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Review Article

Taiwan guidelines for the diagnosis and management of pediatric atopic dermatitis: Consensus statement of the Taiwan Academy of Pediatric Allergy, Asthma and Immunology

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KEYWORDS
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Abstract Atopic dermatitis (also known as atopic eczema) is a chronic relapsing inflammatory skin disease commonly seen in children, with increasing prevalence over the past few decades in many countries including Taiwan. The management of pediatric atopic dermatitis can be challenging, particularly as treatment options are expanding with the emergence of novel systemic and topical anti-inflammatory medications in recent years. The Taiwan Academy of Pediatric Allergy, Asthma and Immunology (TAPAAI) has developed the Taiwan guidelines for the diagnosis and management of pediatric atopic dermatitis, which provides a concise overview of its epidemiology, clinical characteristics and diagnosis, mechanisms, treatments, and education. The contents of this guideline integrate the principles of recent national and international guidelines for the diagnosis and management of atopic dermatitis, latest research findings, and expert opinions of experienced pediatric allergy specialists in Taiwan. For practical purposes, this guideline presents simplified and easy-to-use diagnostic criteria and severity grading for pediatric atopic dermatitis. A stepwise treatment algorithm is also proposed to expedite rational, cost-effective, and evidence-based management strategy. This guideline, developed based on current best evidence and real-world experience of pediatric allergy experts in Taiwan, is intended to facilitate practical, up-to-date management of pediatric atopic dermatitis among physicians.

Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic relapsing, pruritic inflammatory skin disease commonly seen in children, which represents a considerable health and economic burden. The Taiwan Academy of Pediatric Allergy, Asthma and Immunology (TAPAAI) has specifically developed the Taiwan guidelines for the diagnosis and management of pediatric AD with the major input of a working group consisting of seven experienced pediatric allergists. Three working group meetings were held on January 30, April 24, and September 4, 2021, respectively. Consensus statements within the guideline were discussed and approved at the TAPAAI committee meeting on September 4, 2021. This guideline provides a concise overview of the epidemiology, clinical characteristics and diagnosis, mechanisms, treatments, and education for pediatric AD. The contents of the guideline integrate the principles of recent international guidelines,[1–6] latest research findings, and expert opinions of experienced pediatric allergy specialists in Taiwan. For educational purpose, the main content of this guideline has been translated into a Chinese version which is available at the official website of the TAPAAI (http://www.air.org.tw).

Epidemiology (Table 1)

The prevalence of AD has increased dramatically over the past decades in many countries including Taiwan.[7,8] Epidemiological studies have reported prevalence rates of AD among children in Taiwan at 1.4% in 1974, 5.2% in 1994, and 11.3% in 2019.[7,9,10] Its rising prevalence and associated psychosocial burden make AD an important chronic disease in children.[11]

The development and phenotypic expression of AD depend on the complex interactions between genetic factors, environmental exposure to allergens, and nonspecific adjuvant factors, such as pollution, infections, and climates.[12–19] Food allergens may represent the major allergic triggers of AD in early life, after which environmental aeroallergens play a critical role.[14] Aeroallergens have been reported to affect the occurrence and severity of AD.[20–23] Among the aeroallergens, fungi represent a major risk factor for AD in Taiwan where warm and humid climates dominate.[24] In addition, tobacco smoke exposure during pregnancy and early childhood is associated with an increased risk of AD.[24,25] Similarly, exposure to air pollutants may increase AD prevalence and severity,[12,13,26] and exposure to perfluorinated chemicals and phthalate is positively correlated with serum immunoglobulin E (IgE) levels and development of AD.[27,28] Lastly, a study in Taiwan has found that elevated maternal work stress and long working hours during pregnancy increased the risk of AD in young children.[29]

Clinical characteristics and diagnosis (Tables 2–4)

Clinical characteristics

Clinical features of AD include intense pruritus, eczematous lesions, a chronic or relapsing disease course, and a personal or family history of atopy. Approximately 50% of patients with AD develop symptoms in the first year of life and 80% within the first 5 years of life.[30] Intense pruritus and scratching related to skin inflammation are the most troublesome symptoms for children with AD. Skin lesions typically display a symmetrical and age-specific distribution pattern. Depending on disease duration and severity, skin features of AD range from dry, itchy skin to erythema, excoriation, skin thickening, oozing, pigmentation and

Table 1 Consensus statements for epidemiology of AD.

1. AD is a common, chronic relapsing, pruritic inflammatory skin disease.
2. The prevalence of AD has increased over the past decades in many countries including Taiwan.
3. The development of AD depends on the complex interactions between genetic factors and environmental exposures.

