

REVIEW ARTICLE

Childhood Atopic Dermatitis in Taiwan



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The prevalence of atopic dermatitis (AD) appears to have increased dramatically over the past decades. It is generally believed that such rapid increase in prevalence cannot be explained fully by genetic factors. Environmental factors might play a role in such an increment. Children with AD are most likely to suffer considerable school absences, family stress, and health care expenditures. Because the onset of AD occurs relatively early in life, identification of early life risk factors and early management for AD to prevent the development of atopic march are of critical importance. However, there is still no consensus on coordinated prevention and management for AD in Taiwan. In this review, we discuss the specific risk factors of AD and important results of recent articles on AD from Taiwan. The management and prevention strategies of AD for Asian skin are also discussed.

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1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory pruritic skin disease that affects a large number of children in industrialized countries. In Taiwan, the prevalence of AD appears to

have increased dramatically over the past decades.¹ According to Taiwan national birth cohort, AD was noted in 118 of 1760 (6.7%) infants at 6 months of age in 2005 and in 1584 (7.9%) out of 19,968 children at 18 months in 2007.^{2,3} In 6- to 7-year-old schoolchildren in Taipei, the prevalence of AD significantly increased in 2007 (29.8%) compared to 1994 (23.9%) and 2002 (26.3%).⁴ Because population genetic variability does not change with such rapidity, changing environmental factors are likely to be responsible for the rise in the number of AD. The quality of life of children with AD and their families is obviously affected.⁵ It leads to considerable

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financial and psychosocial burden to individuals and society. The rising prevalence in the pattern of skin diseases and psychosocial burden makes AD one of the most important groups of chronic childhood diseases.

Because the onset of AD occurs relatively early in life, identification of early life risk factors among genetically susceptible children and early management for AD to prevent the development of atopic march are of critical importance. However, we still lack a consensus on prevention and management of AD in Taiwan. In this review, we discuss the specific risk factors and important results from recent primary literature articles in Taiwan. Then, we discuss how to take care of the AD skin in our humid climate and how to manage children who do not respond to conventional treatment.

2. Risk factors

The development and phenotypic expression of AD depends on a complex interaction among genetic factors, perinatal environmental exposure to allergens, and nonspecific adjuvant factors, such as pollution, infections, and climates.^{1,6} Food allergens may be the major trigger of AD in early life, after which the role of environmental aeroallergens becomes more important and may be associated with respiratory sensitization.⁶

2.1. Hereditary factors

AD may be inherited preferentially through the maternal line.² It was reported that maternal history of AD, maternal grandparents' history of AD, higher family income, and higher maternal education level increased the risk of pediatric AD.² The mode of inheritance and genes involved are not clear. Genes associated with adaptive immunity and skin-barrier formation have been involved in the development of AD. For example, single nucleotide polymorphisms in Toll-like receptors, ST2, interleukin (IL)-3, IL-4, IL-5, IL12RB1, and IL-13 have been shown to be associated with the pathogenesis of AD.⁷ Genetic mutations in filaggrin (FLG), which is essential for the maintenance of the skin-barrier function, are significantly associated with the risk of AD and disease severity in different ethnic populations.⁸ Among Chinese individuals, the FLG P478S polymorphism may confer susceptibility to the development of AD and may be modified by immunoglobulin E (IgE) levels.⁹ Another recent study indicated that genetic polymorphisms of ORAI1 are involved in the susceptibility to AD in Japanese and Taiwanese populations.¹⁰ Genome-wide association study also identified two new susceptibility loci at 5q22.1 and 20q13.33 for AD in the Chinese Han population.¹¹ Determining the candidate susceptibility genes for AD will not only help us understand the pathophysiology but will also affect the response to therapy, which is important in pharmacogenetics.

