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Contemporary Practice in Paediatrics

Management of Atopic Dermatitis in Children: 2020 Review by the Guidelines Development Panel of Hong Kong College of Paediatricians

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Abstract The Guidelines Development Panel on "Management of Atopic Dermatitis (AD) in Children" has performed the first updated review on the topic since the publication of the management guidelines by the Hong Kong College of Paediatricians in 2013. While most of the recommendations of the original guidelines are still valid, various management issues are further elaborated based on recent evidences in addition to the latest international and regional guidelines. Using validated clinical scores for assessment of severity of AD are advocated by the European guidelines to guide stepwise management and monitor progress. There are more evidences to support the proactive approach with use of topical anti-inflammatory agents as long-term treatment for the control of chronic recurrent AD. Topical corticosteroids remain first line topical agents for AD, while topical calcineurin inhibitors are indicated for sensitive areas and can be used as maintenance treatment. The role of newer therapeutic agents including topical phosphodiasterase 4 inhibitors, biologics and allergen immunotherapy for use in paediatric patients are deliberated. Management of itch, tackling issues of steroid phobia and compliance remain challenges in AD management. The concepts of skin barrier dysfunction in AD and targeting the skin for allergy prevention strategies are discussed.

Key words Allergy; Atopic Dermatitis; Child; Guidelines

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Introduction

The first set of "Clinical Guidelines on Management of Atopic Dermatitis (AD) in Children" was endorsed by the Hong Kong College of Paediatricians (HKCPaed) in December 2012.[1] The guidelines highlighted practical recommendations with reference to National Institute for Health and Clinical Excellence (NICE) guidelines "Management of Atopic Eczema in children, from birth to 12 years" published in December 2007.[2,3] Subsequently, NICE has further produced seven quality statements as standard of care in September 2013, which are regularly reviewed.[4] International guidelines from other countries have also been updated. In 2014, the American Academy of Dermatology (AAD) published a set of guidelines in four sections comprising more comprehensive recommendations as compared with the Joint Task Force practice parameters published in 2012.[5-10] The 2018 European consensus-based guidelines on management of atopic dermatitis in adults and children were issued in the Journal of European Academy of Dermatology and Venereology.[11,12] Regional guidelines were released by the Japanese Dermatology Association and the Japanese Society of Allergology in 2016 and 2017 respectively[13,14] and guidelines from the Asia-Pacific Consensus Group for Atopic Dermatitis were available in 2015.[15] These guidelines have addressed recommendations for children in various areas. The HKCPaed Guidelines Development Panel has reviewed these updated guidelines and together other new evidences, the panel agreed that our local practice recommendations in 2013 are still applicable. Several management issues are further elaborated in this article:

- Clinical scores for severity assessment to guide management
- Proactive approach for maintenance
- New therapeutic agents including topical anti-inflammatory agents, biologics and allergen immunotherapy
- Targeting the skin for prevention of AD and other allergy diseases

Prevalence of AD

Atopic dermatitis (AD) affects children globally with prevalence of up to 20% in some countries and there is a two-to-threefold increase in industrialised countries in the past decades.[16] In Hong Kong, results of the International Study on Asthma and Allergy in Childhood (ISAAC) phase one (1994-95) and phase three (1999-2001) studies revealed that the prevalence of children with current eczema remained similar at 3.8% and 3.9% for 13 to 14 years old, and slightly increased from 3.6% to 4.2% for 6 to 7 years old.[17-20] Another publication in 2007 showed a prevalence of 5.6% in pre-school children.[21] There has been a lack of more recent local prevalence data for more than 10 years. From 2001-2017, a local cross-sectional survey using the ISAAC questionnaire has recruited 2000 parents of children 6 to 7 years old, but results are not yet published at the time when this article is written.[22]

Diagnosis of AD

The diagnosis of AD remains clinical and is based on the widely adopted Hanifin and Rajka clinical criteria.[23] The NICE and Japanese guidelines describe diagnostic features specifically for children, and highlighted AD being an inflammatory, pruritic and chronically relapsing skin disease often occurring in families with other atopic diseases.[6,11,13,14] AD rashes have classical distributions that vary with age.[13] Atopic tendencies can be defined either by (1) a personal or family history of bronchial asthma, allergic rhinitis, allergic conjunctivitis or atopic dermatitis, or (2) an overproduction of immunoglobulin E (IgE).[6,13] There is no pathognomonic laboratory biomarker for the diagnosis of AD.[6] Serum total or allergen-specific IgE levels, and skin prick tests with specific allergens may help the diagnosis of IgE-associated atopic tendencies.[11] Raised total IgE levels are seen in up to 80% of patients with AD and correlate with disease severity,[13] while eosinophilia may be found in some but not all AD patients. Atopy patch testing is useful in diagnosing contact dermatitis that might occur concomitantly in recalcitrant widespread eczema.[11]

Use of Clinical Scores to Document Disease Severity and Guide Stepwise Management

SCORAD (SCORing Atopic Dermatitis),[24] EASI (Eczema Areas and Severity Index)[25] and NESS (Nottingham Eczema Severity Score)[26] are some of the most commonly used validated clinical scores for documenting extent and severity of lesions.[27] These scores are useful to guide management and assess response to treatment.[11] CDLQI

(Children's Dermatology Life Quality Index) is a short term subjective symptom score for monitoring of life impact on various skin conditions including AD.[28] Validated Chinese versions of SCORAD, NESS and CDLQI scores are available.[29,30] PO-SCORAD (Patient-Oriented SCORAD)[31] and POEM (Patient-Oriented Eczema Measure)[32] are useful tools for patients to monitor their own disease activity.

