

## Review Article

# Recent Advances in Childhood Atopic Dermatitis

CK YEUNG, HHL CHAN

### Abstract

Significant progress has been made in the understanding of the pathogenesis of atopic dermatitis but the cure remains elusive. The management strategy is therefore to reduce the disease exacerbation and produce comfort for affected children and their families. Thorough clinical assessment helps to guide the education process which is an essential part of management. Use of topical corticosteroids and emollients remain the first line management together with avoidance of triggers. The topical immunomodulating agents, tacrolimus and pimecrolimus have broadened the armamentarium in the management of atopic dermatitis. Use of systemic immunosuppressants is now proved to be safe and effective for refractory atopic dermatitis provided that proper ways of monitoring side effects are adopted. Novel management approach, such as probiotics, has evolved from advances in our understanding of the pathobiology of this common skin disease.

### Key words

Atopic dermatitis; Children; Eczema; Management review

### Introduction

Atopic dermatitis (AD) is the commonest childhood skin disease. It is a chronic relapsing cutaneous inflammatory disorder associated with asthma, allergic rhinitis, increased IgE and eosinophilia. It is characterised by pruritus, dry skin, inflammation and exudation and flexural involvement. AD usually starts at early age and is subject to strong genetic predisposition, interplaying with the immunological and environmental factors. About 50% of patients develop AD

before the age of 1 year.<sup>1</sup> Patients with AD often have a high degree of sensitisation to environmental allergens. The signs and symptoms of AD also pose a significant impact on the lives of affected children and families. It sometimes results in significant morbidity, disruption of family life and sleep deprivation.

The incidence of atopic dermatitis is increasing over the past 3 decades affecting about 15-22.9% of schoolchildren aged seven to twelve years in Japan.<sup>2</sup> The local prevalence of symptoms of eczema in childhood in Hong Kong has been evaluated in the International Study of Asthma and Allergies in Childhood (ISAAC).<sup>3</sup> In this cross-sectional questionnaire survey, the prevalence of eczema symptoms in children aged 6-7 years increased from 3.9% to 4.6% and from 2.7% to 3.3% in children aged 13-14 years, respectively, in 6 years' time. This trend appears to be related to a change of environmental factors, especially in Westernised societies. The management of AD presents a great challenge to all clinicians taking care of children. Its causes are still poorly understood and therapy focuses on symptomatic relief rather than cure. The clinical course is fluctuating with intermittent exacerbations that are difficult to predict. The long-term treatment objectives for AD are to reduce the clinical manifestations, minimise relapses,

**Division of Dermatology, Department of Medicine, University of Hong Kong, Pokfulam, Hong Kong, China**

CK YEUNG (楊志強) MBBS, MRCP(UK), FHKAM  
HHL CHAN (陳衍里) MD(Lond), FRCP(Lond, Edin, Glasg), FHKAM

**Division of Dermatology, Departments of Medicine and Therapeutics and Paediatrics, Chinese University of Hong Kong, Shatin, N.T., Hong Kong, China**

HHL CHAN (陳衍里) MD(Lond), FRCP(Lond, Edin, Glasg), FHKAM

**Correspondence to:** Dr HHL CHAN

and modify the disease course. Moreover, AD may not always respond to standard therapy. More potent treatment with potential toxicity may be required occasionally. The article reviews new therapeutic modalities for AD based on the recent progress in the understanding of the disease.

## Aetiology and Pathogenesis

AD is due to the complex interactions between genetic, environmental and immunological factors.<sup>4</sup> Approximately 70% of AD patients have a positive family history of atopic disease. There is some recent evidence to suggest primary epithelial defect may be an important incipient event in AD.<sup>5</sup> The allergic sensitisation may occur as a secondary event based on this hypothesis. The genetically predetermined defective skin barrier function in AD is further impaired by the environmental changes such as soaps and detergents. Allergens can then penetrate the damaged stratum corneum and hypersensitivity reactions develop. Infection by *Staphylococcus aureus* can also exacerbate AD.<sup>6</sup>

## Skin Barrier Dysfunction

Many genes encoded for protein products integral to the proper assembly of components of epidermal surfaces, and at least 50 of these genes are encoded in the epidermal differentiation complex (EDC). EDC is a 1.6 MB gene cluster on chromosome 1q21 which has become a fertile area of investigation into inflammatory skin conditions such as AD and psoriasis.<sup>7</sup> The genes from EDC are expressed late during terminal differentiation and maturation of keratinocytes. Two null mutations in the *FLG* gene (R501X and 2282del4) encoding filaggrin are found to be strongly linked to the development of AD and asthma associated with AD, which is not present in subjects who had asthma alone.<sup>8</sup> The inability to establish an association between asthma and *FLG* mutations without coexistent atopic dermatitis suggests that asthma in AD patients is a downstream event which occurs secondary to allergic sensitisation following barrier dysfunction. Although the *FLG* mutations are only associated with susceptibility to eczema-associated asthma and not asthma in the absence of eczema, a recent report suggests that the *FLG* mutations are associated with asthma disease severity even in the absence of a history of eczema.<sup>9</sup> In this study, the frequency of the *FLG* null variants in the children with asthma but

without eczema remains similar to the local population frequency. Therefore, it would appear that *FLG* mutation carriers that have no symptomatic eczema are not more susceptible to mild asthma, but are at risk of developing quite severe disease.