Abbreviation: AD = atopic dermatitis.

lichenification.[31] AD may impact sleep quality, social activity, emotional well-being, and peer interaction. Moreover, AD in early childhood is often accompanied by the development of other allergic diseases such as asthma and allergic rhinitis in the so-called "atopic march."[32]

Diagnosis

The Hanifin and Rajka criteria is the most commonly used diagnostic standard for AD worldwide.[33] Following a survey of pediatric allergy experts in Taiwan and consensus aimed at optimizing practicality, TAPAAI proposes a set of simplified diagnostic criteria adapted from the Japanese AD guidelines[1] (Table 2). Children who fulfill all three of the following criteria are considered to have AD: (1) pruritus, (2) eczema with a symmetrical and age-specific distribution pattern, and (3) chronic or relapsing course (>2 months for infants less than 12 months of age or >6 months for children and adolescents). This simplified diagnostic tool is relatively easy to administer. Laboratory tests or skin biopsies are not always necessary for diagnosis of AD. Of note, other skin disorders, infectious diseases, primary immunodeficiencies, nutritional deficiencies, or skin malignancies may have skin lesions similar to those in AD and therefore should be considered in the differential diagnosis.

Assessment of disease severity is essential for guiding treatment options and evaluating treatment effectiveness. The SCORing AD (SCORAD) index and Eczema Area and Severity Index (EASI), while used widely in clinical research for the assessment of AD severity,[34—36] are time consuming to administer. In contrast, the current TAPAAI guideline proposes a simplified severity grading for AD—modified from the Japanese guidelines[1]—designed to be performed quickly in a busy clinic setting. This grading system categorizes disease severity into four levels: mild, moderate, severe, and very severe (Table 3).

Mechanisms (Table 5)

Immunologic pathways

In the acute phase of AD, significant activation of T helper 2 (Th2) cells occurs, which is characterized by increased expression of interleukin (IL)-4, IL-5, IL-13, and IL-31, and intensifies in chronic lesions.[37] In the chronic phase, Th1 response is induced, resulting in increased expression of interferon (IFN)-γ, IL-12, IL-5, and granulocyte-macrophage colony-stimulating factor. IL-17 may be related to epidermal proliferation and thickening. After migrating to the skin, Th22 cells produce IL-22 via regulation by activated cutaneous dendritic cells, which induces epidermal acanthosis.[38]

Keratinocytes produce thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, all of which play key roles in activation of type 2 innate lymphoid cells and induction of Th2 immune response in AD. Th2-shifted immune activation is shared by all patients with AD; however, AD is also associated with variable involvement of Th1 and Th17/Th22 immune responses, depending on the evolution of lesions and the phenotypic subtypes of AD.[39]

Skin barrier dysfunction

Skin barrier dysfunction is critical to the initiation and exacerbation of AD and subsequent progression of the "atopic march".[32] The genetically determined barrier deficiency and barrier disruption caused by environmental

Table 2 TAPAAI diagnostic criteria for pediatric AD.

Diagnosis requires the presence of all three essential criteria regardless of severity.

1. Pruritus
2. Eczema[a] with symmetrical and age-specific distribution patterns
   - Infancy: usually starts on the cheeks and extends over time to neck, trunk and extensor surfaces of extremities, with notable sparing of the diaper area
   - Childhood and adolescence: more localized and chronic with skin lesions commonly affecting flexor surfaces of extremities
3. Chronic or relapsing course (often with coexisting new and old lesions):
   - Infancy: >2 months
   - Childhood and adolescence: >6 months

[a] Acute lesions: erythema, exudation, papules, and vesiculopapules; chronic lesions: lichenification, prurigo, scales, and crusts.
Note: The content is modified from the Japanese guidelines for atopic dermatitis 2020.[1]
Abbreviations: AD = atopic dermatitis; TAPAAI = Taiwan Academy of Pediatric Allergy, Asthma and Immunology.

Table 3 TAPAAI severity grading for pediatric AD.

Severity	Description
Mild	Only mild eruptions[a] are observed regardless of body surface area involvement.
Moderate	Severe eruptions[b] are observed in <10% of body surface area.
Severe	Severe eruptions[b] are observed in 10–29% of body surface area.
Very severe	Severe eruptions[b] are observed in ≥30% of body surface area.

