CLINICAL PRACTICE GUIDELINES

2018

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MANAGEMENT OF ATOPIC ECZEMA

Ministry of Health Malaysia

Persatuan Dermatologi Malaysia

Academy of Medicine Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2018 and will be reviewed in a minimum period of four years (2022) or sooner if new evidence becomes available. When it is due for updating, the Chairperson of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

- Serum immunoglobulin E levels, skin prick test, patch test and skin biopsy, should not be used as diagnostic tools for atopic eczema.

- Assessment of disease severity and quality of life should be used in the management of atopic eczema.

- Emollient therapy is the mainstay of management at any stage of atopic eczema.

- Topical corticosteroids (TCS) should be used to treat flares in atopic eczema (AE).
- The choice of TCS in AE depends on the:
  - age of the patient
  - location of skin lesions
  - severity of skin inflammation

- Topical calcineurin inhibitors may be considered for atopic eczema patients aged two years and above.

- Ultraviolet A1 may be used to control acute flares in atopic eczema (AE).
- Narrow-band ultraviolet B may be offered in moderate to severe chronic AE.

- Systemic corticosteroids may be considered for short-term control of severe acute exacerbation of atopic eczema (AE).
- Azathioprine, cyclosporin A, methotrexate or mycophenolate may be used in the treatment of severe AE after optimisation of topical treatment.

- Educational interventions should be considered as part of the management of atopic eczema.

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH) and Ministry of Education. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the electronic databases, mainly Medline via Ovid and Cochrane Database of Systemic Reviews, and others e.g. Pubmed and Guidelines International Network (refer to **Appendix 1** for **Example of Search Strategy**). The search was limited to literature published in the last ten years, on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted to identify further studies. All searches were conducted from 22 September 2015 to 20 Jun 2017. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 December 2017 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other CPGs on atopic eczema e.g.:

- Management of atopic eczema in primary care (Scottish Intercollegiate Guidelines Network, 2011)
- Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years (National Collaborating Centre for Women's and Children's Health, 2007)
- Guidelines of care for atopic dermatitis (Journal of American Academy of Dermatology, 2014)

The CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 13 clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 19 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. This CPG is based largely

on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of GRADE (refer to the preceding page). The writing of the CPG follows strictly the requirement of AGREE II.

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/ index.php/pages/view/117).

OBJECTIVES

To provide evidence-based recommendations in the management of atopic eczema on the following aspects:
- diagnosis and severity assessment
- treatment
- referral

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

Inclusion Criteria
- All patients with atopic eczema

Exclusion Criteria
- Other types of endogenous and exogenous eczema
- Congenital syndromic disorders
- Immunodeficiency disorders
- Inborn errors of metabolism

TARGET GROUP/USERS

This document is intended to guide those involved in the management of atopic eczema at any healthcare level including:
i. Doctors
ii. Allied health professionals
iii. Trainees and medical students
iv. Patients and their advocates
v. Professional societies

HEALTHCARE SETTINGS

Primary and secondary/tertiary care settings

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The draft guidelines were reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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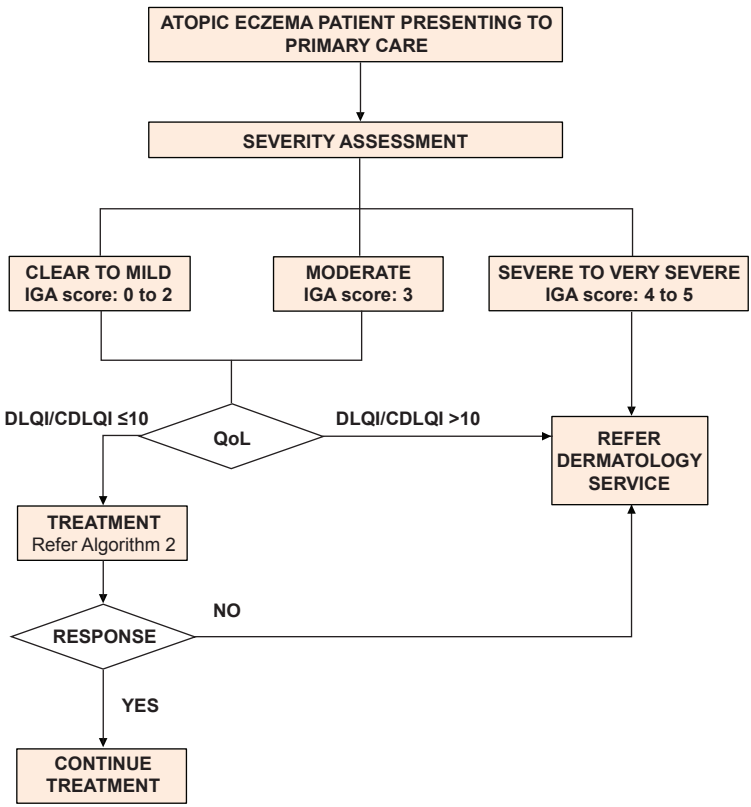
ALGORITHM 1. MANAGEMENT OF ATOPIC ECZEMA IN PRIMARY CARE

