. Therefore, these ingredients deserve special consideration when particular products are recommended. Wet dressing or wet wrap therapy is useful technique along with emollient therapy, but is not commonly practiced in health care as it is a labor-intensive process for parents and patients.

### Table 5: Consensus recommendations for therapeutic patient education.

- Disease nature
- Avoidance of irritants and allergens
- Treatment adherence should be emphasized at each consultation and should encompass the following:
  1. Appropriate treatment doses.
  2. Treatment application frequency.
  3. How to stop up or step down treatment.
  5. Information should be tailored to suit patients’ cultural practices regarding skin care and bathing.
  6. Patients and caregivers should be informed that in patients with more pigmented skin AD may temporarily cause the skin to lighten or darken.

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

- TCIs are recommended and effective for acute and chronic treatment, along with maintenance, in both adults and children with AD, and are particularly useful in selected clinical situations, such as recalcitrance to steroids, sensitive areas (e.g., face, anogenital, and skin folds), steroid-induced atrophy, or long-term uninterrupted topical steroid use.
- Do not use TCIs under occlusion as this may enhance percutaneous absorption and increase risk of immunosuppression, unless under physician’s direction.
- 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.
- TCI may cause skin burning and pruritus, especially when applied to acutely inflamed skin. Initial treatment of patients with AD using topical corticosteroids should be considered to minimize TCI application site reactions. Patients with AD should be counseled about the possibility of these reactions.
- Routine blood monitoring of tacrolimus and pimecrolimus levels in patients with AD who are applying these agents is not recommended at this time.

### Table 7: Consensus recommendations for burst systemic corticosteroids.

- 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.
- Rebound flare and increased disease severity is a commonly observed phenomenon upon discontinuation of systemic steroids.
- 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
- Burst systemic steroids may be considered for individuals with acute flare-ups to achieve rapid and effective symptomatic control.
- Long-term systemic steroids should generally be avoided in adults and children with AD because the potential short- and long-term adverse effects largely outweigh the benefits.

### Table 8: Consensus recommendations for phototherapy.

- Phototherapy treatment of all forms should be under the guidance and ongoing supervision of a physician knowledgeable in phototherapy techniques.
- 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.
- Phototherapy can be used as maintenance therapy in patients with chronic disease.
- 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
- Caution should be used in the treatment of patients with fair skin phenotype, and prior personal or family history of cutaneous malignancy.
- Because the long-term effects of phototherapy have not been elucidated, treatment should be reserved for adults and children older than 12 years with recalcitrant AD.

### Table 9: Consensus recommendations for topical and systemic antibiotics.

- Secondary infection should be suspected in patients with moderate to severe eczema who have weeping dermatitis, folliculitis and overt clinical signs of infection, or who are not responding to first-line topical therapy.
- Topical antibiotic therapy may be appropriate for localized areas of infection.
- 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 atopic dermatitis disease itself (which may include the concurrent use of topical corticosteroids). The use of systemic antibiotics in the treatment of non-infected atopic dermatitis is not recommended.
- In patients with moderate to severe AD and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity.

AD = atopic dermatitis.
dressings involve two layers of open-weave tubular bandage that are applied over topical preparations: a damp bottom layer, which is applied directly over the topical preparation, and a dry top layer. These dressings occlude the affected area and lead to enhanced absorption and reduced scratching by impeding contact with fingernails while providing a general soothing effect. Cold compresses and wet dressings may be helpful to hydrate and soothe the skin.

Topical antiseptics (e.g. triclosan, benzalkonium chloride, chlorhexidine) in bath emollients are popular choices, particularly for children, and can reduce staphylococcal colonization. Bleach baths may be helpful in cases of moderate to severe disease with frequent bacterial infections, and particularly for maintenance, as cultures did not show clearance of the bacteria in the majority of patients. There is less concern about the development of bacterial resistance with use of dilute bleach relative to the use of topical and systemic antibiotics.

Topical hypochlorite products are also available as an alternative to dilute bleach baths. Antiseptic bath products may aggravate atopic dermatitis due to irritant or allergic contact dermatitis and removal of normal commensal organisms.