[a] Mild eruptions: lesions primarily present as mild erythema, dry skin, or desquamation.
[b] Severe eruptions: lesions present as erythema, papules, erosion, infiltration, or lichenification.
Note: The content is modified from the Japanese guidelines for atopic dermatitis 2020.[1]
Abbreviations: AD = atopic dermatitis; TAPAAI = Taiwan Academy of Pediatric Allergy, Asthma and Immunology.

proteases both contribute to the pathogenesis of AD via increasing percutaneous allergen penetration, increasing the risk of allergen sensitization, and enhancing type 2 inflammatory responses.[40] *Filaggrin (FLG)* variants may increase skin permeability leading to higher skin absorption of chemicals and antigens, and thus confer a higher susceptibility for AD.[11,41] Therefore, the paradigm of AD pathogenesis include both immunologic aberration triggering barrier disruption (the "inside-out" hypothesis) and skin barrier dysfunction triggering immunologic imbalance (the "outside-in" hypothesis).[40]

Itch–scratch cycle

The itch–scratch vicious cycle can exacerbate inflammation and perpetuate skin barrier damage and itch. The neuroimmunology of chronic itch centers around three key points of entry into the itch–scratch cycle: the epithelial barrier, immune system, and peripheral nervous system. Exploring the complex network of epithelial-neuro-immune interactions may lead to the identification of novel therapeutic targets.[42]

Treatments (Tables 6–8)

Basic treatment

AD treatment requires a systematic, multifaceted approach including basic skin moisturization, identification and elimination of exacerbating factors, and application of topical and systemic treatments.[43] Risk factors for AD flare-ups include dry skin, excessive sweating, changes in ambient temperature or humidity, exposure to irritants or allergens, infections, and stress. Cool environmental temperature, smooth clothing, and avoidance of irritating fabrics and fibers are essential in the avoidance of primary skin irritation. Moisturizers are the first line of therapy aimed at restoring skin barrier function in AD patients with chronic itch and xerosis. Frequent application of fragrance-free emollient is integral to daily management of AD regardless of disease severity. Topical emollients are preferentially applied immediately after a 10- to 15-min lukewarm bath or shower.[3]

Topical treatments

Regular use of emollient has a short- and long-term steroid-sparing effect in mild to moderate AD.[3] Topical ointments provide an occlusive dressing for maximum penetration of the medicine. Topical creams are water-based, white, and non-greasy. Both topical ointments and creams are suitable for very dry skin or wintertime. In contrast, topical lotions are suspensions of powder in water; they provide

Table 4 Consensus statements for clinical characteristics and diagnosis of AD.

1. Clinical features of AD include intense pruritus, eczematous lesions, a chronic or relapsing disease course, and a personal or family history of atopy.
2. Approximately 80% of patients with AD develop symptoms within the first 5 years of life.
3. Eczematous lesions of AD typically display a symmetrical and age-specific distribution pattern.
4. Other skin disorders, infectious diseases, primary immunodeficiencies, nutritional deficiencies, or skin malignancies that may mimic AD should be considered in the differential diagnosis.

Abbreviation: AD = atopic dermatitis.

Table 5 Consensus statements for mechanisms of AD.

1. The mechanisms of AD include both immunologic aberration triggering barrier disruption (inside-out) and skin barrier dysfunction (outside-in).
2. Cross-talk between skin barrier abnormalities and aberrant immune responses is evidenced by epidermal abnormalities enhancing the release of keratinocyte-derived thymic stromal lymphopoietin, which may enhance Th2 cell differentiation.
3. Repair of skin barrier dysfunction may prevent subsequent atopic march.
4. The itch–scratch cycle can cause more inflammation and perpetuate skin barrier damage and itch.
5. Exploring the complex epithelial-neuro-immune interactions may identify novel therapeutic paradigms.

Abbreviations: AD = atopic dermatitis; Th2 = T helper 2 cells.

Table 6 Classification of TCS preparations.[a]

Potency Group	Generic Name (Vehicle)	Brand Names
Group 1 (super-high potency)	Clobetasol propionate 0.05% (ointment/cream)	Temovate, Dermovate
	Betamethasone dipropionate, augmented 0.05% (ointment/lotion/gel)	Diprolene
	Fluocinonide 0.1% (cream)	Vanos
Group 2 (high potency)	Mometasone furoate 0.1% (ointment)	Elocon
	Halcinonide 0.1% (ointment/cream)	Halog
	Fluocinonide 0.05% (ointment/cream)	Lidex
	Desoximetasone 0.25% (ointment/cream)	Topicort
	Betamethasone dipropionate 0.05% (cream)	Diprolene
Group 3 (high potency)	Fluticasone propionate 0.005% (ointment)	Cutivate
	Betamethasone valerate 0.1% (ointment)	Valisone
Group 4 (medium potency)	Mometasone furoate 0.1% (cream)	Elomet, Elocon
	Triamcinolone acetonide 0.1% (ointment/cream)	Kenalog
	Fluocinolone acetonide 0.025% (ointment)	Synalar
Group 5 (lower medium potency)	Fluocinolone acetonide 0.025% (cream)	Synalar
	Hydrocortisone valerate 0.2% (cream)	Westcort
	Fluticasone propionate 0.05% (cream)	Cutivate
Group 6 (low potency)	Desonide 0.05% (ointment/cream/lotion)	DesOwen
	Alclometasone dipropionate 0.05% (ointment/cream)	Aclovate
Group 7 (least potent)	Hydrocortisone 2.5%, 1%, 0.5% (ointment/cream/lotion)	Hytone

[a] Classified according to the United States system.
Note: The content is modified from the Nelson Textbook of Pediatrics, 21st edition and UpToDate topic on "topical corticosteroids: use and adverse effects" (accessed on November 1, 2021).[31,96]
Abbreviation: TCS = topical corticosteroid.

immediate itch relief as the water content evaporates and the skin cools, making them suitable for the summer season when sweating frequently occurs. Certain moisturizers containing components such as ceramides and filaggrin acid metabolites can improve skin barrier function.