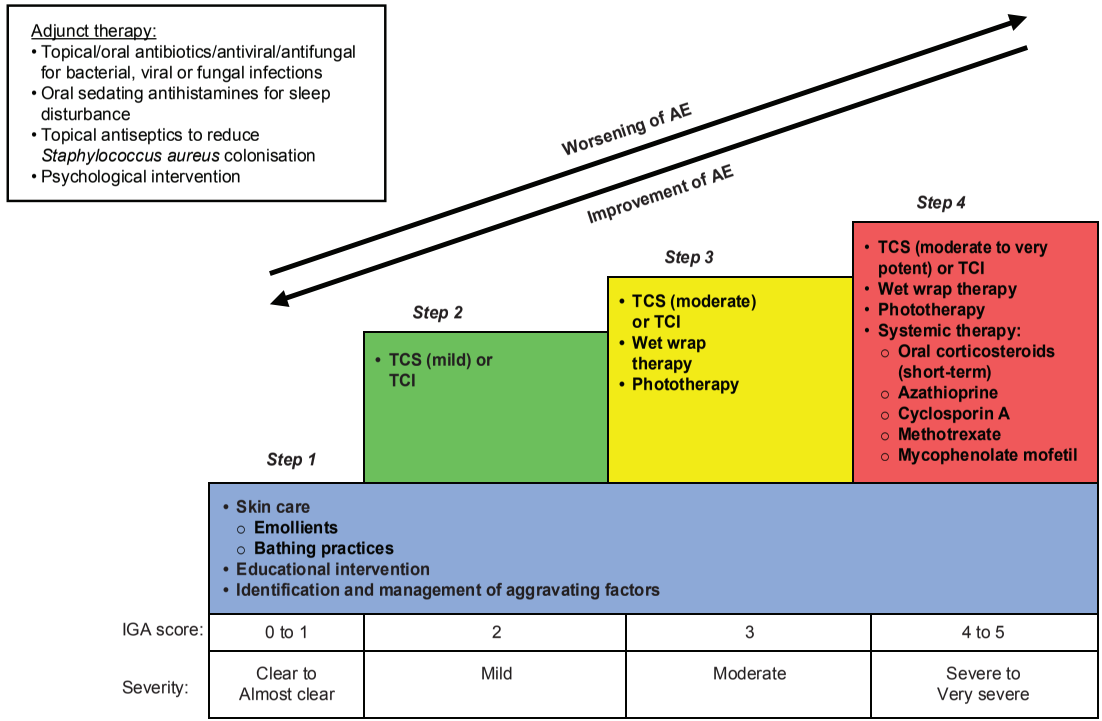


Investigator's Global Assessment

Score	Description
0 = Clear	No inflammatory signs of atopic eczema
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration
2 = Mild disease	Mild erythema, and mild papulation/infiltration
3 = Moderate disease	Moderate erythema, and moderate papulation/infiltration
4 = Severe disease	Severe erythema, and severe papulation/infiltration
5 = Very severe disease	Severe erythema, and severe papulation/infiltration with oozing/crusting

IGA : Investigators' Global Assessment
QoL : Quality of life
DLQI : Dermatology Life Quality Index
CDLQI: Children's Dermatology Life Quality Index

ALGORITHM 2. TREATMENT OF ATOPIC ECZEMA



IGA: Investigators' Global Assessment; TCS: Topical corticosteroids; TCI: Topical calcineurin inhibitors

1. INTRODUCTION

Atopic eczema (AE) or atopic dermatitis is a complex, chronic and recurrent inflammatory itchy skin disorder. This is the commonest type of endogenous eczema. In majority of cases, AE starts to develop in early childhood and may persist into adulthood. The prevalence of AE can be as high as 20% in some countries and this continues to rise affecting not only developed but also developing low-income countries. According to International Study of Asthma and Allergies in Childhood (ISAAC), the 12-month prevalence of AE among Malaysian children has risen from 9.5% in ISAAC-1 (1994 - 1995) to 12.6% in ISAAC-3 (2002 - 2003), with an increase of 0.49% yearly.[1] AE can present with various clinical manifestations according to different age groups. This makes the diagnosis of AE a challenge, leading to misdiagnosis and mistreatment. AE significantly impacts the financial and psychosocial well-being of the patients and families. The direct healthcare cost for a child with AE in developing countries (Malaysia, Indonesia and Philippines) has been estimated to range from USD199 to USD743.[2] The psychosocial impact on the children with AE and their families is as great as children with diabetes. Therefore, it is paramount to have an effective and safe treatment of AE.[3]