**Table 10** Consensus recommendations for systemic immunomodulatory agents.

- 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.
- 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.
- Rebound flare and increased disease severity is a commonly observed phenomenon upon discontinuation of systemic steroids.
- Systemic immunosuppressive agents are indicated for the subset of adult and pediatric 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 immunosuppressive agents may be indicated in patients who are corticosteroid dependent.
- All immunosuppressive 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.
- Potential adverse effects are well documented for each immunosuppressive agent. Thus, patients receiving these systemic immunosuppressive agents should be monitored for such potential consequences.
- Cyclosporine is effective and recommended as a treatment option for patients with AD refractory to conventional topical treatment.
- Azathioprine is recommended as a systemic agent for the treatment of refractory AD.
- Methotrexate is recommended as a systemic agent for the treatment of refractory AD.
- Ciclosporine is effective and recommended as an ancillary treatment for patients with AD refractory to conventional topical treatment.
- Methotrexate may be considered as an alternative, variably effective therapy for refractory AD.
- Biological agents are emerging new treatments for AD, but limited data exist to determine the efficacy of biological agents at this time.

**Table 11** Consensus recommendations for antiseptics.

- Patients and parents should be advised that complementary therapies have not undergone sufficient evaluation of efficacy or safety.
- Clinicians should enquire about and encourage patients to share information about any complementary therapies that are being used.
- Patients should be warned of possible contamination of so-called natural therapies with steroid medication.
- While traditional Chinese herbal medicine may be effective in the treatment of atopic dermatitis, to date, there is limited supporting evidence from well-designed studies.

**TCSs**

TCSs exert anti-inflammatory, immunosuppressive and vasoconstrictive properties and have also been shown to inhibit fibroblast activity. Numerous TCSs are available, and they range from low to high potency. TCSs remain the first-line mainstay treatment for moderate to severe AD. The efficacy of TCSs is well established in both adults and children with AD.

Intermittent therapy, weekend therapy, and intermittent hot spot therapy have been investigated as maintenance strategies due to concerns regarding the prolonged use of TCSs. Previous studies have confirmed that an intermittent TCS regimen does not reduce the efficacy of such regimens. For example, one study found that twice-weekly treatment with mometasone furoate 0.1% fatty cream in stabilized lesion sites following acute flares resulted in 90% of 68 adult AD patients remaining disease-free at 6 months. Topical fluticasone propionate cream 0.05% has also demonstrated efficacy, with a low potential for local or systemic adverse effects and only minimal effects on plasma or urinary cortisol. Over a median exposure of 337 days, there were no reports of skin thinning or atrophy with this regimen.

When prescribing TCS therapy for AD patients, a cream base should be used if the AD is weepy and inflamed, an ointment base should be used if it is dry or lichenified, and a lotion base is recommended in hair-bearing areas. Clear instructions should be given to the patient regarding the quantity and duration of treatment (e.g., 7–14 days for control of acute flares). A TCS should be applied only when there are active lesions and should be discontinued upon lesion clearance. An extended duration of use is permitted when close supervision is ensured. Follow-up reassessment is advised; if there is a flare, retreatment with a TCS may be required.
Potential adverse effects of TCS therapy include skin atrophy, telangiectasias, striae, steroid acne, rosacea, systemic absorption, and hypothalamic–pituitary–adrenal suppression. However, evidence from long-term studies suggests that fluticasone propionate 0.05% cream or 0.05% ointment twice weekly is not associated with significant changes in skin thickness in children and adults with moderate to severe chronic AD treated for up to 44 weeks. Similarly, no significant differences were observed with regard to serum cortisol levels with fluticasone propionate. A retrospective analysis of 100 cases of eczema herpeticum demonstrated that the majority of infections occurred in patients with untreated AD, arguing against the use of TCSs as a cause of this viral infection. Although colonization has been shown to be significantly correlated with disease severity in patients with exacerbation of mild to severe AD, several studies found that Staphylococcus aureus colonization was significantly reduced after TCS therapy. Children may be more prone to systemic reactions given their higher ratio of total body surface to bodyweight. The application of potent TCSs should be avoided on the face, and in particular on the eyelids, flexures, and genital area. Different TCS preparations with different age limits have been approved by the FDA. The consensus recommendations for topical corticosteroids are listed as Table 3.

**Antihistamines**

Data from randomized controlled trials are available for both sedating and nonsedating antihistamines—the results of these trials generally suggest a limited role for antihistamines in the treatment of AD. However, antihistamines may have a place in the management of AD symptoms (e.g., pruritus) if urticarial features are prominent. Sedating antihistamines may have particular utility in children aged <2 years where sleep is an issue. Preliminary data indicated a beneficial effect of cetirizine in the clearance of both signs and symptoms of AD in an 8-week double-blind study in children aged 6–12 years. However, there was no apparent benefit for cetirizine (0.25 mg/kg twice daily) versus placebo in a randomized, double-blind, controlled study of 817 infants aged 12–24 months on TCS therapy. Over a period of 18 months, disease severity was significantly reduced in both study arms (p < 0.001). Nevertheless, cetirizine displayed a steroid-sparing effect through a reduction in the duration of moderate-to-potent TCS use.