Topical corticosteroids

Topical corticosteroids (TCSs) decrease the inflammatory immune response in AD and hence are the cornerstone of treatment for AD flare-ups.[44–46] Patients should be carefully instructed to ensure the prudent use of TCSs to avoid or minimize adverse effects. Reactive therapy with TCSs are usually applied once or twice daily until the lesions are significantly improved. In children with moderate to severe AD, proactive therapy with twice-weekly application of low to medium potency TCSs (e.g., fluticasone or mometasone) to previously affected skin areas for up to 16 weeks may help to prevent relapses.[44,47,48] TCSs can be grouped into seven potency classes (Table 6). High potency TCSs in highly sensitive skin areas (face, neck, and skin folds) should be used with caution to avoid skin atrophy. Low to medium potency TCSs can be used for longer periods to treat chronic AD involving the trunk and extremities. Infants and young children with AD should be treated with less potent TCSs, because they have an increased risk of adrenal suppression from potent TCSs.

Topical calcineurin inhibitors

Topical calcineurin inhibitors (TCIs), including pimecrolimus (Elidel) cream 1% and tacrolimus (Protopic) ointment 0.1% and 0.03%, are steroid-sparing immunomodulators used to treat AD in patients aged 2 years and above. Pimecrolimus has been investigated in short- and long-term studies including over 4000 infants.[49] Therefore, an expert panel of European pediatric allergists and dermatologists claim that pimecrolimus is a safe and effective alternative to TCSs in infants aged 3 months and above.[49] In March 2021, Taiwan also approved pimecrolimus for use in infants aged 3 months and above. Accumulating evidence indicate that TCIs have a favorable safety profile; despite remaining concerns, there is no evidence that the use of TCIs are associated with increased risk of lymphoma and non-melanoma skin cancer.[50,51] In contrast to TCSs, TCIs do not induce skin atrophy. TCIs are indicated for patients who are either poorly responsive to TCSs or have steroid phobia, and those with face and neck dermatitis. Proactive therapy with twice-weekly application of TCIs extends the interval between flare-ups and the total number of disease-free days. The most frequent localized side effect is a transient warm, tingling or burning sensation at the application site during the first few days of use.

Wet-wrap therapy

Dressings serve as effective barriers against persistent scratching, thus promoting healing of excoriated lesions. Wet dressings promote trans-epidermal penetration of TCSs. Therefore, wet-wrap therapy with TCSs is an effective and relatively safe short-term second-line treatment for moderate to very severe AD. Wet-wrap therapy of 3–7 days is recommended, with possible extension to a maximum of 14 days in severe cases.[3,52] Wet–wrap therapy should be considered as a treatment option ahead of systemic immunosuppressive therapies for patients failing conventional topical therapy and the

Table 7 Consensus statements for basic and topical treatments of AD.

1. Several risk factors can induce AD flare-ups, including dry skin, excessive sweating, changes in temperature or humidity, irritants, allergens, infections, and stress.
2. Regular use of emollients has a short- and long-term steroid-sparing effect in mild to moderate AD. Certain moisturizers can improve skin barrier function.
3. TCSs are considered as the first-line treatment for flare-ups and are effective in reducing the inflammatory immune response in AD. Duration of exposure to potent TCSs in sensitive skin areas (face, neck, and skin folds) should be limited to avoid skin atrophy. Children should be treated with less potent TCSs than those prescribed for adults.
4. TCIs are steroid-sparing immunomodulators used to treat AD.
5. Proactive therapy with twice-weekly application of TCSs or TCIs to previously affected skin areas may help to prevent relapses in children with moderate to very severe AD.
6. Wet-wrap therapy with TCSs is an effective and relatively safe short-term second-line treatment for moderate to very severe AD.
7. Long-term application of topical antibiotics is not recommended because of increased risk of resistance and skin sensitization.
8. The role of topical antihistamines in AD treatment remains controversial. Topical antihistamines might increase the risk of contact dermatitis.
9. Topical PDE-4 inhibitors have been approved for the treatment of mild to moderate AD.
10. The benefits and risks of irritants in bleach baths should be weighed prior to application.