Filaggrin is an important component of terminal keratinocyte differentiation. Mutations in *FLG* gene also cause ichthyosis vulgaris, a common inherited disorder of keratinisation that is associated with the atopic diathesis. The findings suggest that epidermal dysfunction manifesting as a compromised skin barrier results in aberrant responses to microbial infection and allergen exposure. However, *FLG* mutations are not solely responsible for the significant genetic linkage of AD to the EDC region on Chromosome 1q21.<sup>10</sup> Genome-wide linkage studies also revealed that at least several chromosomal regions other than 1q21 were linked to AD. Genome screens for AD provide genome-wide significant evidence of linkage on chromosomes 3q21, 3p22-24 and 17q25 ( $P < 0.001$ ).

The role of epidermal barrier protection in the control of AD has been well recognised. The increase in incidence of AD coincides with a soaring way of exposure to environmental agents which break down the skin barrier. The stratum corneum provides the epidermal barrier to water loss from the skin and the lamellar lipid acts like waterproof cement embedding the corneocytes. This prevents the penetration of irritants and allergens through the skin barrier. It is recognised that the barrier function of the skin in patients with AD is impaired with increase in water loss from the stratum corneum.<sup>11</sup> In patients with AD, there are decreased levels of several lipids such as ceramides due to a higher epidermal pH which might affect the activity of enzymes in the lamellar lipid matrix of the stratum corneum involved in ceramide synthesis.<sup>5</sup> With the loss of water from stratum corneum, the corneocytes shrink and cracks develop between the cells which permit the penetration of irritants and allergens, thereby triggering the development of eczematous lesions.

## Hygiene Hypothesis

It is observed that atopic dermatitis is more prevalent in children growing up in urban areas and in families of higher socioeconomic status.<sup>12</sup> The associations with environmental factors are consistent with the hypothesis that more crowded houses, increased family size and birth order, which may possibly increase early exposure to infections, may offer protection from subsequent

development of eczema.<sup>13</sup> Neonates have an immune system that is skewed towards the T-helper 2 (Th2) response with a cytokine profile of interleukin 4, 5 and 13. Th2 cells force B cells to differentiate into IgE-producing plasma cells. These allergen-specific IgE antibodies reach the skin through the circulation and bind to mast cells and dendritic cells. It has been hypothesized that T-helper 1 (Th1) driving forces in the environment transform the Th2 response towards Th1 with cytokine profile of interleukin 2 and  $\gamma$ -interferon.<sup>14</sup> Improved hygiene, which is associated with Westernised style of living, diminishes this swing towards Th1 immune response and thus increase the number of immediate allergic reactions. It has been suggested that this may be owing to a lower exposure to certain viral and bacterial pathogens and postulated that allergic diseases occur when the developing immune system is deprived of the necessary stimulation through certain microbial antigens.<sup>15</sup> There might be a lack of stimulation of T-cell-mediated anti-inflammatory cytokines, such as IL-10 and transforming growth factor- $\beta$ . This hypothesis has led to the trial of probiotics as a potential preventive measure for allergic diseases.

## Role of Immunoglobulin E

The role of allergy mediated through IgE in the pathogenesis of AD remains controversial.<sup>16</sup> Patients with AD often have allergen-specific IgE antibody responses to common antigens and are considered to suffer from extrinsic form of the disease.<sup>4</sup> However, serum IgE levels correlate poorly with the activity of AD and around 20% of AD patients have normal total IgE levels and lacks sensitisation to common allergens. Besides, patients with high IgE levels can present without atopy and atopic dermatitis.

Intrinsic AD is a variant of AD with identical clinical features of that fulfills the most extrinsic AD. These patients show normal total serum IgE levels, no specific IgE, and negative skin prick tests to environmental or food allergens.<sup>17</sup> Intrinsic AD accounts for around 20% of all AD patients.

Immunologic differences between intrinsic and extrinsic AD in cell and cytokine pattern can be located not only in the affected skin, but also in peripheral blood.<sup>17</sup> Differences in the capacity to produce IL-13 by skin T cells might be responsible for the variation of IgE production. Differences of IgE regulation may be explained by a different genetic background in intrinsic and extrinsic AD patients, but also by varying exposure to environmental stimuli. However,

an increased susceptibility of the skin to external and internal stimuli can be observed in the intrinsic type in the same manner as in the extrinsic type of AD.

## Management of Atopic Dermatitis

The diagnosis of AD is usually based on clinical features, namely patient's history, family history and pattern of eruption (Table 1).<sup>18</sup> Adequate assessment helps to delineate the individualised management plan and evaluation should include aggravating factors, sleep disturbance and effect on schoolwork, concomitant atopic diseases, familial atopic tendency, frequency of flares and previous treatments. Examination focuses on the extent of eczema that reflects the severity of the condition. As AD is non-life threatening, the severity of the disease should be defined by both clinical severity and the patient's psychosocial impact. The importance of explanation and education of the patients cannot be overemphasized. Patients' understanding can enhance the compliance that is the pre-requisite of satisfactory response to treatment. Time is worth spending on the education regarding the application of topical preparations and the quantity to use. Management comprises basic skin care for cutaneous rehydration with liberal use of emollients, intermittent use of anti-inflammatory therapy for acute flares and avoidance of triggering factors (Figure 1). It is important to optimise treatment at each step before moving onto the next line of treatment. The main objective in managing AD is to control it rather than cure it, minimising the disruption to daily life. As approximately 70% of children grow out of eczema after adolescence, the risk and benefits of potent treatment with more potential side effects need to be carefully balanced individually.