2.2. Allergens

Allergens play an essential role in AD, either intrinsic or extrinsic.¹² They provoke cutaneous inflammation via IgE-dependent and cell-mediated immune reactions.¹² Sensitization to food allergens (egg, milk, wheat, soy, and peanut) is

associated with AD and related to disease severity and persistence.¹³ Only in a minority of those with food sensitization (about 33% with moderate to severe AD) are food allergens of clinical relevance, as demonstrated by food challenge tests.¹³ It is well established that food can exacerbate AD both through allergic and nonallergic hypersensitivity reactions. Furthermore, direct food contact with the skin might be an important factor for the aggravation of AD.¹⁴ Beyond the age of 5 years, food allergy is frequently outgrown, but sensitization to inhalant allergens is common.⁶ Exposure to aeroallergens (mites, animal danders, cockroach, molds, and pollen) has been clearly shown to increase the risk factors for AD and AD severity.¹ In humid climate such as that found in Taiwan, fungi are especially important and their impacts might start at the early infant stage.¹⁵ Skin lesions can develop after inhalation challenge with aeroallergens in patients with AD. Moreover, epicutaneous application of aeroallergens on uninvolved skin of patients with AD elicits eczematoid reactions in patients with AD.¹⁴ Therefore, identification of individualized allergen sensitization by skin prick tests or allergen-specific IgE may provide a strategy for better control of AD and avoidance of atopic march.¹²

2.3. Infection

The hygiene hypothesis offers an explanation of why certain environmental exposures early in life may suppress or activate clinical disease. There is evidence to support an inverse relationship between AD and endotoxin, early day care, and farm animal and dog exposure in early life.¹⁶ Helminth infection at least partially protects against AD. This is not the case for viral and bacterial infections.¹⁶ The effect of routine childhood vaccinations on AD risk is controversial. There is a potential risk for AD after receiving Hib combination vaccines. However, the vaccination is important to public health, and therefore the observation requires further investigations.³

2.4. Pollutants and chemicals

During the same period that modern pollutants and chemicals have increased, there has been a remarkable increase of allergy in children. Smoke exposure during pregnancy has been demonstrated to increase the risk of AD in children.¹⁷ Exposure to environmental tobacco smoke in childhood is associated with the development of adult-onset AD.¹⁸ Moreover, air pollutants, such as hydrogen sulfide, nitrogen dioxide, carbon monoxide, and formaldehyde, may increase the prevalence and severity of AD.^{1,19} Exposures to perfluorinated chemicals, a kind of endocrine-disrupting chemicals, were reported to be positively correlated with blood IgE levels and AD.²⁰ Early phthalate exposure may also increase the risk of allergic sensitization and AD.²¹ The biological effects of these pollutants are different depending on the presence or absence of an antigen, which is called an adjuvant effect.²²

2.5. Gene and environment interaction

AD is a complex genetic disorder influenced by environmental factors. Based on hereditary and environmental

factors, boys, maternal education levels >12 years, both parents with AD, renovation and painting of the house during pregnancy, and fungus on walls at home have the highest predicted probability of AD.²³ Genetic polymorphisms in GSTM1 and GSTP1 were reported to be responsible for the susceptibility to AD with regard to smoke exposure.²⁴ Moreover, the effect of smoke exposure on the risk for AD may be mediated through DNA methylation.²⁵ We also found that FLG genetic polymorphisms may be modified by allergen exposure to confer susceptibility to the development of AD.⁹ Future studies to assess the effect of epigenetic changes after environment exposures on the risk of AD are warranted.

3. Mechanisms

3.1. Immunologic pathways

AD inflammation is associated with increased Th2 cells in acute skin lesions, but chronic AD results in the infiltration of inflammatory dendritic cells, macrophages, and eosinophils. IL-12 production by these various cell types results in the switch to a Th1-type cytokine milieu associated with increased interferon- γ expression.²⁶ Skin injury by environmental allergens, scratching, or microbial toxins activate keratinocytes to release proinflammatory cytokines that induce the expression of adhesion molecules on vascular endothelium and facilitate the extravasation of inflammatory cells into the skin. Keratinocyte-derived thymic stromal lymphopoietin may enhance Th2 cell differentiation. Keratinocyte apoptosis, which was induced by soluble Fas ligand, may break down epithelial integrity and initiate the development of AD.²⁷

3.2. Skin barrier dysfunction

Skin barrier dysfunction has emerged as a critical driving force in the initiation and exacerbation of AD and the "atopic march" in allergic diseases.²⁸ The genetically determined barrier deficiency and barrier disruption by environmental proteases in skin are considered to enhance penetration of allergens, increase the risk of sensitization to allergens, and contribute to the exacerbation of allergic diseases. It is proposed that the paradigm of AD primarily due to immunologic aberration "inside-out" should be shifted to include a primary defect in barrier function "outside-in."²⁹ Cross-talk between skin barrier abnormalities and aberrant immune responses is evidenced by epidermal abnormalities enhancing the release of keratinocyte-derived cytokines and chemokines, resulting in modulation of skin immune responses.¹⁸