AE is typically an episodic disease of flares and remission. However, it may be continuous in some patients. A multicentre allergy study done in Germany, involving 1314 children from birth to seven years old, showed 43.2% of cases went into complete remission by three years of age, 38.3% had an intermittent pattern of disease and 18.7% had symptoms of AE every year.[4] The disease is caused by complex interactions of genetic predispositions, environmental triggers and immune dysregulation leading to epidermal barrier defect. The defect in epidermal barrier may be caused by genetic alterations in the filaggrin gene. Based on a study done in Singapore, 20.2% of AE patients cohort carried at least one filaggrin-null mutation compared with 7.3% of the control population.[5] Besides genetic determination, the epidermal barrier function also depends on the immune system. It has been demonstrated that T-helper 2 cytokines such as interleukin-4 inhibit the expression of filaggrin and S100 proteins and thus impair the epidermal barrier. Mechanical (e.g. scratching) or physical (e.g. hot water, ultraviolet exposure, sweating) irritation further weakens the epidermal barrier. With the breakdown of skin barrier, affected skin is more susceptible to trigger factors including irritants and allergens, which can further aggravate AE.[6]

Clinically, AE has both acute and chronic presentations. Acute eczema is characterised by papulo-vesicular eruption with erythema, weeping, oedema and excoriation. Whereas chronic eczema is characterised by

lichenification and dry skin (xerosis). The choice of treatment depends on the clinical presentation of AE.

The aim of this CPG is to provide an evidence-based guidance for all physicians and other healthcare providers in the management of AE.

2. DIAGNOSIS

2.1 Diagnostic Criteria

AE is diagnosed clinically. In a systematic review, the most extensively validated diagnostic tools were 'U.K. Working Party's Diagnostic Criteria' (refer to **yellow box** below) and 'Hanifin and Rajka Diagnostic Criteria' (refer to **Appendix 3**). The former had a sensitivity and specificity as high as 100% and 99% respectively. While the later had a sensitivity and specificity of 96% and 93.8% respectively.[7, level III]

In the local setting, the most commonly used diagnostic tool is U.K. Working Party's Diagnostic Criteria.

- **The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis**:[8, level III]
  Patient must have an itchy skin condition (or parental report of scratching or rubbing in a child) plus three or more of the following:
  - history of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles or around the neck (including cheeks in children under 10 years old)
  - a personal history of asthma or hay fever (or history of atopic disease in a first-degree relative in children under four years old)
  - a history of a general dry skin in the last year
  - visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under four years old)
  - onset under the age of two (not used if child is under four years old)

2.2 Investigations

There is no specific laboratory investigation to confirm the diagnosis of AE. A systematic review found lack of evidence to suggest the use of specific immunoglobulin E (IgE) in supporting the diagnosis of AE.[9, level III] Skin prick test and patch test are only useful to exclude concomitant environmental and food allergies, and contact dermatitis respectively. Skin biopsy is sometimes used to exclude other AE mimickers.

Recommendation 1
- Serum immunoglobulin E levels, skin prick test, patch test and skin biopsy, should not be used as diagnostic tools for AE.

3. SEVERITY ASSESSMENT

There are numerous tools used to assess and score disease severity of AE. A systematic review of 382 randomised control trials (RCTs) showed the commonly used tools in descending order were:[10, level I]

- SCORing Atopic Dermatitis (SCORAD)
- Eczema Area and Severity Index (EASI)
- Investigators' Global Assessment (IGA)
- Six Area, Six Signs Atopic Dermatitis (SASSAD)
- Others [e.g. Patient-Orientated Eczema Measure (POEM)]

Scoring tools most extensively validated are SCORAD, EASI, SASSAD and POEM[11, level III] Patient-oriented SCORAD (PO-SCORAD) is a simplified version of SCORAD. It correlates well with SCORAD index and POEM ($r \geq 0.70$).[12, level II-2]

The above-mentioned scoring tools are mainly used for research purposes. For clinical purposes, the CPG development group advocates the use of IGA to assess severity of AE (refer to **Appendix 4**).