**Therapeutic patient education**

Patient education has been shown to be essential and effective in the management of AD. Patient education should include clear explanations of the nature of AD (i.e., the pathogenesis and natural course of the disease should be communicated in lay person language), its aggravating factors and relieving factors and how short- and long-term treatments can be used to help modify and manage it. The short-term and long-term goals of therapy should be established and reviewed regularly. It should also be clear to caregivers how the different treatment modalities would help to achieve the goals of therapy.

A comprehensive education program can improve children’s coping behavior, as well as parents’ handling of their affected children. Age-related structured educational programs may be particularly useful in the long-term management of AD. Even brief educational sessions have been shown to have a marked therapeutic effect. One 30-minute education session with a specialist dermatology nurse led to an 89% reduction in the severity of AD. After successful education sessions, a five-fold increase in the volume of emollients used was observed. In parents and
children with AD, nonadherence to treatments is influenced by fear of TCSs, stinging or itching caused by topical treatment, children being uncooperative with treatment, and treatment being too time consuming. Therefore, adherence, and ultimately successful treatment, can be optimized by addressing these factors appropriately. Providing verbal and written information and giving practical demonstrations of topical therapy applications and techniques will typically lead to better patient understanding, acceptance and empowerment.

**TCIs**

The TCIs, including pimecrolimus and tacrolimus, are topical immunomodulators that have demonstrated beneficial effects in reducing the severity of AD. Topical tacrolimus is available as an ointment for adults and children aged > 2 years, and pimecrolimus is a cream available for adults and children aged > 2 years. Several guidelines recommend TCIs as a treatment option for moderate-to-severe AD. TCSs may be useful in children requiring long-term treatment or frequent use of mild TCSs for facial AD. TCS have been shown to be effective in both the treatment and prevention of flares. Short-term studies of 4–6 weeks’ duration have shown that pimecrolimus is effective in children with mild-to-moderate AD. Previous studies have also confirmed the efficacy of tacrolimus 0.03% ointment in children with mild to severe AD. In adults with mild-to-moderate AD, pimecrolimus cream 1.0%, administered for 26 weeks at the first signs and/or symptoms of a subsequent recurrence, reduced the number of flares requiring TCS therapy. Pimecrolimus also demonstrated a steroid-sparing effect, increasing the mean number of TCS-free days. However, concomitant use of pimecrolimus and narrowband UVB is not advisable in treating moderate to severe AD in children and adolescents due to the lack of short-term additive therapeutic efficacy and potential concern of increased immunosuppression.

Tacrolimus ointment can also be used for the proactive treatment of AD. Twice-weekly application of tacrolimus 0.1% ointment to normal appearing skin that has previously been affected by eczema was shown to prevent, delay and even reduce the occurrence of flares. Over a 12–month period in adults with AD, tacrolimus significantly reduced the number of flares requiring substantial therapeutic intervention and the percentage of flare treatment days, while also increasing the time-to-first flare. In Taiwan, an open-labeled, noncomparative, single-center study showed a 90% improvement in AD after topical tacrolimus in both adults and in children.

A higher incidence of viral infections has been reported with pimecrolimus usage. Skin infections reported to be associated with pimecrolimus include varicella, herpes simplex, and eczema herpeticum. Furthermore, in 2005, the United States Food and Drug Administration issued a ‘black box’ warning for TCIs due to the lack of long-term safety data and the potential risk of the development of malignancies. This warning was based on several case reports of lymphoma and skin cancer in patients treated with TCIs. However, there is currently no direct scientific evidence of an increased risk for malignancy due to TCIs.

A meta-analysis involving over 4000 patients in 25 randomized, controlled trials reported that tacrolimus 0.1% was as effective as moderate TCS therapy, an effect that was evident after 3 weeks of treatment. Conversely, pimecrolimus was less effective than betamethasone valerate 0.1%. At present, there is a lack of direct comparative data among TCIs. Furthermore, long-term studies demonstrating the safety of tacrolimus and pimecrolimus are required before any recommendations can be made indicating a preference for these agents over TCS therapy. Topical tacrolimus may have particular clinical utility in the long-term treatment of patients with resistant AD where adverse effects from TCSs are likely to develop. Unlike TCSs, these agents do not cause adverse effects of skin atrophy or folliculitis, and can therefore be used on thinning skin and sensitive areas such as the face.