4. Treatment

The management of AD should better follow the stepwise treatment to reduce the use of systematic steroid (Figure 1). The need for more effective AD therapies with fewer side effects has pushed researchers to develop new therapies and to recycle traditional treatments for use in a novel way. First-line therapy includes topical corticosteroids and

emollient use, followed by topical calcineurin inhibitors, phototherapy, and systemic therapy in difficult cases. Innovative therapies include proactive treatment, barrier therapy, novel antistaphylococcal treatments, new immune modulatory agents, exclusionary diets, and probiotics.

4.1. Topical treatment

4.1.1. Topical corticosteroids

This is the most common and effective treatment. Corticosteroids are grouped into different classes (mild, moderate, strong, and very strong preparations). For younger children, lowest potency corticosteroids are recommended. When all lesions have mostly cleared by an intensive topical corticosteroid, proactive treatment with long-term and low-dose intermittent application (2 to 3 weekly) to the former affected areas is suggested. This strategy is different from reactive treatment in which the treatment consists of daily application of topical corticosteroid on "as-needed basis."³⁰ The proactive treatment is being increasingly promoted because the overall quantity of corticosteroid used is smaller than that used with the reactive treatment. Moreover, the risk of an exacerbation of the AD is minor.³⁰ Glazenburg et al³¹ studied the biweekly application of fluticasone propionate cream in a 16-week, placebo-controlled, randomized study of moderately to severely affected children. The risk of an AD flare in the reactive treatment group was more than twice as high as in the proactive treatment group.³¹

4.1.2. Calcineurin inhibitors

Although the U.S. Food and Drug Administration (FDA) set a boxed warning for topical calcineurin inhibitors, they are still officially licensed topical medications for AD in other guidelines (National Institute for Health and Care Excellence 2007, American Academy of Dermatology (AAD) 2014, and International consensus conference on atopic dermatitis II (ICCAD II)). The U.S. FDA recommends caution when prescribing or using Pimecrolimus cream (Novartis Pharma) and Tacrolimus ointment (Astellas Pharma US Inc.) because of a potential cancer risk. These medicines may only be used as directed and only after trying other treatment options.³² Calcineurin inhibitors are not approved for children younger than 2 years of age.

4.1.3. Wet wrap therapy

After the medication or moisturizer has been applied onto the affected area, it is wrapped with a few layers of wet gauze, followed by layers of dry gauze and secured with elastic stretch. Such therapy is very effective for severe AD because it reduces pruritus and inflammation by preventing scratching, enhancing moisturizing of the skin, and improving the penetration of topical corticosteroids.³³ Generally, wet wrap therapy is applied for no more than 2 weeks, and significant improvement can be seen after 3 days.

4.2. Systematic treatment

Systematic steroids are not recommended for children with AD unless they are required to manage asthma exacerbations; they are given as a short-term transition protocol to

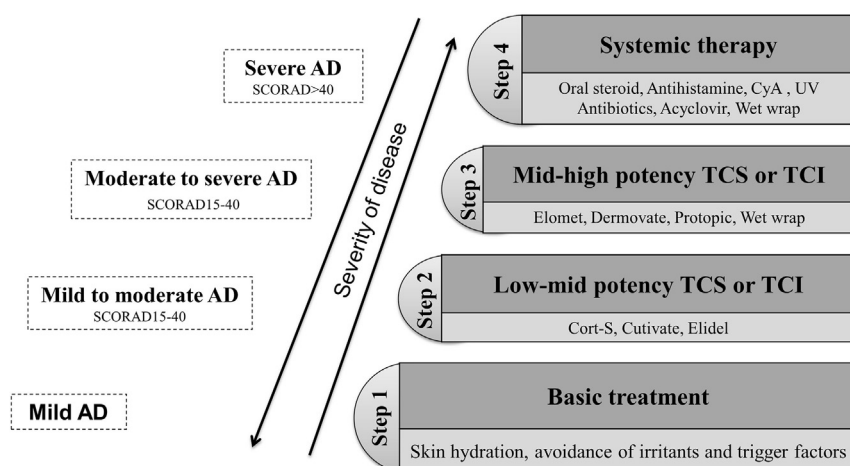


Figure 1 Stepwise management of AD. AD = atopic dermatitis; CyA = Cyclosporine A; SCORAD = scoring atopic dermatitis; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids.

nonsteroidal systemic immunomodulatory agents, or the rash covers large areas of the body. Most providers use a dosage range of 0.5–1.0 mg/kg/d.³⁴ Flare of the AD upon steroid discontinuation may be expected.