In a systematic review, 15 AD severity scores were found to be in good correlation. Assessment of itch and sleep disturbance are the two parameters common to most eczema scores.[33] In the latest European guidelines, SCORAD is included to guide management.[11] If clinical scores are not used in practice, the following should be assessed and documented to guide stepwise management of AD as in Table 1[3,11,13]

- Signs: extent and severity
- Symptoms: itch and sleep
- Quality of life (QoL): psychological well-being of child and family

Goals of Management

The goals of AD management in children should aim at disease control to prevent chronic skin damage using therapeutic agents with minimal side effects, and to ensure the physical and psychological well-being of the child and family.

Basic Management

Basic management for all severities of AD involves (1) skin hydration with emollients; (2) identification and avoidance of triggers; and (3) education and psychological support.

1. Emollients and Bathing Practices

Genetic defects in filaggrin (FLG), an epidermal protein responsible for aggregating the cytoskeleton, contribute to skin barrier dysfunction in AD and are linked to

Table 1 Stepwise treatment of atopic dermatitis in children[12]

Level of severity	Physical signs	Quality of life (QoL) assessment	Treatment
Severe or persistent SCORAD >50	Widespread areas of dryness Redness Swelling Lichenification Oozing/Scabs Scratch marks and alteration	Incessant itch Sleepless nights, disruption of QoL Loss school days	- Hospitalisation - Potent to very potent TCS - Systemic immunosuppressants (e.g. Cyclosporin A, Azathioprine, Methotrexate) - Dupilumab if age appropriate
Moderate or recurrent SCORAD = 25-50	Localised areas of dry skin Redness +/- excoriation or localised skin thickening	Frequent itching Sleep disruption Moderately affects QoL	- Moderate to potent TCS - TCI - Proactive therapy with TCS or TCI - Wet wrap therapy - Phototherapy for older children
Mild or transient SCORAD <25	Areas of dry skin Small areas of redness	Infrequent itching Some disturbance in sleep Minimal impact of QoL	- Mild to moderate potent TCS - TCI - Antiseptics and antimicrobials for secondary infections
Dry skin only and for all severity	Basic management: - Skin hydration, emollients - Addressing specific triggering factors - Education and psychological support		

STEP UP according to severity*

SCORAD: SCORing Atopic Dermatitis

*For each step:

- Add on treatment to previous level as appropriate
- Consider the need for treatment of superimposed infections
- Ensure compliance and review for alternative diagnoses before stepping up
- Referral to dermatological specialist as indicated

development of other allergic diseases in later life.[34] Maintenance of skin barrier function is the cornerstone of AD therapy for controlling transepidermal water loss, itch, inflammation and infections. Emollients should be used as basic skin care even when the skin is clear of active lesions.[35]

1.1 Choice of Emollients

Cochrane review in 2017 and recent studies revealed that regular use of emollients could improve symptoms, decrease flares, and reduce the need for topical corticosteroids in AD.[36,37] Emollients containing glycerol, urea or glycyrrhetinic acid were reported to be better compared to controls (vehicles, placebo or without emollients). Newer formulations of emollients containing ceramides, cholesterol, fatty acids and new technologies are developed to enhance delivery of these substances to enhance skin barrier. However, current evidences do not support demonstrate any emollient being significantly better than another.[36,37]

Most emollients are found to be safe but adverse effects have been reported. Urea-containing emollients are effective but irritation has been reported especially when applied to skin with lesions. Though the risk of 5% urea cream in causing renal dysfunction in infants has not been established, it might best be avoided for children younger than 2 years old and a more diluted concentration is preferred for toddlers.[11,37,38] Emollients containing proteinaceous allergens such as oat-meal, peanut oil, lanolin may cause contact allergy,[11,37] while other emollients containing antiseptic or antibacterial agents like benzalkonium chloride may produce contact dermatitis.

Sodium lauryl sulphate (SLS) is a surfactant commonly found in bathing substitutes and leave-on emollients such as emulsifying ointment and aqueous cream. In the past decade, studies suggested that SLS might cause skin irritation, dryness and thinning especially in children with AD.[39,40] The adverse effects depend on concentration of SLS, duration of exposure, individual skin condition and age.[41] With review of available evidences, authorities in European Countries (EU),[41] United Kingdom (UK),[42] United States (US)[43] and Australia[44] have issued recommendations concerning the use and proper labelling of SLS in topical emollients. In general, SLS-containing emollients are safe to use as soap substitutes when applied briefly and washed off, while their use as leave-on emollients have a potential risk of irritation. The recommended threshold concentration of SLS in these products is 1% in US and 1.5% in Australia[43,44] and labelling of products containing any concentration of SLS is needed for EU.[41,42] Yet, side effects vary among individuals and there has been long history of use by patients who do not report significant adverse effects. SLS-containing products can be applied upon weighing of risks and benefits while patients should be alerted to the possible adverse effects. SLS-free emollients shall be prescribed instead when irritation arises.[42] It is worth mentioning that other than SLS, emollients may contain other surfactants, preservatives or components that can also cause irritation.

"Natural" oils are getting more popular as non-conventional emollients. However, it has been shown that olive oil can disrupt the skin barrier, increase dryness and worsen AD. Further research is needed for other natural oils, such as sunflower oil and coconut oil, before any recommendations can be made.[45]

The best emollient is one that is acceptable and affordable to patient and family. Ideal emollients from patients' and parents' perspectives include non-fragrant, non-herbal, white or transparent preparations that require applications of no more than two to three times per day.[46] Oily ointments have higher moisture retaining properties but should be balanced with comfort and tolerability which may affect compliance.[13] Different emollients may be needed for different times of the day, seasons and body parts depending on patient's preference and enviromental conditions.