Abbreviations: AD = atopic dermatitis; PDE-4 = phosphodiesterase-4; TCIs = topical calcineurin inhibitors; TCSs = topical corticosteroids.

Table 8 Consensus statements for systemic treatments of AD.

1. Oral antihistamines are recommended as adjuvant therapy for reducing pruritus in AD.
2. Dupilumab, the first approved biologic treatment for AD, is recommended for the treatment of severe to very severe AD that is refractory to conventional topical treatment.
3. Immunomodulators, including cyclosporin, azathioprine, and methotrexate, may be used in children with very severe AD. Immunomodulators should be adjusted to the minimal effective dose once treatment response is attained and sustained. The combination of immunomodulators and phototherapy is not recommended.
4. Use of systemic antibiotics is considered exclusively in children with clinical evidence of bacterial infection while on standard treatment.
5. Long-term use of OCSs in AD is not recommended because of an unfavorable risk—benefit profile.
6. Phototherapy is not recommended for children younger than 12 years as the long-term safety profile remains unclear.

Abbreviations: AD = atopic dermatitis; OCSs = oral corticosteroids.

application needs to be performed with caution for secondary infection. Wet-wrap therapy must be followed by topical emollient application to avoid potential drying and fissuring from therapy.

Topical antibiotics

Long-term application of topical antibiotics is not recommended because of increased risk of resistance and sensitization. In moderate to severe AD with clinical signs of secondary bacterial infection, intranasal mupirocin and bleach bath may be recommended to reduce disease severity.[53—56] Topical anti-inflammatory therapy with TCSs or TCIs also can reduce the colonization with *Staphylococcus aureus* by decreasing inflammatory reaction and improving skin barrier function.[57—59]

Topical antihistamines

Current evidence from randomized controlled trials (RCTs) is insufficient to demonstrate the efficacy of topical antihistamines in the treatment of itch in AD. Limited available data suggest that doxepin cream may reduce itching by 27% in comparison with the vehicle.[60] However, topical antihistamines might increase the risk of contact dermatitis. Therefore, the role of topical antihistamines in the treatment of AD remains unclear.

Topical phosphodiesterase-4 inhibitors and emerging drugs

There are several emerging topical medications for AD, including phosphodiesterase-4 (PDE-4) inhibitors, aryl hydrocarbon receptor agonists, and Janus kinase inhibitors (JAKi).[61] Crisaborole is a topical, steroid-sparing PDE-4 inhibitor. Efficacy and long-term safety of crisaborole ointment has been proved from phase III studies for the treatment of mild to moderate AD in aged 2 years and above.[62,63] A multicenter, open-label, single-arm, phase IV trial also showed the safety and effectiveness of crisaborole in infants aged 3 to <24 months with mild to moderate AD.[64] Crisaborole has been approved by the Taiwan FDA in Dec 2021 for treatment of mild to moderate AD in patients aged 3 months and above. Crisaborole may serve as an alternative to TCSs or TCIs. The most common adverse effect associated with crisaborole is stinging or burning at the application site.

Bleach bath

Adding antiseptics such as sodium hypochlorite to bathwater may be useful for some patients with AD.[65] A recent meta-analysis showed that bleach bath was effective in decreasing AD severity, but not more effective than water baths alone.[66] Nonetheless, the benefits and risks of irritants in bleach baths should be weighed prior to application.

Systemic treatments (Table 8)

Systemic antihistamines

Histamine is not the major itch contributor to AD. There is inconclusive evidence for antihistamines in the treatment of itch in AD, but sedating antihistamines may improve sleep quality in children. Antihistamines may provide some benefits for patients with concomitant atopic conditions such as rhino-conjunctivitis or urticaria.[5] Special caution should be taken in patients with epilepsy. Ketotifen is contraindicated in patients with epilepsy, while convulsions have been reported as an adverse effect of cyproheptadine, chlorpheniramine, and loratadine.[1]

Immunomodulators

Cyclosporin. Cyclosporin is a calcineurin inhibitor that inhibits the transcription of cytokines and activation of T lymphocytes. Cyclosporin can be an effective and well-tolerated treatment for severe AD in children with onset of action as rapid as 2 weeks. Starting dose of oral cyclosporin is 2.5—5 mg/kg/day for children and 150—300 mg/day for adults, administered over a period of 3—12 months.[67] Nephrotoxicity and hypertension are the most common side effects, which are dose- and duration-dependent. Therefore, blood pressure and serum creatinine should be monitored while on therapy.[67] Other adverse effects include infection, gastrointestinal (GI) upset, hyperlipidemia, hyperuricemia, hypomagnesemia, hyperkalemia, hypertrichosis, and increased risk of malignancy.[68]