**Table 1** Diagnostic criteria for atopic dermatitis

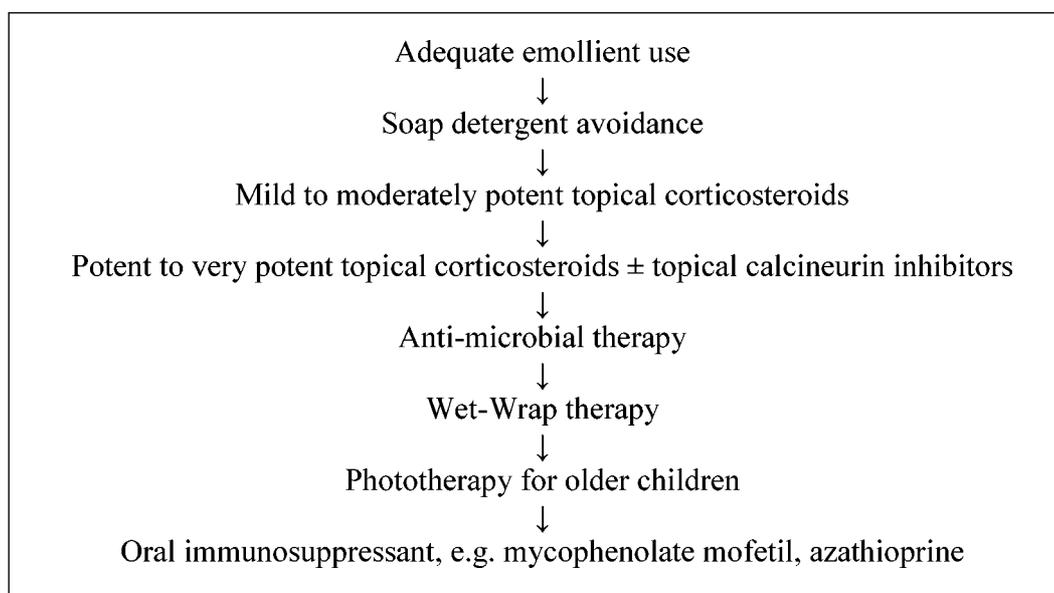
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**Essential criteria:**

- An itchy skin condition

**Plus three or more of the following:**

- History of itchiness in flexures
  - History of asthma or allergic rhinitis (or history of atopic diseases in a first degree relative)
  - General dry skin in the past year
  - Visible flexural eczema (or eczema affecting the cheeks in children under 4 years)
  - Onset in the first two years of life
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**Figure 1** Algorithm in the management of atopic dermatitis.

## Skin Barrier Protection

The ordinary soaps and detergents remove natural lipid from the skin surface, leading to further water loss and drying of the skin in AD patients, promoting the development of AD. Prevention of AD can therefore be directed at reducing the agents that damage the skin barrier particularly soaps and shower gel. Emollient-based cleansers can be used instead. Ameliorating barrier dysfunction will be an important strategy in preventing AD. The stratum corneum will need to be targeted for the development of novel therapies.

Bathing is useful in cleansing and hydrating the skin. Patients with AD should have bath daily provided that bath substitutes such as emulsifying ointment helping to replenish the lipid and water content are used. Regular and adequate use of emollients that provide a surface lipid film restore the skin barrier function and prevent water loss through evaporation from the epidermis. Emollients should be applied just after bathing while the water content is highest. Adequate use of emollients at least twice daily has been proven to reduce xerosis, itching, risks of infections and reduce the total use of topical corticosteroids by limiting water loss and restoring the lipid composition of the stratum corneum.<sup>19</sup> The best emollient for AD is the one patients find most suitable for their skin.

## Control of Infections

Deterioration of atopic dermatitis is often associated with secondary bacterial infection. The cutaneous inflammation in AD encourages *Staphylococcus aureus* colonisation. *Staphylococcus aureus* can be detected on the skin of more than 90% of patients with AD.<sup>6</sup> The risk of superficial and invasive *Staphylococcus aureus* infections significantly increase in children with AD, manifesting as impetigo, folliculitis and paronychias.

Studies have suggested that skin of AD patients has increased affinity for binding to *Staphylococcus aureus* and is deficient in its ability to produce antimicrobial peptides such as defensins and cathelicidin required to eradicate the infectious agents.<sup>20</sup> Similar immune defects are not observed in other inflammatory skin disorders, such as psoriasis. Interleukin-4 induced fibronectin expression in the corneal layer of AD and fibronectin can facilitate the anchorage of *Staphylococcus aureus* on the skin surface.<sup>21</sup> Damage of the epidermal barrier through scratching facilitate the adhesion of *Staphylococcus aureus* by exposing the extracellular matrix protein.

On the other hand, *Staphylococcus aureus* can trigger skin inflammation and sustain the disease as a result of pro-inflammatory properties of microbial products, particular the production of potent bacterial toxins. These

superantigens markedly activate broad populations of T lymphocytes and macrophages.<sup>22</sup> IgE is also produced against these superantigens, which further drives the Th2 immune response. Staphylococcal superantigens have been shown to inhibit the immunosuppressive activity of regulatory T-cells, thus further promoting inflammatory activity in AD. There is also evidence that staphylococci can interfere with the action of corticosteroids by affecting steroid receptors, rendering AD resistant to topical corticosteroid treatment.<sup>4</sup>

Flucloxacillin or first generation of cephalosporins remain reliable antibiotics to treat *Staphylococcus aureus* which is the most important pathogens in AD. Macrolides can be used for those patients who are allergic to penicillin but up to 25% of *Staphylococcus aureus* are now resistant to erythromycin in our locality. Isolation of  $\beta$ -haemolytic streptococci warrants a course of penicillin. The temporary clearance of *Staphylococcus aureus* by systemic or topical antibiotics have been shown in several studies to improve AD disease activity if there is clinical evidence of skin infection.<sup>4</sup>