1.2 Quantities of Emollients

Adequate quantities of emollients are estimated according to the age of patients. Infants require about 125 grams per week, small children 250 grams per week, while large children or adults may need around 500 grams per week.[4,11] Emollients should be applied at least twice a day or more liberally depending on skin conditions.[13]

1.3 Bathing Practices

Bathing daily in lukewarm water thoroughly but gently for not more than 5-10 minutes is recommended.[11,47] Recently, the BATHE study showed no difference in symptom scores with and without addition of bath emollients for AD management in children.[48] Bathing followed by emollient application (referred to as the "soak and seal" method) is probably more relevant.[47] Bathing and showering practices are influenced by culture. Showering can remove sweat and it is preferred to bathing especially during humid summer seasons in Hong Kong.[13,49] The use of antiseptics is discussed in the section of management of infections.

2. Identification and Avoidance of Triggers

2.1 Common Triggers and Avoidance

Common triggers of AD include mechanical or chemical irritants, extreme temperatures, tobacco smoke, local and systemic infections, and specific allergens (Table 2).[3,11,13] Heat and sweat are the commonest triggers during the hot humid weather in Hong Kong. General advice include the use of light breathable clothing and bedding, wiping off sweat properly, ensuring cool and smoke-free environment.[50] Clinical studies on specific aeroallergen avoidance against house dust mites have been ambivalent. Climate therapy and relocation to mite-free environments have been shown to be beneficial to some AD patients.[11] For pet avoidance, studies have demonstrated a correlation between cat exposure with AD, while dog exposure at early life seems be unrelated to or even protective against AD.[11] Clothing and cleanser choices should be non-irritating,[11] but large scale studies are lacking in terms of protective clothing. Psychological stress is also a major contributor to itch and AD especially in late childhood and adult populations.

2.2 Food Allergy and AD

Food allergy is a contributing factor in up to one-third of young children with moderate to severe AD.[11,13] Based on current evidences, food allergy is a trigger rather than a cause of AD. Recent data suggest that AD precedes and contributes to the development of food allergy.[51] It is postulated that cutaneous exposure of food antigens through the inflammed skin in AD in early life give rise to sensitisation.[52]

Type I IgE-mediated food hypersensitivity skin reactions are typically non-eczematous urticarial rashes presenting along with systematic reactions including anaphylaxis, angioedema, or gut dysmotility symptoms within 2 hours of exposure and usually resolve within a day.[3,11] Eczematous flares triggered by food antigens are Type IV delayed-type hypersensitivity reactions appear at around 6-48 hours after exposure. A combination of Type I and Type IV reactions occurs in approximately 40% of children.[11] Diagnosis of food allergies is made by detailed history taking, allergen tests, food elimination and provocation test as indicated.[13] Skin prick tests are used for the diagnosis of type I reactions. Type IV food hypersensitivities may be confirmed by atopy patch tests.[11] Other allergy tests with unproven diagnostic value provided by community and online suppliers are discouraged.[3] Definitive diagnosis of food allergy is confirmed by supervised double-blind placebo-controlled food challenges which is contraindicated in patients with severe allergic reactions or anaphylaxis.[11]

For non-breastfed infants younger than six months old with moderate to severe AD resistant to standard treatment, the British guidelines recommend empirical trial of extensively hydrolysed protein or amino acid based milk formulas for six to eight weeks.[3] In Hong Kong, parents commonly practice dietary exclusion of foods, in particular fish, seafood and beef for their children with AD.[53] Comprehensive reviews showed that there were insufficient data to support indiscriminate elimination diets for AD.[53,54]

Table 2 Common triggers of atopic dermatitis

Triggers of AD	Common examples
Irritants	Sweat, wool fabrics, soap
Environment	Extremes of temperature, dryness, smoke, air pollutants
Infections	Local infections with microbes, systemic infections (e.g. viral illness)
Psychosocial	Stress, anxiety
Allergens	Food, animal dander or saliva, house dust mites (HDM), mould, pollen, fragrances contact allergens

3. Education and Psychological Support

Patients and their carers should be empowered to participate in management of AD according to the personalised treatment plan. Misconceptions and fallacies about eczema are common and frequently lead to problems of non-compliance, treatment failure and psychosocial stress.[55] Healthcare providers should allow sufficient time during consultations to provide education, agree on a plan to achieve the goals of management, and address concerns on the various aspects of eczema management including diagnosis and prognosis, triggering factors, therapeutic options and the related side effects. At every clinical visit, compliance and proper application of AD prescriptions have to be reinforced, use of alternative treatments, and impact on quality of life and psychosocial issues should be explored.[3] Studies have shown that non-compliance to treatment is a major issue in AD management.[12] Psychological stress exacerbating the itch-scratch cycle, and intrafamilial psychodynamics can contribute to non-compliance. Education of patients and caregivers through nurse-led or digital mediated educational programmes, eczema workshops or camps to provide multidisciplinary

age-related structured group training programmes have been recommended as adjuncts to conventional AD treatment.[12,56]

Psychosocial issues are often untended to with depression, anxiety, stress and guilt feelings of patients and caregivers complicating the management of eczema. Severe complications and tragedy with deaths due to malnutrition, suicide and homicide related to eczema have been reported locally.[57-59] Provision of psychosocial and psychiatric intervention are of paramount importance to allow timely support of individuals and their caregivers[3,11] Psychotherapy, counselling, behavioural therapy and relaxation techniques could help patients and family to better cope with disease.[9,12,13]

Topical Anti-inflammatory Agents for Acute Flare and Maintenance Treatment

Therapeutic agents used for management of AD depend on severity assessment (Table 1). Most children with AD can be effectively managed with topical anti-inflammatory agents. Adjunctive therapies include anti-pruritic medications for management of itch, antiseptics and antibiotics for management of infections.