Methotrexate. Methotrexate is a folic acid antagonist that inhibits dihydrofolate reductase and in turn suppresses lymphocyte proliferation. Low-dose methotrexate is an alternative treatment for severe AD.[68] Oral methotrexate has an onset of action of 8—12 weeks and can be administered at a starting dose of 10—15 mg/m^2/week for children and 5—15 mg/week for adults.[67] Common side effects of methotrexate include liver enzyme elevation, GI upset, and pancytopenia.[67,68] Methotrexate is absolutely contraindicated in pregnancy because of its teratogenic effect.[67]

Azathioprine. Azathioprine is a 6-mercaptopurine analog that inhibits purine synthesis to achieve immunosuppression.[68] The dose range is 1—2.5 mg/kg/day.[69,70] For carriers of mutant alleles of *thiopurine methyltransferase (TPMT)*[71] or the *nudix hydrolase 15 (NUDT15)* gene[72] and/or individuals with reduced activity of either enzyme, a lower dose is used to minimize bone marrow toxicity. Azathioprine has a slow onset of action of 8—12 weeks, with side effects including bone marrow suppression, liver toxicity, GI upset, infection, and increased risk of malignancy.[67,68]

Biological agents and small molecules

Dupilumab. Dupilumab is a monoclonal antibody (mAb) that binds to the IL-4 receptor alpha subunit, blocking both IL-4 and IL-13 signaling and Th2 immune response. Dupilumab has been approved by the US FDA and Taiwan FDA for patients aged 6 years and above with moderate to severe AD inadequately controlled by conventional therapies. In a recent meta-analysis, dupilumab achieved EASI-50, EASI-75, and EASI-90 improvement in 85.1%, 59.8%, and 26.8% patients, respectively, and a 69.6% weighted mean reduction in EASI score.[73] In two phase III RCTs, dupilumab demonstrated EASI-75 improvement in 41.5% of adolescents with uncontrolled moderate to severe AD and in 69.7% of children 6—11 years old with severe AD after 16 weeks of treatment.[74,75] Current evidence demonstrates a long-term safety profile of dupilumab; common adverse effects include conjunctivitis, facial redness, injection—site reactions, and herpes simplex virus (HSV) infection.[73]

Small molecules. Oral small molecule JAKi, including upadacitinib (JAK1i), abrocitinib (JAK1i), and baricitinib (JAK1/2i), have demonstrated effectiveness in inflammation and pruritis control for AD.[68] Baricitinib 4 mg/day and upadacitinib 30 mg/day demonstrated EASI-75 improvement in 70% and 77% of patients with moderate to severe AD and inadequate response to topical corticosteroids, respectively.[76,77] Baricitinib and upadacitinib have been approved by Taiwan FDA for patients aged above 18 and 12 years, respectively, with moderate to severe AD inadequately controlled by conventional therapies. Common side effects include nausea, nasopharyngitis, and acne/folliculitis. Laboratory monitoring of hemogram, liver enzymes, and lipid levels is recommended.

Systemic antimicrobial agents

S. aureus colonization is a major cause of AD flares. Existing evidence is inconclusive regarding the effects of systemic antibiotics for treating patients with infected or uninfected eczema.[78] Systemic antiviral therapy with acyclovir is indicated for eczema herpeticum, a disseminated cutaneous infection with HSV that may progress rapidly to systemic infection in the absence of antiviral therapy. Eczema coxsackium, a cutaneous coxsackievirus A6 infection typically affecting children with AD, can be treated with TCSs, similar to acute AD flares.[79]

Systemic corticosteroids

Routine use of systemic (oral or parental) corticosteroids for AD is generally discouraged and should be reserved only for special circumstances. Oral corticosteroids (OCSs) are effective for the induction of remission in patients with severe acute exacerbations of AD. However, rebound flare is common upon discontinuation of OCSs. Low dose and short-term (<7 days) use of OCSs may be considered as clinically necessary. Long-term use of OCSs is not recommended because of their well-known adverse effects.[80] Of note, recent evidence suggests that short-term use of OCSs is associated with a small but significantly increased risk of severe adverse events in children and adults.[81,82]

Phototherapy

Phototherapy is a second-line therapy for moderate to severe AD refractory to topical agents. Ultraviolet light exhibits immunosuppression, anti-inflammation, immunomodulation, and antipruritic effects on the skin. Narrowband ultraviolet B (NB-UVB) is currently the