The understanding of the mechanisms has important implications in the development of new strategies for the management of AD. It was found that use of topical corticosteroids or topical calcineurin inhibitors reduce the bacterial flora on the skin surface of AD patients.<sup>23</sup>

Treatment is not required for isolation of SA from a bacteriological swab unless the eczema appears clinically infected. Re-colonisation occurs relatively rapidly when antibiotic are withdrawn. Extended courses of oral or topical antibiotics may favour the emergence of resistant strains. The development of antibiotic resistance is an increasing problem in staphylococcal infections and of major therapeutic implication.<sup>24</sup> Resistance to fusidic acid is increasing in Europe following its frequent use in that locality. The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) is ever increasing in hospital worldwide and in community such as the United States. Fortunately, there is no evidence of outbreak of community-acquired MRSA infections associated with AD so far in Hong Kong.

## Elimination of Triggering Factors

Identifying the aggravating factors, such as contact allergy, can further reduce the flares of stable eczema. Potential allergens can be identified by careful history taking. The best guide to the relevance of a dietary allergen is a clear and consistent parental observation of exacerbation

of AD following ingestion of the particular food product. Negative skin prick tests or serum tests for serum-specific IgE are more helpful in ruling out suspected allergens.<sup>4</sup> On the contrary, the identification of specific IgE antibodies to common allergens using skin prick test or radioallergosorbant test (RAST), especially to food, often do not correlate with clinical symptoms and should be confirmed with controlled food challenges. Thus, these tests alone seldom helps the management in mild to moderate cases of AD without incorporating the history of exposure in relation to AD flares.<sup>25</sup> These tests are often unable to predict the outcome of avoiding appropriate antigens in AD.

The role of food allergy is controversial and probably most relevant in a subset of patients with AD primarily in infants and young children. Food allergies might exacerbate AD, whereas in others urticarial reactions, or non-cutaneous symptoms, such as abdominal pain and diarrhoea. IgE-mediated clinical reactivity to food proteins, as diagnosed by double-blind, placebo-controlled oral food challenge (DBPCFC), and serum levels of food-specific IgE has been reported in 37% of paediatric patients with severe AD.<sup>26</sup> The gold standard for the diagnosis of food allergy is considered to be the DBPCFC, that has been shown to best predict the clinical improvement on dietary restriction.<sup>16</sup> Most children who are allergic to food outgrow their food hypersensitivity in the first few years of life, making it less important as triggers for older children.

In general, dietary restriction based on the tests for allergy is difficult treatment of AD with unpredictable effects. It is because many children with AD have a positive skin-prick tests to several foods and the food sensitised are common in the food supply, making strict avoidance difficult to achieve. Moreover, an extensive avoidance diet can lead to nutritional deficiencies and compromise of child growth potential. A trial of dietary restriction is only worth attempting when one gives a history strongly suggestive of a specific food allergy or when widespread active eczema is refractory to the first line treatment. The AD children undergoing dietary restriction should be carefully monitored for growth impairment. The diet should be supervised by a dietitian to ensure that it is nutritionally adequate.

## Topical Anti-inflammatory Therapy

Topical corticosteroids (CTS) remain the mainstay of treating the inflammatory component for AD.<sup>1</sup> Intermittent

use of topical CTS to treat the signs and symptoms of acute flare-ups of AD together with the regular application of emollients has been the standard treatment. It can be used safely if certain principles are observed. The well-reported adverse effects owing to the previous abuse of topical CTS have caused considerable confusion. Lack of confidence in topical CTS safety can compromise the compliance and under-treatment of children with AD is very common because of clinicians' and parents' concerns about the side effects of CTS.<sup>27</sup> The safety concerns are especially relevant in children with moderate to severe AD with prolonged use of topical CTS of considerable extent. It is important to explain to parents that topical CTS are very safe if they are used appropriately. The basic principle is to use the least potent preparation that is effective to control the eczema.<sup>28</sup> The potency of preparation may need to be changed from time to time due to the variation of extent and activity of AD.

Very potent or ultrapotent topical CTS should be used cautiously in selected sites for limited period of time to induce remission of acute flares. It must be followed by long-term topical maintenance strategies.<sup>29</sup> Hanifin et al used twice-weekly topical fluticasone as maintenance to areas of skin previously affected once disease activity has been stabilised.<sup>30</sup> Alternatively, shorter periods of medium-potency topical CTS use are found to be as effective as a longer course of low-potency CTS in controlling flares.<sup>31</sup>

Topical CTS can sometimes be used in conjunction to wet wrap bandaging in young children under supervision.<sup>32</sup> Wet wrap therapy can enhance the effects of CTS, reduce water loss from skin surface and damage of skin from scratching. This modality is often reserved for inpatient use of the treatment of an acute exacerbation of eczema with over 70% body surface area involved in which diluted steroid ointment is applied directly to the eczematous areas and the body is covered with tubular bandages dampened with warm water, followed by a dry layer on top and applied twice daily for 3-5 days only. It is not uncommon for patients to have wet wrap dressing over the weekend to obtain optimal control while during weekdays, patients should continue topical application of CTS. In a recent randomised study of wet wrap therapy versus conventional treatment for AD in 50 children under the age of 27 months using 1% hydrocortisone ointment, there was no significant difference between the two groups in terms of improvement in eczema severity and amount of topical steroid use.<sup>33</sup> More skin infections requiring antibiotics were observed in the wet wrap group and carers found wet wrap more difficult to apply than conventional treatment. However, the results

may not be generalised to older children or wet wrap with more potent topical steroids.