Principles of Topical Anti-inflammatory Agents Use

Topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) are the most commonly used topical anti-inflammatory agents for treatment of acute flares and maintenance therapy.

Acute flares: Treat with topical anti-inflammatory (usually TCS) with potency appropriate for the severity at the first sign of active flare and continued at least until visible lesions are cleared, then followed by step-wise tapering with either a less potent TCS or less frequent application can prevent rebound of AD symptoms. It must be stressed that tapering of TCS should not be done too early as subclinical inflammation persists.[11,14,60]

Proactive versus reactive approach for maintenance therapy: AD is a chronic inflammatory condition with subclinical inflammation present in skin without visible lesions.[61] The classical reactive approach of using topical anti-inflammatory agents only during acute flares for short duration is applicable to mild transient disease (Table 1). The proactive management strategy of AD control has emerged for prevention of flares in moderate to severe and recurrent disease as supported by recent evidences and international guidelines.[9,11,14,62] The proactive approach is the induction of remission of acute eczema with topical anti-inflammatory agents, followed by maintenance treatment with low dose TCS or TCI intermittently two to three times per week to the treated areas, while using emollients for skin care over all affected and unaffected areas.[11,62-64] Studies have shown the effectiveness in preventing AD flares and safety of proactive use of TCS for up to 20 weeks and TCI for up to 52 weeks.[3,11,60,62,65] There is no consensus on the exact length of proactive therapy.

1. Topical Corticosteroids (TCS)

TCS remains the mainstay of medical therapy for AD.[11,13,60] Appropriate strength, dosage and correct application of topical anti-inflammatory agents are the three main pillars of effective AD treatment.[11] There are different classification systems for TCS potency in different countries. In this article, we have used the Niedner's classification (used in UK, Australia and New Zealand) with 4 classes of steroids namely mild, moderate, potent and very potent, instead of using Roman numbers (I, II, III, IV) to avoid confusion with other classification systems.[66] Common TCS formulations available in Hong Kong are listed in Table 3.

Dilution of TCS with emollients will not reduce its potency or side effects.[11,60] With the same compound and concentration, ointments are more potent than creams and lotions. In the same class of potency, newer TCS (e.g. mometasone furoate and fluticasone diproprionate) have less adverse effects like skin atrophy then old halogenated TCS (e.g. fluocinolone acetonide), and are therefore more appropriate for infants and sensitive skin areas.[1,5,63] Dosage of TCS can be measured by the fingertip unit (FTU),[67] which approximates to 0.5 gram of the ointment squeezed from a tube with a 5 mm nozzle along the index finger from the tip to the first finger joint. One FTU of ointment applied "even and thin" is adequate to cover skin area equivalent to two adult hands with fingers together. The maximal amount of FTUs applied can be estimated according to age and body parts (Table 4).[68]

Evidences to support recommendations on how to apply TCS are limited. A Cochrane review protocol on the effectiveness and safety of different practices in application of TCS for people with eczema has been recently submitted in 2019.[69] Its generally recommended to apply TCS for once or twice daily, and more recent studies suggest that once daily application of newer TCS may suffice.[3,7,70] At least 15 minutes should lapse between application of different topical medications and emollients. Whether a

formulation should be applied first or last depends solely on patient's preference.[3]

TCS applied two to three times per week as maintenance treatment with a monthly amount of 15 g in infants, 30 g in children and 90 g in adolescents is generally safe.[11] Duration of therapy depends on individual AD severity, site of application and the choice of TCS formulation.[1] NICE guidelines in 2006 recommended TCS to be applied 7 to 14 days for acute flares of AD.[3] Studies suggest that proactive intermittent use of low potency TCS (e.g. 1% hydrocortisone cream or ointment) to mid potency TCS (e.g. 0.05% fluticasone diproprionate cream or 0.1% methylprednisolone aceponate) twice per week for up to 20 weeks are considered safe and effective.[11,65,71,72]

Local adverse effects of TCS like hypertrichosis, skin atrophy, telangiectasis, striae are uncommon and found mainly after inappropriate usage.[60] Hypopigmentation or hyperpigmentation is related to the clearing of the eczema rather than due to side effects of TCS. Use of TCS has to be more cautious over sensitive areas and skin folds including face, axilla, neck and napkin area.[11,13] Severe side effects including cataracts, hypothalamic-pituitary-adrenal axis suppression and Cushing's disease are rare. Risks of adverse effects increased with high potency TCS, prolonged use

Table 3 Potency of common topical corticosteroids available in Hong Kong

Potency	Generic name	Strength	Formulation*
Mild	Hydrocortisone acetate	0.1%-2.5%	L/C/O
Moderate	Clobestasone butyrate	0.05%	C/O
	Desonide	0.05%	L/C/O
	Fluocinolone acetonide	0.005-0.0125%	C/O
	Triamcinolone acetonide	0.1%	C/O
Potent	Betamethasone dipropionate	0.025-0.05%	L/C/O
	Betamethasone valerate	0.1%	L/C/O
	Fluocinolone acetonide	0.025%	C/O/gel
	Fluticasone proprionate	0.05%	C
	Methylprednisolone aceponate	0.1%	C/O
	Mometasone furoate	0.1%	L/C/O
Very potent	Betamethasone dipropionate in propylene glycol	0.05%	C/O
	Clobetasol propionate	0.05%	L/C/O/S
	Diflucortolone valerate	0.1%	C/O/fatty ointment