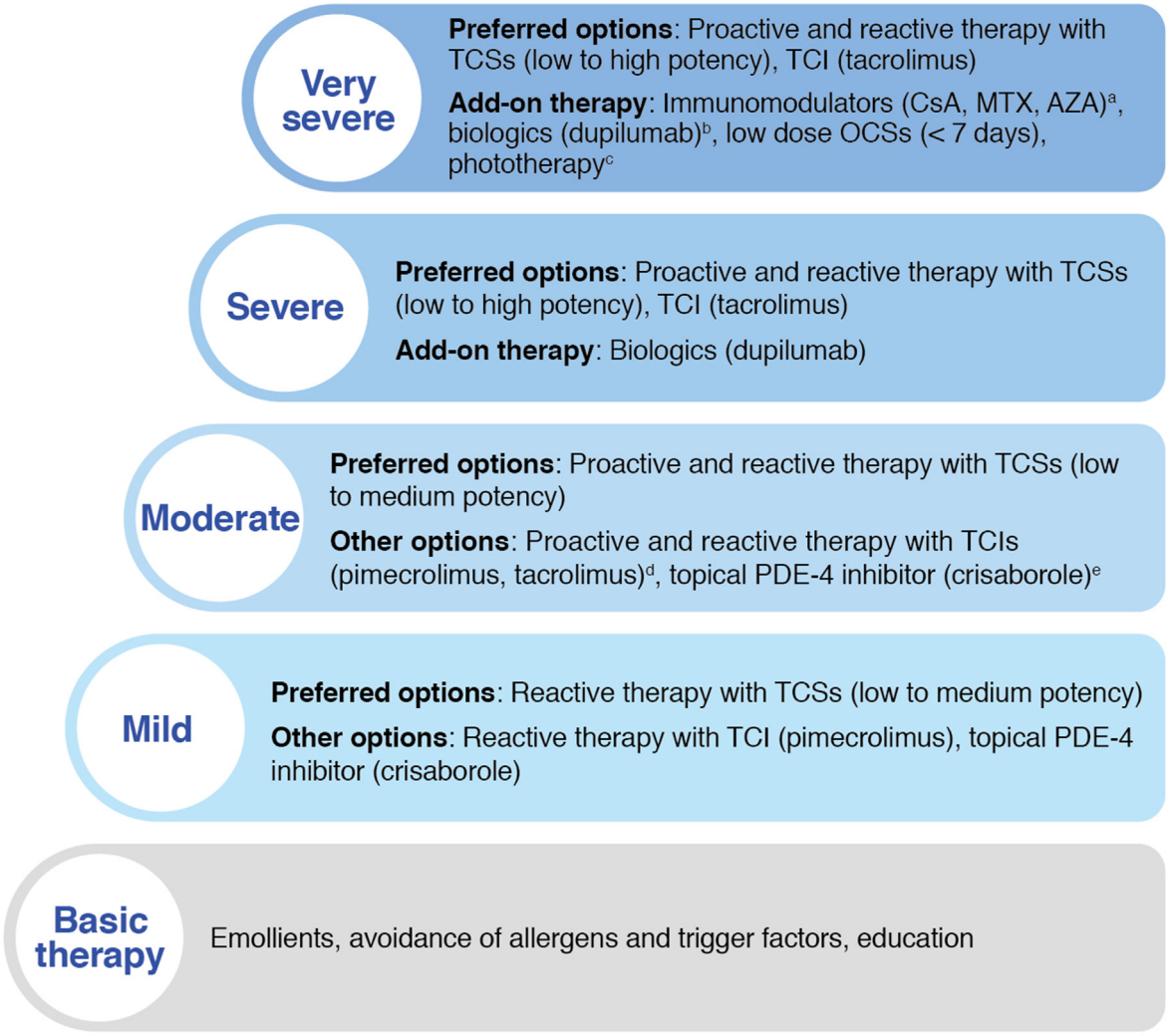

Figure 1. Stepwise treatment algorithm for pediatric AD. [a] Off-label use. [b] Dupilumab has been approved for patients aged 6 years and above in Taiwan. [c] Phototherapy is not recommended for children younger than 12 years. [d] Pimecrolimus (Elidel ointment 1%) is approved for patients aged 3 months and above in Taiwan. Tacrolimus ointment is approved for patients aged 2 years and above (Protopic 0.03%) and aged 16 years and above (Protopic 0.1%) in Taiwan. [e] Crisaborole is approved for patients aged 3 months and above in Taiwan. **Note:** The content is modified from the consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children.[67] Adjunct therapy such as oral antihistamines can be considered for each phase. Wet–wrap or psycho-behavioral therapy can be considered for moderate to very severe AD patients. Consider antibiotics in children with evidence of bacterial infection. Consider poor treatment adherence and/or other diagnoses if treatment response is inadequate. **Abbreviations:** AD = atopic dermatitis; AZA = azathioprine; CsA = cyclosporin; MTX = methotrexate; OCSs = oral corticosteroids; PDE-4 = phosphodiesterase-4; TCIs = topical calcineurin inhibitors; TCSs = topical corticosteroids.

Table 9 Consensus statements for education in AD.