Clinical experience demonstrates that TCIs may be safely used as therapy to prevent relapses and prolong remission when used for 2–4 weeks after the acute inflammation has settled with TCS use. Consensus recommendations for topical calcineurin inhibitors are listed in Table 6.

**Systemic corticosteroids**

Systemic corticosteroids are the most frequently used systemic treatment for severe AD in routine care. Some clinicians find them useful as short-term therapy, i.e., for a maximum of up to 6 weeks, in combination with other standard modalities such as TCIs or TCSs (e.g., for acute flares). However, oral corticosteroids are not recommended as a means to induce stable remission of AD or long-term control because of well-documented side effects and the high likelihood of relapse after short-term therapy. Consensus recommendations for systemic corticosteroids are listed in Table 7.

**Phototherapy**

Phototherapy is a well-established treatment modality for severe AD in both adults and children. It is widely used by dermatologists in the management of severe AD. Common modes of phototherapy include broadband UVB, narrowband UVB, photochemotherapy, and high dose UVA1. Narrowband UVB and UVA1 are the most frequently used efficacious regimens in patients with AD. Phototherapy is a second-line treatment after failure of first-line treatment, and can be used as maintenance therapy in patients with chronic disease.

While the mechanism of action in phototherapy treatment of AD has not been elucidated, UV is thought to have local anti-inflammatory and immunosuppressive effects. A meta-analysis study concluded that UV phototherapy is probably the most effective treatment modality in AD, with significant clinical improvement evident as early as 2 weeks. In general, phototherapy has a rapid loss of effect once treatment is discontinued, indicating that it is a good treatment for the management of acute flares. UVB phototherapy was found to reduce the overall body surface area affected by AD. It has been recommended that phototherapy with medium-dose (50 J/cm²) UVA1 should be used to control acute flares, while UVB modalities (e.g., narrowband UVB, or NB-UVB) should be used in the management of chronic AD. In a recent systematic review of phototherapy in AD, Garritsen et al. found 19 randomized controlled trials (RCTs) for evaluating the effect of treatment with photo(chemo)therapy in patients with AD. They conclude that both medium-dose UVA1 and NB-UVB should be considered first-choice treatment modalities. UVA1 was initially introduced for the treatment of acute AD and some guidelines do recommend UVA1 for the acute cases and NB-UVB for the more chronic cases. However, based on the evidence included in their review, they cannot confirm these recommendations. For the decision-making in daily practice (whether preference is given to UVA1 or NB-UVB), other considerations, such as patient-reported outcomes, the availability of the treatment options and the duration of treatment, may play a role.

In pediatric patients, there are some case series that have reported benefits from phototherapy in a percentage of patients. However, the use of phototherapy is generally not suitable for children younger than 8 years as the long-term safety of phototherapy remains unknown. However, there is a potential for...
increased nonmelanoma skin cancer and photoaging. In adults, the long-term risk of skin melanoma appears to be greater with PUVA compared with UVB. It is important to identify which patients are most likely to benefit from phototherapy and to provide individually tailored therapy to ensure optimal treatment outcomes.

Consensus recommendations for phototherapy are listed in Table 8.

**Topical and systemic antibiotics**

Patients with AD can develop a secondary infection with a variety of microbial organisms, including *Staphylococcus*, *Streptococcus*, herpes simplex virus, molluscum contagiosum virus, human papillomavirus, and *Malassezia furfur* fungal infection. Infection with *S. aureus* is the most common infectious complication of AD. It is estimated that patients with AD carry *S. aureus* in 90% of clinically affected areas and 75% of uninvolved areas. Staphylococcal superantigens may penetrate the skin barrier and contribute to the persistence and exacerbation of allergic skin inflammation in AD. Approximately 30% of the general population are also carriers, so routine skin swabs from AD patients may not be helpful in differentiating colonization from infection. AD that is infected and oozing requires treatment with an antimicrobial or antiseptic.

Topical antimicrobial therapy may be effective in the treatment of localized infected AD; however, there is limited evidence for such effectiveness from clinical studies.