L = Liquid which includes lotion# and those label as "scalp application" S= Shampoo

C = Cream

O = Ointment

*For the same drug, in order of potency L<C<O

References: (15, 119)

Table 4 Maximal amount of TCS applied to body parts according to age[68]

	Infants 3-6 months	Infants 1-2 year	Small child 3-5 years	Child 6-10 years	Adolescent >12 years
			Finger-tip unit (FTU)#		
Face and Neck	1	1.5	1.5	2	2.5
Trunk (Front)	1	2	3	3.5	7
Trunk (Back + buttock)	1.5	3	3.5	5	7
1 Arm + Hand	1	1.5	2	2.5	3+1
1 Leg + Feet	1.5	2	2	4.5	6+2

Finger-tip unit (FTU)= 0.5 gram of the ointment squeezed from a tube with 5 mm nozzle along the index finger from the tip to first finger joint of adult hand. One FTU of ointment applied

and occlusion.[60] Tachyphylaxis is not proven in TCS.[13] There is good evidence to support the safety of appropriate TCS use for paediatric AD.[60]

Steroid Phobia

Steroid phobia is an important reason for treatment failure. A systematic review of 16 worldwide studies including two local studies found that the prevalence of steroid phobia ranged from 21% to 83.9% in various countries. The main concerns are skin thinning and other skin adverse effects, growth and development problems and other non-specific long term effects.[73] Steroid phobia influences acceptability and usage of TCS by patients and caregivers, which in turn leads to poor AD control.[74]

In our local population, misconceptions and fallacies on AD are related to mistrust and unrealistic expectations about Western Medicine, phobias of anti-inflammatory agents, and use of complementary and alternative therapies.[55] On-going education by healthcare professionals and provision of updated information to caregivers are of topmost priority.[60]

2. Topical Calcineurin Inhibitors (TCI)

TCI is indicated for acute and proactive treatment of AD, especially over sensitive body areas like face, eyelids, intertriginous and anogenital areas. For acute flares, initial use of TCS to induce remission followed by TCI may be considered.[7] The age indications for the three available TCIs have remained unchanged (see below). With the availability of safety data of the two TCIs, the latest American and European guidelines recommend off-label use of 0.03% tacrolimus and 1% pimecrolimus ointment for children less than 2 years old if clinically indicated.[7,11]

TCI	Age indication	AD severity
1% pimecrolimus cream	≥2 years old	Mild-Moderate
0.03% tacrolimus ointment	≥2 years old	Moderate-Severe
0.1% tacrolimus ointment	≥16 years old	Moderate-Severe

Duration and dosage of TCI for proactive therapy depend on individual AD severity. Studies have shown that TCI use twice per week up to one year is safe and effective in reducing AD flares and improving quality of life.[11,12,65,71] Dosage recommendation of 0.03% tacrolimus ointments applied per day for children aged 2-5 years (or body weight <20 kg) is ≤1 g; children 6-12 years (or 20-50 kg) is ≤2-4 g; while children 13 years or older (>50 kg) is ≤5 g.[13]

Side effects of TCI are mild, tingling or burning sensations that occur within an hour of application, tend to resolve after a few days or with emollient application. TCI has the advantage of increasing skin thickness contrast to the risk of skin atrophy for TCS. Systemic absorption of TCI is minimal with no increase in infection or carcinogenic risks. Although the FDA has not withdrawn its black box warning issued in 2006 with concerns of lymphoma risks shown in animal studies, subsequent clinical studies have not shown any increase in risk of lymphoma or other related cancers from TCI use.[63,75] However, UV protection for TCI use to reduce the potential risk of carcinogenicity is still recommended.[11,13] Clinicians are advised to alert patients and caregivers to the black-box warning before starting treatment.

3. New Topical Anti-inflammatory Agents

Crisaborole 2% topical ointment (topical phosphodiesterase 4 inhibitor) - Efficacy and safety of twice daily application of Crisaborole topical ointment for up to one year treatment of mild to moderate eczema has been demonstrated. The drug has been recently approved for patients 3 months and older and may soon be available locally. Other new selective topical phosphodiesterase 4 inhibitors are currently under investigation. However, their efficacy when compared with TCI and TCS is not yet determined.[11,76]

Sodium cromoglycate 4% emulsion - A new formulation of an old drug has been investigated with positive results for eczema in children and safe for long term use up to 15 months.[76,77] However, this is not available in Hong Kong.

Other novel topical anti-inflammatory agents under investigations including lipoxins and janus kinase inhibitors (JAKi) e.g. tofacitinib[76] require further studies to prove the efficacy and safety in paediatric population.

Adjunctive Therapy

1. Dry Wrap and Wet Wrap Therapy

Bandages or cotton clothing can be used for dry or wet wrapping. Localised wrapping after application of emollients and TCS is indicated for chronic lichenified AD with acute flares.[3] The treatment can be maintained for 3 to 14 days to control flares effectively and improve patients' tolerance to corticosteroids.[3,11,78] Effects may last for one month and can be continued with emollients alone until AD resolves.[3,78] Whole body dry or wet wrap therapy

with emollients and TCS should not be the first-line therapy and must be supervised by healthcare professionals.[3] Occlusive dressings, dry or wet wrap therapy should not be used for infected AD and these are not recommended for TCI due to uncertainty of systemic absorption.[13]

2. Anti-pruritic Agents

Itch is the most disturbing symptom which affects sleep and quality of life and the itch-scratch cycle further aggravates AD. The pathogenesis of itch in eczema is contributed by multiple factors including skin barrier dysfunction, abnormal Th2 immune response, various itch mediators and hyperinnervation of skin. Exacerbating factors trigger cytokines and mediators release that induce itch through stimulating nerve endings.[50] Effective treatment of AD with emollients and topical anti-inflammatory medications are the cornerstone for the management of itch. Identification and avoidance of external triggers of itch are essential.