Antihistamines are often used to treat itching and to help patients sleep when severe night itching is a problem. However, histamines are not always involved in AD itching, so these medicines may not help all patients with the condition.

Antibiotic, antiviral, or antifungal medicines are used to treat an infected rash. AD skin has been found to be deficient in antimicrobial peptides needed for host defense against pathogens.³⁵ Patients with AD have an increased propensity toward disseminated infections with *Staphylococcus aureus*, herpes simplex or vaccinia virus because of deficiency in antimicrobial peptides.³⁶ Combination therapy of anti-inflammatory drugs and antibiotics in AD patients with secondary bacterial infection, exacerbated AD, or poorly controlled AD is suggested.³⁵ However, a 2010 Cochrane review of randomized control trials did not find any clear benefit for topical antibiotics/antiseptics, antibacterial soaps, or antibacterial bath additives in AD.³⁷ Although the addition of a topical antibiotic to a topical steroid reduces the amount of *S. aureus* isolated from the skin, the combination has not been found to improve either global outcomes or disease severity compared with the steroid alone. Thus, topical antimicrobial preparations are not generally recommended in the treatment of AD. They can be associated with contact dermatitis, and there is also concern that their use could promote wider antimicrobial drug resistance.³⁷ The new AAD guidelines also state that the use of systemic antibiotics in the treatment of noninfected AD is not recommended. Systemic antibiotics are recommended in patients with clinical evidence of bacterial infections in addition to standard treatments for AD.³⁸ Generally, a systematic first- or second-generation cephalosporin for 7–10 days is recommended.

UV light, UVA1 and narrowband-UVB, with or without additional medicine, appeared to be effective treatment modalities for the reduction of clinical signs and symptoms of AD.³⁹ It is interesting to ascertain whether combination therapy using narrowband UVB and pimecrolimus has an

additive or synergistic effect. However, a study in Taiwan, supporting the consensus of the European Working Group on Atopic Dermatitis, did not show any significant therapeutic difference between monotherapy and combination therapy.^{40,41} Combining phototherapy with pimecrolimus is inadvisable, not only for the concerns of long-term safety but also for the lack of short-term additive therapeutic efficacy.⁴⁰

Cyclosporine is sometimes used if other treatments are not successful.⁴² The dosage of cyclosporine used ranged from 3 mg/kg/d to 5 mg/kg/d. Both continuous long-term (up to 12 months) and intermittent short-term courses (3 months or 6 months) are efficacious. Continuous dosing is associated with better efficacy and longer sustained effects relative to intermittent use. However, adverse effects include infection, nephrotoxicity, and hypertension, and increased risk of skin cancer and lymphoma should be monitored.

In those who do not respond to conventional treatment, alternative diagnoses, lack of education and compliance, hypersensitivity reactions to treatment, secondary skin infections, other food and aeroallergens, or psychosocial factors should be considered. Personalized medicine possesses a great potential to propel the development of new therapeutic agents for severe AD.

5. Prevention

In 45% of children, the onset of AD occurs during the first 6 months of life, during the 1st year of life in 60%, and prior to the age of 5 years in at least 85% of affected individuals.³⁵ In those children with onset prior to the age of 2 years, 20% will have persisting manifestations of the disease, and an additional 17% will have intermittent symptoms by the age of 7 years.⁴³ Of those with AD during the first 2 years of life, 50% will have asthma during subsequent years.⁴⁴ The main risk factors for progression and persistence of asthma are early onset, IgE sensitization, and severity of AD. Because AD develops early in life and is the first step of the atopic march, early prevention is very important. Primary prevention is directed at preventing the clinical manifestations of atopy by suppressing or delaying the onset of allergic

sensitivity (Figure 2). Secondary prevention is directed at reducing or removing triggers in the environment of the sensitized individual. Comprehensive intervention programs dealing with both allergens and other potential triggers appear beneficial.⁴⁵

5.1. Skin management

Proper skin care consists of skin hygiene, moisturizing, and avoidance of irritants and scratching.