## Topical Calcineurin Inhibitors

Two macrolide molecules in topical preparation have been specifically developed for the treatment of AD, tacrolimus and pimecrolimus. Its mechanism of action is to inhibit the inflammatory cytokine transcription in activated cells and other inflammatory cells through inhibition of calcineurin.<sup>34</sup> The molecules bind the cytoplasmic immunophilin receptor macrophilin 12. This complex inhibits the phosphatase – calcineurin. This prevents the dephosphorylation of the nuclear factor of activated T-cells, the subsequent translocation into the cell nucleus and the resulting transcription of key activation cytokines such as interleukin-2. The immunomodulating effects are more specific than CTS. Skin atrophy, glaucoma, hypothalamic-pituitary-adrenal-axis suppression and growth retardation do not occur as in the case of CTS.<sup>1</sup> Thus, topical calcineurin inhibitors (TCI) can be used on all body sites including the delicate skin areas such as the face, eyelids, neck and skin folds for extended periods as they are devoid of the typical side effects of topical CTS. These agents have the potential to prevent disease progression with their long-term uses in AD patients.<sup>35</sup> It also complements the current treatment options especially for application to delicate areas and for patients scared of use of topical CTS or already developed side effects of topical CTS. Use of TCI focuses on prevention of flares that result in the fluctuating course of the AD. The efficacy and safety data support the potential role of TCI as maintenance therapy for AD with use of topical CTS being reserved for acute control of AD exacerbations.<sup>36</sup> TCI is particularly useful in the case of persistent disease or frequent recurrences in reducing the total requirement for topical CTS. There are a series of long-term, multicentre, randomised, double-blind, controlled studies to demonstrate their efficacy and safety in paediatric population.<sup>37-39</sup>

### *Tacrolimus*

Tacrolimus is a systemic immunosuppressant originally used to prevent organ transplant rejection. It is formulated to an ointment preparation of 0.03% and 0.1% concentration. It is the 0.03% ointment that is licensed to use in children from 2 to 16 years of age.<sup>40</sup> Efficacy and safety in the treatment of AD has been demonstrated in randomised, double-blinded clinical studies.<sup>39,41</sup> Tacrolimus

ointment has a rapid and sustained effect on signs and symptoms of AD in children with moderate-to-severe AD. The onset of action is rapid with symptomatic improvement often noted after 1 week of therapy and efficacy maintained over 12 months, suggesting that tachyphylaxis is not significant for topical tacrolimus.<sup>40</sup> Comparative study was conducted with topical CTS in children using hydrocortisone acetate ointment 0.1%. There was a trend for 0.1% tacrolimus to be more effective than 0.03% tacrolimus and for both formulations to be more effective than hydrocortisone acetate.<sup>42</sup> No significant adverse effects were observed apart from transient discomfort at sites of application. Systemic tacrolimus levels were not significant except in Netherton syndrome with features of erythroderma and skin barrier defect.<sup>43</sup> A local study of tacrolimus 0.03% ointment has demonstrated its efficacy and good tolerance of its ointment-based preparation in hot and humid weather in Chinese children in Hong Kong.<sup>44</sup>

### **Pimecrolimus**

Pimecrolimus 1% cream has been shown to be a safe and effective treatment in AD of mild to moderate severity, including infants and children.<sup>35-38</sup> It primarily focuses the use in paediatric population and studies demonstrating safety have been conducted in infants as young as 3 months of age.<sup>45</sup> It has been demonstrated to have low risk of systemic immunosuppression with minimal systemic absorption through cutaneous penetration.<sup>46</sup> The strategy of pre-emptive treatment with pimecrolimus at the first sign and symptom of flare may achieve better overall disease control compared with conventional therapy with topical CTS and emollients by preventing progression of disease to flare.<sup>35,36</sup> Several large, controlled studies have shown that significantly more patients in the pimecrolimus group remained flare-free during the first six months of the study compared to the control group with only 34% of patients flare-free ( $P < 0.001$ ).<sup>38</sup> The beneficial effects can also be maintained over time with 51% of pimecrolimus group compared to 28% in conventional treatment group over 12-month period.<sup>36</sup> Its use also has significant steroid-sparing effect as shown in an infant study in which 64% of infants on pimecrolimus required no steroids throughout the 12-month period compared with 35% in conventional group. The trend of gradual reduction in use of pimecrolimus over time reflects its potential to prevent flare progression and improve disease control. Pimecrolimus cream should be applied to the affected areas on all body sites twice daily until clearance occurs and then reapplied if the disease flares up.

### **Safety Concerns of TCI**

Two aspects of safety concerns have been addressed, namely, the potential systemic side effects owing to percutaneous absorption and local adverse events. Tacrolimus blood levels have been shown to be dose-dependent, related to the severity of the disease and degree of lichenification.<sup>47</sup> The blood tacrolimus levels generally remain low and have shown to decrease over time as dermatitis improves. Blood levels of pimecrolimus have been shown to be consistently low. No systemic toxicity has been demonstrated in clinical trials for both topical tacrolimus and pimecrolimus. Absence of skin atrophy and tolerability for application to sensitive areas has been demonstrated for both tacrolimus and pimecrolimus. Transient local burning discomfort associated with application of TCI is the most common local reaction. Thirty-six percent of paediatric patients experience local burning sensation at the time of application for tacrolimus 0.03% ointment.<sup>48</sup> The local discomfort usually disappears on continuation of TCI application within a week or so. The concomitant use of topical CTS to modulate this side effect in the initial phase of TCI therapy is often practised.