2.1 Oral Antihistamines

1st and 2nd generation oral H1 antihistamines have long been used in AD. However, a recent Cochrane meta-analysis of studies in adults and children showed no evidence that oral H1 antihistamines are effective as "add-on" treatment of AD.[79] Antihistamines may be considered for type I hypersensitivity reactions like urticaria and allergic rhinitis that coexist with AD. First generation antihistamines may be beneficial in AD through its sedative effect.[11] However, there are also concerns on the adverse effects on sleep quality with long term use of antihistamines.

2.2 Other Anti-pruritic Therapy

There is insufficient evidence to prove that topical antihistamines, topical cannabinoid receptor antagonists, topical non-steroidal anti-inflammatory drugs ("NSAIDs") or topical anaesthetics are effective antipruritic therapy.[11,13] Provision of adequate education, age-appropriate distraction techniques such as breathing and relaxation exercises, and activity involvement are adjunctive treatments for itch relief.[80]

3. Anti-microbials and Antiseptics for Management of Infections

Microbial dysbiosis by an overgrowth of Staphylococcus aureus has been found to be associated with AD flares. Secondary infections can be due to bacteria such as Staphylococcus aureus and Streptococcus pyogenes, viruses like herpes simplex and molluscum contagiosum and fungi. Routine skin swab sampling is not recommended and are only needed when antibiotic resistance or when organisms other than *S. aureus* or methicillin-resistant *S. aureus* (MRSA) are suspected.[3,8] Antibiotic use for non-infected AD skin is not recommended.[3,9,12] Topical antibiotics can be applied alone or combined with TCS on AD skin with localised infections.[3] Systemic anti-staphylococcal antibiotics like oral flucloxacillin or first generation cephalosporins could be prescribed as first line antibiotics when bacterial superinfection is found.[12]

Upon diagnosis of eczema herpeticum, prompt initiation of antiviral therapy with systemic acyclovir and referral to specialists or emergency medical service is indicated.[3,4,12] Add-on systemic antibiotics may be required in cases with secondary bacterial infection or when such possibility cannot be ruled out.[3] Treatment of other viral infections such as molluscum contagiosum and Coxsackie infection is mainly symptomatic.[12] Antifungal therapy including topical ketoconazole shampoo or systemic itraconazole, fluconazole may be indicated to add on to topical anti-inflammatory agents for head and neck dermatitis or patients with *Malassezia spp*. IgE sensitisation.[12] In general, TCS should be continued during antimicrobial use in most conditions provided specific treatment for the infections are given.[12] Topical steroids are not recommended during the acute illness of eczema coxsackium but can be reintroduced to treat eczema once the child is afebrile.[81] TCI should be stopped during acute infection.

Diluted bleach bath with 0.005% bleach (i.e. 1:1200 of home-used bleach containing 6% sodium hypochlorite) twice per week can be used as an antiseptic for moderate to severe or infected eczema for its benefits in reduction of bacteria and repair of skin barrier.[7,11,12,82] Coal tar has been shown to have anti-inflammatory and antiseptic effects. A local randomised control trial (RCT) on adding pine tar for bathing showed significant improvement in symptom scores and decrease in Staphylococcus aureus colonisation in paediatric subjects with moderate to severe AD compared with vehicle.[83] There is no evidence for using antiseptic bath soaps in non-infected AD patients.[84]

Phototherapy, Systemic Agents and Other Therapies

Phototherapy, systemic immunosuppressive agents and biologics are second line therapeutic options for more

severe or recalcitrant AD. Before considering these treatment modalities, the patient should be evaluated for possible alternative diagnoses, treatment compliance, optimisation of management with topical therapy, avoidance of triggers and adequate education. The severity of AD and impact on quality of life has to be balanced with risks of therapy.[85] Referral to specialist care is highly recommended should these therapies be considered. Detailed discussions and recommendations on these advanced therapies are beyond the scope of this article.

1. Phototherapy

Exposure to natural or artificial ultraviolet ("UV") light has been found to be mostly beneficial on AD patients, though some may worsen following UV exposure. Explanations for its benefits vary but include the immunomodulatory and anti-inflammatory effects of UV and vitamin D.[8,11,13] Phototherapy is considered an effective and safe second-line therapy with anti-pruritic effects for moderate to severe AD in adults and children. Systematic review of small studies on narrowband UVB (NB-UVB) and UVA (UVA1) showed that both are effective in improving clinical scores of AD and safe with minimal side effects.[86,87] There is little evidence on differences on comparative studies.[88] In Hong Kong, NB-UVB is more commonly used. Choice of wavelength and dose shall be individualised depending on the skin type and tolerance.[8] The common side effects of phototherapy include photodamage, xerosis, erythema, actinic keratosis, sunburns and tenderness.[86] There has been limited clinical data on the long-term risk of skin cancer associated with UV therapy in children.

Emollients and TCS can be continued until 2 hours before the phototherapy while TCI shall be avoided.[63] The enclosed hot environment and compliance issues have limited the application of this treatment modality in children. Patients need to travel to designated centres with the equipment to receive treatment 2-3 times per week for 6-12 weeks. However, the relatively small size of our city could be an acceptable option for older children with moderate to severe AD who do not respond to the usual topical treatment.[8,11,13] Targeted phototherapy delivers high energy UV light to the involved areas only. It allows treatment of localised areas such as the scalp, nose, genitals, etc; it is easy to administer and is better tolerated by children.[89] More research is needed to demonstrate its effectiveness for localised AD in children. Moreover, the use of daylight phototherapy and home-based phototherapy are currently being explored.