Flucloxacinil (dicloxacillin) is considered to be the first-line therapy for pediatric AD, but cephalaxin may be preferred, especially in children. Clinicians should be familiar with local patterns of antimicrobial resistance. Strains of *S. aureus* from AD children had a high prevalence of methicillin-resistant *S. aureus* and multidrug resistance. Trimethoprim—sulfamethoxazole, rifampin, fusidic, acid and mupirocin appear to be more suitable for treatment and decolonization of *S. aureus* in AD children. There is a surprising lack of good evidence supporting use of systemic antibiotics in the treatment of AD. However, clinical practice has shown that long-term, low-dose antibiotics (i.e., cephalaxin, trimethoprim/sulfamethoxazole, erythromycin and tetracyclines), can be used to treat recalcitrant eczema, with good effect. They have been shown to decrease staphylococcal skin colonization and enhance neutrophil activity. Consensus recommendations of using antibiotics for AD are listed in Table 9.

**Systemic immunomodulatory agents**

Systemic immunomodulatory agents are indicated and recommended for the subset of adult and pediatric patients in whom optimized topical regimens using emollients, topical anti-inflammatory therapies, adjunctive methods, and/or phototherapy do not adequately control the signs and symptoms of disease. Systemic immunomodulating agents may also be used in patients whose medical, physical, and/or psychological states are greatly affected by their skin disease, which may include negative effects on work, school performance, or interpersonal relationships.

The management of AD with systemic corticosteroids, although used frequently and shown to temporarily suppress disease, should be avoided because of short- and long-term adverse effects and an overall unfavorable risk-benefit profile. Short courses of oral corticosteroids may lead to atopic flares. Therefore, cyclosporine has been recommended as a first-line option in AD refractory to conventional treatment. Patients with such cases are better handled by experienced clinicians.

Cyclosporine can suppress cytokine expression and production by T cells via inhibition of calcineurin. A systemic review of clinical trials has shown cyclosporin to be the most consistently effective treatment for adult and pediatric AD. For example, one randomized, controlled trial used quality of life as the primary outcome and found cyclosporin to be superior to placebo. In head-to-head trials, cyclosporin was also found to be more efficacious than prednisolone in causing the stable remission of atopic dermatitis. Although higher doses (5 mg/kg of body weight) of cyclosporin are more effective, lower starting doses (2.5 mg/kg of body weight) with adjustment to the individual lowest effective dose are preferable because most side effects are dose-related. Moreover, because of an increased risk for skin cancer, cyclosporin therapy should not be combined with phototherapy. Randomized controlled trials in both adults and children have confirmed that cyclosporin is effective in the short-term management of severe AD at doses of 3–5 mg/kg/d. However, treatment is limited by short-term side effects (e.g., nausea and paresthesia) and long-term side effects (e.g., hypertension, renal impairment, and cutaneous changes), and by frequent rebound after cessation of therapy. Treatment with mycophenolate mofetil, a purine biosynthesis inhibitor with immunosuppressive effects, at doses of up to 2 g/d has been reported to have efficacy in uncontrolled studies in adults with severe AD and those with widespread refractory AD.

Both methotrexate (10–22.5 mg/wk) and azathioprine (1.5–2.5 mg/kg/d) have demonstrated clinically relevant improvements in severe AD, and are relatively well tolerated in the short term. In a small comparative study (n = 42), similar clinical improvements were observed with these two agents, with approximately 40% of patients demonstrating a reduction in the severity of AD after 12 weeks and 24 weeks of treatment. While hematological abnormalities were more common with azathioprine, no serious adverse events occurred with either agent. Disease severity was reduced within 3 months of use, and significant improvements were noted for pruritus (p = 0.001) and dryness (p = 0.033). Adverse hematological and biochemical effects appeared to be acceptable although longer-term monitoring is advised.

Omalizumab is a humanized monoclonal anti-IgE antibody that limits the release of mediators of the allergic response by reducing the surface-bound IgE on its high-affinity receptor on mast cells and basophils, and also by reducing high affinity IgE receptor expression on basophils and tracheobronchial submucosal gland cells. Although there are many case series showing the effects of omalizumab in AD, the role and efficacy of omalizumab in the treatment of AD may need more placebo-controlled prospective trials to clarify.

Consensus recommendations for systemic therapies are listed in Table 10.

**Antiseptics**

Topical antiseptics (e.g., triclosan, benzalkonium chloride, chlorhexidine) in bath emollients are popular choices, particularly for children, and can reduce staphylococcal colonization. However, topical antiseptics have a limited role in the management of AD. There are two mechanisms by which antiseptic bath products may aggravate AD: irritation and removal of normal commensal organisms. There are several reports of irritant or allergic contact dermatitis. In adults, the long-term risk of skin melanoma appears to be greater with PUVA compared with UVB. The chronic use of diluted bleach baths has been shown to be effective in patients with AD who have clinical signs of a secondary bacterial infection. In a randomized, investigator-blinded, placebo-controlled study in 31 patients receiving oral cephalexin for 14 days and emollient therapy for 3 months, bleach baths twice weekly reduced the severity of AD and were well tolerated with no
withdrawals due to intolerance. Consensus recommendations for antiseptic therapy are listed in Table 11.