For the theoretical concerns of local immunosuppression with TCI, no notable increase in local cutaneous infections was observed with topical tacrolimus and pimecrolimus compared with placebo.<sup>36,49</sup> There is a trend of decrease in risk of bacterial cutaneous infections on their prolonged uses probably related to the control of dermatitis. TCI may reduce immune surveillance, and in the long term may increase the potential for skin cancer induction. Although the risk of photocarcinogenicity of TCI remains uncertain in humans, it is conceivable for patients on TCI to minimise exposure to sunlight by sun avoidance and sun-protection measures.<sup>38</sup>

The FDA recommended a black-box warning be issued against TCI because of the concerns about potential long-term risks of malignancy especially lymphoma as a result of decreased immunosurveillance. The American Academy of Dermatology (AAD) has provided recommendations regarding use of TCI in paediatrics: the 0.03% tacrolimus ointment should be used for second-line therapy of moderate to severe AD in children older than 2 years for episodic, but not prolonged, continuous use. Pimecrolimus 1% cream should be used as second-line therapy for mild to moderate AD in children older than 2 years for episodic, not prolonged continuous use.<sup>50</sup> In essence, TCI should not be used in patients younger than two years or in those who are immunosuppressed, should be second-line therapies in

other AD patients according to the AAD guideline.

Various authorities did not find any causal evidence supporting an association between use of TCI and malignancy based on existing data.<sup>51</sup> On the contrary, immunologic studies suggest that topical pimecrolimus cream is more selective in its anti-T cell effects than topical CTS, which depleted both T cells and Langerhans cells.<sup>52</sup>

Given the debatable safety profile of TCI, they may be used as maintenance therapy or given at the earliest signs of local recurrence to prevent disease progression. In practice, topical CTS is used first for 3-5 days to improve the condition, TCI is then added for another week to enhance disease control. This particularly applies to body sites prone to the side effects of topical CTS, such as the intertriginous areas and eyelids. Comparisons with other treatments regarding their respective cost effectiveness is warranted since TCI is much more expensive than topical CTS, while its superiority and relative safety to the latter has yet to be proven on long-term basis. In practice, pimecrolimus 1% cream and tacrolimus 0.03% ointment are of similar anti-inflammatory potency and both are licensed to use in paediatric patients. Pimecrolimus 1% cream induced less irritation and is better tolerated for facial application for its cream-based preparation than tacrolimus 0.03% ointment.

## Antihistamines

Recent studies revealed that histamine does not appear to be the only crucial agent inducing pruritus in AD. Other mast cell mediators such as TNF- $\alpha$ , IL-4, IL-5, IL-6 may play a more important role in the etiology of itching in AD. Thus, antihistamines did not show any conclusive evidence of reducing itch when compared with placebo.<sup>53</sup> The therapeutic value of antihistamines appears to rely on solely their sedative properties. They can be used before bedtime during flares of AD associated with marked pruritus and difficulty getting to sleep.

## Systemic Anti-inflammatory Therapy

Managing severe eczema is a challenge to all physicians who take care of these children. Before considering systemic treatment, it is important to exclude non-compliance, under-treatment and all relevant aggravating factors. Systemic treatment includes oral steroids,

azathioprine, cyclosporin and mycophenolate mofetil. Other modality of treatment suitable for older children is phototherapy with narrowband UVB or photochemotherapy with psoralen and UVA.

Systemic corticosteroids should be used with extra-caution during the rapid adolescent growth phase beyond the age of 11. It may be used to tide over the acute crisis but it has to be followed by a definite plan for maintenance treatment such as phototherapy, cyclosporin or azathioprine. Systemic treatments are indicated for severe cases that are refractory to conventional therapy with topical agents, associated with growth retardation and significant disruption of daily life. All systemic immunosuppressants need regular monitoring for their potential effects on organ toxicity, increased risk of sepsis and possibly lymphoma.

## Phototherapy

Narrow-band ultraviolet B (311 nm) and ultraviolet A-1 (340-400 nm) can be useful adjuvants in treatment of AD for older children preferably over 12 years of age, but the availability of the latter is very limited.<sup>29,54</sup> Photochemotherapy with psoralen and ultraviolet A (PUVA) should be reserved to patients with severe, widespread AD. Adverse effects with phototherapy include erythema, pruritus, skin pain and pigmentation. This physical treatment is inconvenient and may carry a risk of future cutaneous malignancy and photoaging especially for PUVA. Having stated that as skin cancer risk in Asians is much lower than Caucasian, phototherapy can be particularly applicable among Hong Kong population and should be considered as the therapy of choice among patients that failed to improve after topical therapy.