2. Systemic Immunomodulatory Therapy

In a systematic review which include limited paediatric data, cyclosporin A is recommended as the first-line systemic immunomodulatory treatment, while azathioprine and methotrexate could be recommended as alternative options for moderate to severe AD.[90]

2.1 Short-term Oral Glucocorticoids

Systemic steroids may be considered in adults but should not be used for AD in children as risks outweighs the benefits.[8,12,13]

2.2 Cyclosporine A (Cys A)

For severe AD, Cys A can be started at 2.5 mg/kg/dose twice daily and reduced by 0.5-1.0 mg/kg/day every 2 weeks when treatment effect has been achieved. Trials for children 2-16 years old revealed similar results with intermittent short-term treatment of 12 weeks or low dose continuous treatment for 1 year. Side effects including nephrotoxicity and hypertension shall be closely monitored. There is no role of drug trough levels in monitoring of cyclosporine A treatment.[11,13]

2.3 Azathioprine

An off-label treatment for children with severe AD starting at 1-3 mg/kg/day can be considered if cyclosporine A is ineffective or contraindicated. Apart from risks of malignancies and teratogenicity, azathioprine can induce severe fatal myelosuppression in patients with thiopurine methyltransferase (TPMT) deficiency more commonly found in Caucasians, or nucleotide diphosphatase (NUDT15) deficiency which is particularly relevant for Asians and our local Chinese population.[91] FDA recommends prior laboratory screening for TPMT genotype or phenotype and NUDT15 genotype before initiation of treatment.[92] Regular monitoring of complete blood profile and liver function tests are needed during Azathioprine use.[11,63]

2.4 Methotrexate

A few retrospective studies on low dose methotrexate in children with AD demonstrated that it is safe and effective with similar efficacy compared to cyclosporin.[63]

Limited data is available for other systemic therapy like mycophenolate mofetil (MMF), interferon gamma, montelukast or immunoglobulins.[11,63,90]

3. Biologics

Dupilumab is a fully human monoclonal antibody and

dual interleukin-4 (IL-4) and interleukin-13 (IL-13) receptor inhibitor. Since 2019, it has been the only biologic approved for moderate-to-severe AD in patients 12 years and older who are not responsive to topical or systemic treatments in USA and Europe. Emollients and TCS or TCI should be continued during subcutaneous dupilumab use and its maintenance effect has been shown to last for over 1 year with minimal side effects.[12,76] Off-label use of dupilumab with injection every 2 weeks or 4 weeks in children <12 years old has been reported.[93] Based on the positive results of the phase 3 study for children 6 to11 years old being treated for 16 weeks, US Food and Drug Administration (FDA) lately approved the drug to be used from 6 years old.[94] Its clinical use is however limited by the high cost.

Other biologics like rituximab, omalizumab or ustekinumab are not recommended for AD, while some guidelines recommend short-term use of mepolizumab, an anti-interleukin-5 antibody, in selected cases.[12]

4. Allergen Specific Immunotherapy (ASIT)

Subcutaneous immunotherapy ("SCIT") and sublingual immunotherapy ("SLIT") are two regimens for treatment of allergen sensitisation commonly used for allergic rhinitis and allergic asthma. There are some evidences suggesting ASIT with house dust mite is an effective treatment for selected, highly sensitised patients with severe AD flares after exposure.[12] The Cochrane systematic review found only limited evidences that ASIT could be an effective treatment for AD and future studies with high quality allergen formulations were suggested.[95] Currently, ASIT remains an "off-label" treatment option and should only be considered when clearly informed decision is made with patients and caregivers.

5. Vitamin D

Current data supports that vitamin D deficiency is associated with AD severity especially in children.[96,97] It is important to be alerted to vitamin D and other nutritional deficiency in AD and provide supplementation in cases of documented deficiency. Effects of empirical supplementation of vitamin D supplementation are inconsistent.[96,98] Further research on dosage, timing, duration of vitamin D for management of various severity of AD are needed before specific recommendations could be made . The role of Vitamin D supplement for prevention of AD and allergic diseases is also uncertain.

6. Traditional Chinese Medicine (TCM)

Various Traditional Chinese Medicine (TCM) formulations are being used in our locality as an adjunctive therapy or sole treatment for AD. A local study of a Chinese herbal concoction had shown efficacious improvement in quality of life and reduction in TCS use.[99] Cochrane review of 28 randomised controlled trials was not able to draw definitive conclusions on the benefit of either oral or topical TCM on AD for children and adults due to the heterogeneity and poorly designed studies.[100] The NICE guidelines stressed the possible presence of hepatotoxic ingredients and the use of corticosteroids in certain TCM preparations.[3] Use of unfounded complementary alternative medicine followed by cessation of original medical prescriptions may cause worsening of AD.[11-13] Patients and caregivers are advised to consult registered TCM practitioners for proper assessment and prescription of TCM.