Alternative medicine

Complementary and alternative therapies are commonly used for AD. In a secondary care UK-based survey, almost 50% of parents of children with AD were using current complementary therapies, with a further one third reporting that they planned to use them in the future. Traditional Chinese medicine (TCM), as a whole medical system of complementary and alternative medicine, is popular in Taiwan. TCM treatment for AD is based on the principles of heat-clearing, dampness-elimination, blood-cooling and moistening. Ethnicity, belief that complementary treatments were safer, and a belief that traditional therapies were not working were given as reasons for the use of complimentary therapies. A placebo effect is highly probable in these reports, although adequate controlled studies are lacking.

Probiotics

The use of probiotics, which may modulate the immune system, represents a novel treatment for AD. Current evidence on the efficacy of probiotics in AD is inconsistent, and data are inadequate and inconsistent to support the use of these treatments in children or adults with AD. In infants aged 6–18 months with moderate to severe AD, supplementation with the probiotic Lactobacillus reuteri VR-003 PCC improved the extent and severity of the disease. Evidence from a small study in infants reported a significant improvement in skin condition with probiotic-supplemented formulas. Probiotics have also been shown to be effective in the primary prevention of AD. Prenatal Lactobacillus GG reduced the frequency of atopic eczema by 50% in children aged 2 years who were at risk of developing AD. However, a number of studies have failed to demonstrate any benefits. In infants with moderate-to—severe AD, probiotics did not provide any additional improvement over standard therapy. A double-blind prospective trial also reported no beneficial effect of probiotic supplementation with Lactobacillus GG in pregnancy or early infancy for the prevention or treatment of AD.

Furthermore, there are often considerable differences in the strains and dosages of various probiotics. Therefore, results supporting the efficacy of a particular formulation may not be applicable to probiotics in general.

TCM

The use of TCM treatments for AD has become popular due to the side effects of current conventional treatments. While TCM may be effective in the treatment of AD, to date there is limited supporting evidence from well-designed studies. A Cochrane review reported heterogeneous results based on four poorly designed studies of Zemaphyte, which is no longer being manufactured. This particular TCM improved erythema, skin surface damage, sleep disturbance, and itching, although adverse effects were not well described. At a major hospital in Taiwan, a cross-sectional survey of 4,145 patients showed that 2841 (68.54%) chose TCM only, while 1304 (31.46%) chose to combine TCM and western medicine therapies. Among the 87,573 prescriptions written for Chinese medicine, the most frequently prescribed herbal formula and single herb were Xiao-Feng-San (Eliminate Wind Powder; 16.98%) and Bai-Xiao-Pi (Cortex Dictamni; 12.68%), respectively. In a prospective, randomized, double-blind, placebo-controlled trial, 71 patients with severe intractable atopic dermatitis were given an 8-week treatment with oral Xiao-Feng-San (47 patients) or placebo (24 patients). The results showed that Xiao-Feng-San formula might improve lesion scores, pruritus symptoms and sleep conditions.

Optimal AD management may be influenced by the different healthcare systems, variable access to medical care, climates, and cultural diversity. The frequency and severity of AD is also significantly influenced by environmental and cultural factors, as well as dietary intake.

TCS therapy in conjunction with long-term emollient-based therapy is the mainstay of AD management. TCS therapy has an important role in the treatment of AD and should be initiated early in the course of the disease. TCIs have been shown to be effective in both the treatment and prevention of flares. Short-term studies of 4–6 weeks’ duration have shown that TCIs are effective and well tolerated. TCIs may also be safely used as therapy to prevent relapses and prolong remission after TCS use.

Wet dressings or wet wraps are effective in the treatment of moderate-to-severe oozing AD. However, their usefulness may be limited by the humid climate in Taiwan, which makes this a less popular form of therapy. Systemic immunomodulatory therapy should generally be reserved for severe and refractory AD when other therapies have failed. Phototherapy has been shown to be highly effective in reducing disease severity in AD. Meanwhile, there is inconsistent evidence to support the use of complementary therapies in the treatment of patients with AD.

The management of AD may be challenging. Dermatologists should emphasize the use of emollient-based therapy in combination with TCS therapy.

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