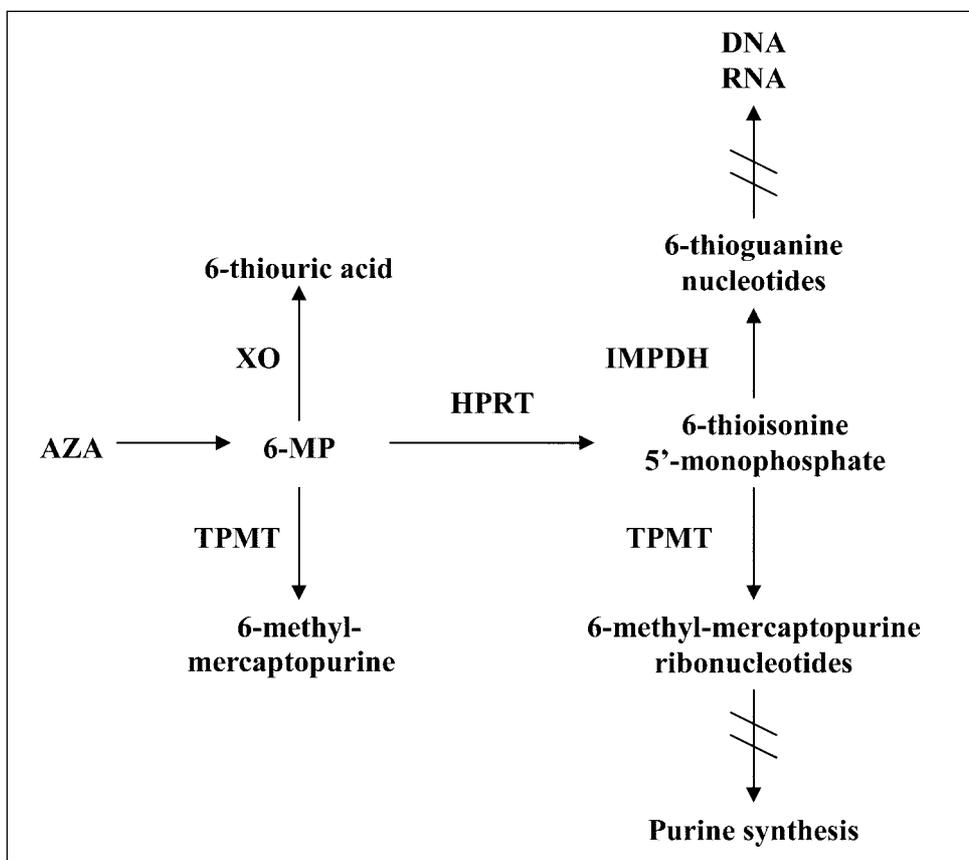
## Mycophenolate Mofetil

Mycophenolate mofetil (MMF) has recently been shown to be effective in the treatment of severe atopic dermatitis. MMF acts by inhibiting de novo purine synthesis, through inhibition of the inosine monophosphate dehydrogenase, resulting in depletion of intracellular guanine nucleotides. Therefore, the proliferative responses of T lymphocytes and B lymphocytes are blocked. In an open pilot study, 10 patients with severe eczema were treated with MMF 1 g twice daily for 4 weeks, followed by reducing the dose to 500 mg twice daily for another week.<sup>55</sup> All patients had

significant disease reduction but one had to discontinue due to herpes retinitis. Herpes zoster and herpes simplex activation were reported in another retrospective study that examined twenty patients treated with MMF.<sup>56</sup> Among these subjects, 17 reported significant improvement within four weeks of treatment. More recently, another retrospective study that examined the use of mycophenolate among patients with severe atopic dermatitis indicated complete resolution in 29%, almost complete (more than 90%) improvement in 29%, while 35% had 60-90% improvement and 7% failed to respond.<sup>57</sup> The dose used in this study was 40-50 mg per kg daily in younger children and 30-40 mg per kg daily in adolescents. The medication was well tolerated in all patients, with no infectious, haematological or hepatological complications.

## Azathioprine

Azathioprine can be used with caution at a dose of 2-3.5 mg/kg/day in severe atopic dermatitis refractory to topical treatment.<sup>58</sup> Azathioprine is an anti-metabolite with *in vivo* conversion to 6-thioguanine nucleotides, which are responsible for immunosuppression and myelotoxicity in patients (Figure 2). Polymorphism in the thiopurine methyltransferase (TPMT) gene predicts haematological adverse effects occurring in 5-10% patients taking azathioprine. Homozygotes for low enzyme activity (TPMT<sup>L</sup>) with prevalence of 1 in 300 predispose someone taking azathioprine to profound myelosuppression. Azathioprine should not be used in patients with very low or absent TPMT activity (below 3 nm/h/ml RBC).



**Figure 2** Azathioprine (AZA) is initially converted to 6-mercaptopurine (6-MP) by a non-enzymatic process. 6-MP is further transformed by one of three competing enzymatic pathways (XO, xanthine oxidase; TPMT, thiopurine methyltransferase; HPRT, hypoxanthine phosphoribosyltransferase). Once formed, 6-thioisoinine 5'-monophosphate can either be converted into 6-thioguanine nucleotides by the rate-limiting inosine monophosphate dehydrogenase (IMPDH), or be methylated into 6-methyl-mercaptopurine ribonucleotides.

Conversely, homozygotes for high enzyme activity (TPMT<sup>H</sup>) may show inadequate response to conventional doses of azathioprine. Pretreatment TPMT levels is advocated to stratify patients at different risk of myelosuppression and to determine the optimal doses more accurately.<sup>58</sup>

In a retrospective study on treatment of severe atopic dermatitis with azathioprine in 48 children, 28 had an excellent response, 13 had a good response and 7 had a poor response.<sup>59</sup> No patient developed neutropenia after screening with TPMT. Reversible abnormalities in liver function tests were seen in five children without other serious toxicity. The results of previous studies suggest that azathioprine may be effective in some patients with atopic dermatitis and the improvement is modest.<sup>58</sup> This drug has been used for many years as a treatment for severe atopic eczema, but only recently has a double-blind, placebo-controlled study been undertaken. This double-blind, 12-week study, a TPMT-based dose regime produced a mean decrease in disease activity by 39% with azathioprine and a 24% decrease with placebo. Those responders often showed prolonged improvement 3-6 months after treatment.<sup>60</sup> The main drawbacks to the use in AD are the slow onset of action (4-6 weeks).