5.1.1. Avoiding dry skin

Asian skin is more susceptible to being dry. Dry skin makes children itch. Itchy skin leads to scratching, forming a vicious cycle. The number one Asian skin care technique is to moisturize. Baths are drying to the skin as is hot water. Therefore, when taking a shower, lukewarm water and bathing for 10–15 minutes is best.⁴⁶ Skip the fancy shower gels with fragrances and alcohol and use neutral or weakly acidic pH soaps. After children step out of the bath or shower, they should be put on any prescription medication, and moisturizer should be applied within 3 minutes.⁴⁶ If an emollient is not applied within 3 minutes of leaving the bath or shower, evaporation may cause excess drying of the skin. Children with AD may use more skin care products containing fragrance (phthalates), resulting in a higher internal burden of phthalates when they also have increased transdermal absorption as indicated by the *FLG* P478S variants.⁴⁷ Thus, more attention should be paid to chemicals in skin care products especially for *FLG* variant carriers.

5.1.2. Avoidance of irritants

Avoid irritants that cause a rash or make a rash worse. These include detergents that dry the skin, perfumes, scratchy clothing or bedding, and sweating. From Taiwan

National Insurance data, the numbers of visits for AD were highest in late spring to midsummer. This implies that sweating is the common exacerbating factor in AD in hot and humid climate.⁴⁸

5.1.3. Controlling scratching

Upon scratching, staphylococcal superantigens may penetrate the skin barrier and contribute to the persistence and exacerbation of allergic skin inflammation in AD.³⁵ Therefore, fingernails should be trimmed to help prevent damage to the skin when scratching.

5.2. Dietary management

5.2.1. Avoiding allergens

These may include eggs, peanuts, milk, wheat, fish, or soy products. Asians eat soy and drink soy milk. Determining which allergens are contributing to AD is important. Because the results of allergy tests are not always consistent with symptoms, food cannot be restricted based only on the result of a laboratory test. A food diary and challenge test are necessary for the confirmations. The American Academy of Paediatrics recommends that for babies without symptoms, there is no need to restrict high allergenic foods and delay the introduction of complementary foods beyond 4–6 months of age.⁴⁹ If a certain food must be avoided, appropriate diets that will not hamper normal growth should be prepared by choosing a substitute food. A few weeks of diet restriction and then slowly adding back the food may also be tried without the eczema coming back.⁵⁰ According to a research by the German Paediatric Academy, nonbreast-fed infants with confirmed cow's-milk protein allergy should receive an extensively hydrolysed protein-based formula. Soy protein formula is an option beyond 6 months of age. Cow's-milk-based formula or other unmodified animal milk proteins (e.g., goat's milk, sheep's milk) should be strictly avoided.⁵¹

5.2.2. Breastfeeding

A recent meta-analysis suggested that the incidence of infantile AD is reduced by breastfeeding for at least 4 months.⁵² However, a recent study in Taiwan indicated that increased duration of breastfeeding may increase the risk of AD.⁵³ However, we cannot exclude the other potential benefits of breastfeeding. Sometimes, the maternal diet can produce symptoms of AD.⁵⁴ Mothers of exclusively breastfed infants are suggested to restrict highly allergenic foods if AD symptoms become severe in infants.

5.2.3. Supplements

5.2.3.1. Probiotics. Prenatal and postnatal probiotic supplementation for prevention and treatment of pediatric AD has been studied in clinical trials, but results have been mixed and hindered by the heterogeneity of study design, bacterial strains, dosages, and durations for different allergic diseases of children.^{55,56} Current evidence is more convincing for probiotics' efficacy in prevention than treatment of AD.⁵⁶