7. Other Complementary Alternative Therapy

Currently, there is no evidence to support the use of probiotics or prebiotics, acupuncture, topical unsaturated fatty acids, topical crude plant extracts, autologous blood therapy, bioresonance, homeopathy, aroma therapy, massage therapy, salt baths, avocado oil and vitamin supplementation for treatment of AD.[3,12,13]

Referrals and Collaborations with Other Professionals

Collaborations between nurses, social workers, allied health workers, psychologists and psychiatrists may be needed especially for but not limited to severe cases.[3,11] When AD is recalcitrant to treatment, referral to dermatology specialists or specialised centres is recommended for consideration of differential diagnoses like contact dermatitis, cutaneous lymphoma or mycosis fungoides.[3,4] Other specialists shall be involved when comorbidities such as immunodeficiencies are suspected or complications like retinal detachment, cataract, or stunting of growth have occurred.[13]

Prevention of AD and Atopic March

'Atopic march' refers to the progression of allergic conditions which often begins with AD in early infancy

followed by food allergy, allergic rhinitis and asthma in later childhood. The skin barrier theory is being postulated as the biological mechanism for atopic march. The disrupted epidermal barrier in AD, environmental factors, and infections predispose to cutaneous antigen penetration, which stimulates local Th2 immune responses and subsequent development of other allergic diseases. Hence, intervention strategies targeting the skin to prevent atopic march are implicated.[101] The concept of disease progression in atopic march may in fact be more complex as heterogenous phenotypes of allergic diseases and co-manifestation of multiple allergic diseases are observed. There are ongoing studies on differential mechanisms, prognosis and development of targeted strategies to search for effective treatment and prevention of allergic diseases.[102]

A group of local allergists published guidelines on measures for allergy prevention including recommendations on diet for mothers and infants, environmental avoidance of smoking and air pollution, immunisation and judicious use of antibiotics. The guidelines also suggest early treatment and control of allergy diseases of which eczema is usually the first to present in infants.[103] Preventive strategies for infants at risk of eczema include empirical emollients, modification of maternal and infant diets, probiotics and prebiotics are discussed in more details below.

1. Empirical Emollients

Two earlier studies on empirical application of emollients within the first month of life for at risk infants have shown reduction of AD incidence at 6 months by 32-50%.[104,105] Subsequently, various countries have carried out further studies. The PEBBLES pilot study (A randomised controlled trial to prevent eczema, food allergy and sensitisation using a skin barrier improvement strategy) in Australia use ceramide containing emollients as prophylaxis for high risk neonates. The study did not show reduction in AD at 6 months and 1 year, while food allergen sensitisation was reduced only in the subgroup with frequent application of emollients five times per day.[106] The Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) study conducted in Sweden and Norway, with application of emollients from 2 weeks old, also failed to show any preventive effect of AD or food allergy at 1 year old.[107] The results of these two studies were limited by problems of compliance. There are still ongoing research to investigate on the optimal timing, frequency and type of emollients for this potentially safe and inexpensive strategy that could be beneficial in clinical practice.

2. Dietary Intervention

International and local guidelines on allergy prevention recommend no dietary restriction for breastfeeding mothers, exclusive breastfeeding for 6 months and substitution with hydrolysed milk formulas for high risk infants if exclusive breastfeeding is not feasible.[103,108] Historically, it was believed that delayed introduction of antigenic foods exposure for high risk infants can prevent development of allergic diseases including eczema. However, with recent publication of the landmark studies LEAP (Learning Early About Peanut Allergy)[109] and EAT (Enquiring About Tolerance)[110] on food allergy prevention, the concept about food immune tolerance and sensitisation with early exposure has changed dramatically. The hypothesis of dual antigen exposure postulates that immune tolerance occurs as a result of oral exposure to food antigens while sensitisation develops through skin exposure. Currently, most authorities support the introduction of complementary foods from 4 months old and should not be delayed beyond 6 months.[108,111] For infants high risk for peanut allergy, it is recommended to introduce peanuts at 4-6 months, while for infants with a low to moderate risk, peanuts can be introduced before first year of life.[108] Exclusion is only needed if there is documented adverse reactions. However, whether these recommendations can be generalised to other foods and populations of different genetic and cultural background is still uncertain. A study on earlier introduction of complementary foods from 3 months old cannot prevent eczema or subsequent food allergies.[107] A recent systematic review suggested that a diversity of complementary foods in infancy may reduce development of allergy diseases in childhood.[112] In practice, complementary foods as available in different cultures can be introduced from 4 to 6 months when the child is developmentally ready.

3. Prebiotics, Probiotics and Synbiotics

Microbial dysbiosis of the gut has been linked to allergic diseases including AD.[113] Prebiotics, probiotics and synbiotics have been shown to have mixed effects on treatment and prevention of AD.[11] The recently updated Cochrane review and a meta-analyses of paediatric studies on probiotics for treatment of AD showed no or little

evidence that probiotics are effective treatment for established AD.[114,115] Studies on various prebiotics and synbiotics combination are even more heterogenous and so far without definitive evidence of treatment benefit.

World Allergy Organisation (WAO) and McMaster University published the Guidelines for Allergic Diseases Prevention (GLAD-P) on probiotics and prebiotics in 2015 and 2016 respectively.[116,117] The guidelines recommend that probiotics may be used for prevention of eczema in (1) high risk infants and (2) their mothers during pregnancy and breastfeeding. For prebiotics, it is only recommended in non-exclusively breast-fed high-risk infants. The guidelines emphasized that the recommendations are only based on very weak evidences. Subsequent studies do not support the supplementation of probiotics for infants at risk for eczema.[118] These products are heterogenous and any clinical effects of one product shall not be generalised for another.

Conclusions

AD is a common chronic inflammatory skin disease with genetic predisposition and environmental aggravating factors characterised by atopic tendencies, skin barrier dysfunction and microbial dysbiosis. It has a large impact on the medical and psychological well-being of a developing child. With appropriate evidence-based treatment and patient education, symptoms of AD can be well controlled. Despite availability of all the guidelines, health care providers shall devise individualised management plans according to the clinical needs and preferences of patients and their caregivers. The advancement of new treatment modalities is intended to offer more promising developments to improve the quality of life of AD sufferers and their families in the near future.

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