## Cyclosporin

Cyclosporin is a potent immunosuppressive drug that down-regulates cytokine production by inhibiting calcineurin, leading to reduced transcription of the genes for IL-2 and other lymphokines.<sup>61</sup> Cyclosporin is a rapid-acting and effective treatment for severe AD. At a dose of 5 mg/kg/day, a 55% reduction in severity scores was observed within eight weeks. Its major side effects are nephrotoxicity and hypertension, limiting its long term use beyond 12 months. An open-label trial of cyclosporin at 5 mg/kg/day in children with AD (age 2-16 years) led to significant improvement to total clearing in 22 of 25 patients.<sup>62</sup> Systemic therapy is usually conducted with an initial dosage of 2.5-5 mg/kg/day. Treatment can be continued for up to 12 months. However, most patients relapse within weeks of stopping this drug, and so cyclosporin dose must be reduced gradually. Harper et al showed that under continuous therapy the course of the disease is more controllable than intermittent administration of cyclosporin over 1-year period in children.<sup>63</sup>

## Traditional Chinese Herbal Medicine

As a result of considerable dissatisfaction with existing standard management of AD, some patients have tried complementary medicine and Chinese herbal remedies are the most popular in our locality. Few randomised controlled trial have been performed for the efficacy of Traditional Chinese Herbal Medicine (TCHM), and the results are conflicting.<sup>50</sup> Hepatotoxicity and cardiomyopathy has been reported following administration of TCHM, and patients are advised to have regular monitoring of liver function tests.<sup>64</sup> A study in the United Kingdom investigated the contents of 24 herbal creams bought in by parents of children with AD. It found that 19 "herbal creams" contained steroids and 12 creams contained the ultrapotent steroid, clobetasol.<sup>65</sup>

There is a recent report on a local randomised, double-blind, placebo-controlled study evaluating efficacy of a Chinese herbal medicine concoction for treatment of AD.<sup>66</sup> Eighty-five children with long-standing moderate-to-severe AD were randomised to receive a 12-week treatment with twice-daily dosing of three capsules of either TCHM or placebo. There was no significant difference in the scores at the corresponding time points between the two groups. However, the Children's Dermatology Life Quality Index in TCHM-treated patients was significantly improved compared with patients receiving placebo at the end of the 3-month treatment and 4 weeks after stopping therapy ( $P = 0.008$  and  $0.059$ , respectively). The total amount of topical CTS used was also significantly reduced by one-third in the TCHM group ( $P = 0.024$ ).

## Future Direction and Challenges

No therapy exists yet with proven evidence on altering the natural course of AD. Regarding the prevention of AD, the role of breast feeding in protection against atopy is still conflicting. There is no conclusive evidence that dietary intervention and allergen avoidance for the pregnant mother prevent AD in the child.<sup>50</sup> Probiotic treatment during pregnancy and nursing may delay the onset of AD in infants and children. A double-blind RCT using *Lactobacillus* GG has shown a significant effect on newborns at high risk of developing AD.<sup>67</sup> In this trial, mothers with atopic tendency ingested *Lactobacillus* GG or placebo during pregnancy. After birth, therapy was continued for the babies for

6 months. After 2 years, children from the treatment group showed a decrease in incidence of AD by 50% compared with placebo group. The findings suggest that early treatment with microbial probiotics may be more beneficial by boosting Th1 immune response in AD.

The intestinal flora plays an important role in postnatal development of the immune system. Dietary prebiotics, comprising mixture of galacto-oligosaccharides and long-chain fructo-oligosaccharides, stimulate an intestinal flora dominated by bifidobacteria. In a prospective, randomised, controlled trial on infants at risk of atopy, the intervention group received prebiotic supplemented with hydrolysed protein formula at the start of bottle feeding. 9.8% of the intervention group and 23.1% in the control group developed AD.<sup>68</sup> Prebiotic supplements were associated with a higher number of faecal bifidobacteria compared with control. It appears that oligosaccharides modulate postnatal immune development by altering the bowel flora and might have a role in primary allergy prevention during infancy. Certainly, larger studies are required before recommendations for this specialised diet during pregnancy and the postnatal period can be given.

## Summary

Atopic dermatitis is increasingly common in children. Skin barrier dysfunction and immune dysregulation is central to the pathogenesis of AD. The evolution of AD is also contributed by provoking factors, particularly infections. The complex etiologies warrant a comprehensive and holistic individual treatment strategy directed at both prevention and symptom control. Knowledge of these factors has led to the development of effective immunomodulating agents as exemplified by topical pimecrolimus and tacrolimus.

Genetic defects in skin barrier function should be recognised as major risk factors for the development of AD. Counselling of the patient about the nature of the disease and its treatment is essential for optimising the control of AD. Basic care like adequate use of emollients to restore the function of the skin barrier remains important. The modalities for the treatment of AD have expanded rapidly over the past decade. Topical corticosteroids remain the first line treatment. TCI offer a lower risk-to-benefit ratio in certain situations and so supplement the role of topical corticosteroids. It awaits further observation if TCI

will produce a disease-modifying effect with an earlier remission and if the long-term safety is ascertained. Advances in enhancing safety in potentially toxic drug helps to widen the therapeutic options of refractory AD.

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