5.2.3.2. Vitamin D. In addition to its classical role in calcium homeostasis, vitamin D has been recognized for its

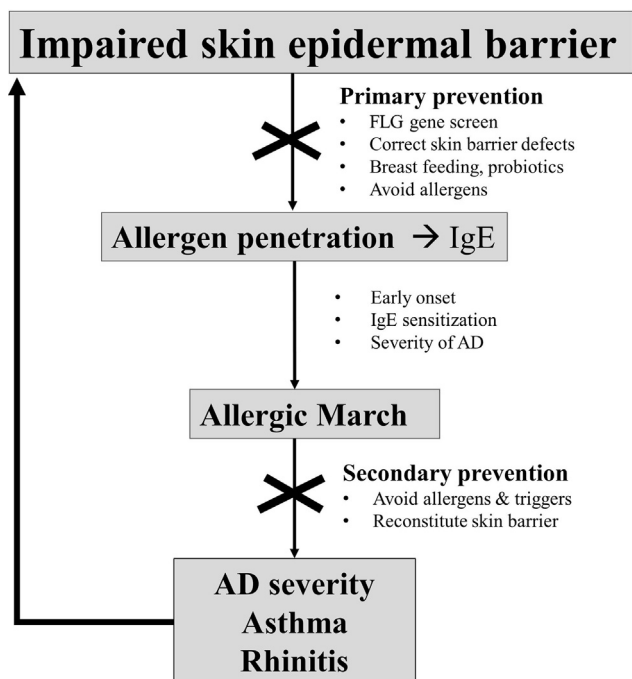


Figure 2 Prevention of atopic march.

effect on immunomodulation. Studies have shown that repletion of vitamin D results in decreased severity of AD in individuals with AD who are deficient in vitamin D.⁵⁷ Reduced vitamin D status in pregnancy may also be a risk factor for the development of AD in the 1st year of life.⁵⁸

5.2.3.3. Fish oil. Provision of fish oil, containing long-chain n-3 polyunsaturated fatty acids, during pregnancy may reduce sensitization to common food allergens and reduce prevalence and severity of AD in the 1st year of life. However, it is not clear if these are of clinical significance and whether they persist.⁵⁹

Other supplementation, such as prebiotics and black currant seed oil (γ -linolenic acid and ω -3 combination), was effective in reducing the development of AD and the severity of AD.⁶⁰

5.3. Environmental management

Children spend most of their time in indoor environments, so reducing pollution in the indoor environment is important for AD management. A study on the therapeutic effect of a low-pollutant (PM10, formaldehyde, bacterial, and mold suspension) ward also revealed that improvement of the environment had a positive effect and reduced the duration of treatment.⁶¹

5.3.1. Ventilation

Aeroallergens and pollutants from second-hand smoke, new furniture, wallpaper, air conditioning, and cooking utensils should be decreased by ventilation. An air cleaner is also helpful.

5.3.2. Adequate humidity

Humidity should be maintained at about 50%. Excessive humidity can promote the propagation of house dust mites, fungi, and bacteria.

5.4. Psychological management

Stress-induced immunomodulation is altered in patients with AD, but the exact mechanisms are not well understood. Increased levels of nerve growth factor and substance P can be found in the plasma of patients with AD and correlate positively with the disease activity.⁶² The nerve growth factor levels were significantly higher in AD patients than in controls.⁶³ Maternal work stress was also reported to be associated with AD.⁶⁴ The most common problem in severely affected AD children is exhaustion from not sleeping well, leading to poor concentration at school. Poor sleep efficiency in AD can be predicted by the Scoring Atopic Dermatitis index, nocturnal melatonin secretion, total serum IgE levels, and allergic sensitization to dust mite and staphylococcal enterotoxins.⁶⁵ Not only is treatment of the AD indicated, but if behavioral, emotional, or sleep abnormalities are noted, these should be tackled early when intervention can be more effective. Improved education and support for children with AD and their families may overcome the emotional burden and improve quality of life.

6. Conclusion

In conclusion, the complex interplay between the variety of the environmental exposure and the interactions between the genetic and epigenetic background are likely to affect the development of AD. It is important to identify infants at risk to provide early intervention. Prevention should start in early life, a critical window of exposure. Repair of the epidermal barrier in infants with AD may prevent the subsequent atopic march. Beyond skin barrier repair, control of inflammation and the itch-scratch cycle is also important for quality of life. Further studies for a tailored therapy for AD in Asian children are warranted.

Conflicts of interest

The authors declare no conflicts of interest.

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