1. Comprehensive education can reduce disease severity and improve quality of life.
2. The core of education lies in maintaining the integrity of the skin barrier (by applying emollients and bathing) and avoiding triggers such as food and inhalant allergens, scratching, environmental irritants, weather conditions, infections, and stress.
3. Early interventions for prevention of AD, such as breastfeeding, hydrolyzed formulas, early introduction of diversified complementary foods, and early application of skin emollients, may be recommended in high-risk infants, albeit evidence of their clinical benefits and impact on disease severity remains equivocal.
4. Complementary therapy such as probiotics and vitamin D has yet to demonstrate convincing benefits for AD.

Abbreviation: AD = atopic dermatitis.

mainstay of phototherapy for AD, despite its slow onset of efficacy.[83] Regarding safety, phototherapy should be avoided in combination with systemic immunomodulatory agents and should only be applied with caution in patients receiving TCIs.[67,69] In general, phototherapy is not recommended for children younger than 12 years as the long-term safety profile and effectiveness in AD children remains unclear.[1,67,83]

Allergen immunotherapy

Allergen immunotherapy (AIT) involves the administration of specific allergens in gradually increasing doses to achieve allergen-specific immune tolerance. AIT has long been used in asthma and allergic rhinitis. However, there is insufficient evidence confirming the efficacy of AIT in AD.[67,84]

Stepwise treatment algorithm (Fig. 1)

The TAPAAI proposes a stepwise treatment algorithm for pediatric AD, modified from the European guidelines,[67] with the aim of expediting rational, cost-effective, and evidence-based management strategy (Fig. 1).

Education (Table 9)

Education

Education is a key component in AD management, encompassing basic knowledge about the disease, maintenance of skin barrier integrity, avoidance of trigger factors, and treatment across acute and maintenance phases. Comprehensive education can reduce disease severity and improve quality of life. The use of moisturizers to maintain a healthy skin barrier is essential for AD of any severity. Symptoms can be exacerbated by allergic (e.g., food and inhalant allergens) and non-allergic factors (e.g., scratch, environmental irritants, weather conditions, infections, and stress). Therefore, children with AD must keep their skin moisturized and avoid disease triggers.[85]

Early intervention for the prevention of AD

There is evidence suggesting that early application of moisturizers from birth may be effective for AD prevention in high-risk infants.[86,87] However, a recent RCT did not support the application of early skin emollients to prevent AD in non-selected infants.[88] The TAPAAI experts suggest that high-risk infants who have a first-degree relative (a parent or sibling) with allergic diseases are recommended to start using moisturizers when demonstrating clinical features of dry skin.

Current evidence does not support maternal dietary restrictions during pregnancy or lactation for prevention of allergic diseases.[89] A meta-analysis found that exclusive breastfeeding for 3—4 months decreased the risk of AD in the first 2 years of life. There is a lack of consensus on whether partially or extensively hydrolyzed formulas prevent allergic diseases. There is insufficient evidence that AD can be prevented by delaying the introduction of allergenic foods (e.g., peanuts, eggs, and fish) beyond 4—6 months of life.[12] In contrast, emerging evidence suggests that early introduction of diversified complementary foods to infants may prevent food allergies.[90]

Complementary therapy

Complementary therapy such as probiotics and vitamin D has yet to demonstrate convincing benefits for AD. Therefore, patients considering complementary therapy should be encouraged to maintain conventional therapies.

Probiotics may improve intestinal barrier by modulating the general microbiome and immune status, thereby reducing AD severity.[91] Limited evidence suggest that certain probiotics might be useful in the prevention and adjuvant treatment of AD.[92,93] The benefits of probiotics for prevention and treatment of allergic diseases are still controversial that no firm recommendation can be made at this time.

Vitamin D is known to play a role in skin barrier function and modulate innate immunity which may help reduce the risk of skin infection. Limited evidence suggests that vitamin D supplementation may reduce the severity of AD in children.[94] However, no conclusive benefits have been demonstrated with vitamin D supplementation for the primary prevention of allergic diseases.[95]

Conclusion

AD in children is a critical health issue, with rising prevalence over the past few decades in many countries including Taiwan. Clinicians face numerous challenges in the management of AD, particularly as treatment options are expanding with the emergence of novel systemic and topical anti-inflammatory medications. The TAPAAI herein presents simplified, easy-to-use diagnostic criteria and severity grading for pediatric AD, along with a stepwise treatment algorithm that facilitates a rational, cost-effective, and evidence-based management strategy.

Taken together, the Taiwan guidelines for the diagnosis and management of pediatric AD integrate the principles of recent national and international guidelines, latest research findings, and expert opinions of experienced pediatric allergy specialists in Taiwan. This guideline is based, to the best our knowledge, on current best evidence and real-world clinical experience of pediatric allergy experts in Taiwan at the date of publication and is intended to facilitate a practical, up-to-date management strategy for pediatric AD among practicing physicians.

Declaration of competing interest

The authors have no conflict of interest to declare.

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