Quality of Life (QoL) assessment is important in the management of AE. The most commonly validated tools used are:[10, level I]

- Dermatology Life Quality Index (DLQI) (refer to **Appendix 5**)
- Children's Dermatology Life Quality Index (CDLQI) (refer to **Appendix 6**)
- Infant's Dermatology Quality of Life Index (IDQOL)
- Dermatitis Family Impact (DFI).

Recommendation 2

- Assessment of disease severity and quality of life should be used in the management of atopic eczema. The preferred tools are:
  - Investigator's Global Assessment
  - Dermatology Life Quality Index/Children's Dermatology Life Quality Index

4. CO-MORBIDITIES

The impact of AE often extends beyond the skin. Several co-morbidities are found to be associated with AE.

4.1 Skin Infection

Eczematous skin is prone to secondary infection. A population-based study of school children in Japan confirmed that children with AE had an increased risk of developing impetigo. The risk due to staphylococcal and streptococcal infection among them was 1.80 (95% CI 1.16 to 2.80) compared with non-AE children. There was no association between AE and molluscum or herpes infections.[13, level III] However, eczema herpeticum should be suspected in patients with rapidly deteriorating AE.[14]

4.2 Atopy

On average, one in three children with AE develop asthma at six years and older.[15, level II-2] There is an association with allergic rhinitis (OR=3.4, 95% CI 1.3 to 9.0) especially in the early-onset persistent AE patients.[16, level II-2]

4.3 Contact Dermatitis

In daily clinical practice, AE patients are observed to be susceptible to develop contact dermatitis.[17, level II-2] However, a recent meta-analysis showed no significant correlation between AE and contact sensitisation.[18, level I]

4.4 Food Allergy

AE is also associated with food allergy (OR=13.4, 95% CI 2.9 to 61.4) especially in the early-onset persistent AE patients.[16, level II-2] In a systematic review of low quality on the association of AE and food allergy in adolescence and adults, the prevalence of allergy to wheat was only 4.5%, egg 6.1% and cow's milk 0.6%.[19, level II-2] Unpublished local data on food sensitisation in children with AE showed similar findings on egg, cow's milk and peanut.[20, level I]

4.5 Cardiovascular Disease

A chronic inflammatory disease like AE is associated with cardiovascular disease. There are modest associations between severe AE and angina pectoris (RR=1.17, 95% CI 1.12 to 1.23), hypertension (RR=1.04, 95% CI 1.02 to 1.06) and peripheral arterial disease (RR=1.15, 95% CI 1.11 to 1.19) but no association with myocardial infarction and

stroke.[21, level II-2] There is also an increased risk of AE among the overweight (OR=1.27, 95% CI 1.19 to 1.36) and obese (OR=1.42, 95% CI 1.34 to 1.50) compared with normal weight adults and children.[22, level III]

4.6 Psychological and Psychosocial Dysfunction

Children with AE may demonstrate psychological and psychosocial dysfunction. There is independent association between AE and attention deficit hyperactivity disorder (OR=1.47, 95% CI 1.01 to 2.15). Prevalence of schizophrenia and affective disorders are also higher in AE compared with control (1.2% vs 0.5% and 7.7% vs 4.5% respectively).[23, level II-2]

Prevalence of AE is increased with exposure to active and passive smoking. However, it is not associated with maternal smoking during pregnancy.[24, level II-2]

- Co-morbidities e.g. skin infection, atopic disease, food allergy, cardiovascular disease, psychological and psychosocial dysfunction may co-exist in AE.

5. AGGRAVATING/TRIGGERING FACTORS

There are many potential aggravating factors which can worsen flares in AE, either independently or in combination. Potential aggravating/ triggering factors include the following:

- aeroallergen
- physical irritants
- environmental factors
- food
- microbial colonisation/infection
- patient factors (e.g. pregnancy)

5.1 Aeroallergen

House dust worsens itch in AE.[25, level III]

Severity of skin symptoms is associated with indoor house dust mites levels ($p<0.05$).[26, level III] The association of HDM sensitisation and AE severity is inconclusive.[26 - 27, level III]

Grass pollen does not worsen itch in AE.[25, level III]

Unfamiliar pets (not own pets) worsen itch in AE.[25, level III]

5.2 Physical Irritants

Nylon or wool clothing worsens itch in AE.[25, level III]

Irritants such as soaps, detergents, disinfectants and many chemical reagents may worsen flares in AE. Chemicals (e.g. shampoo exposure) and natural irritants (e.g. sweat) worsen itch.[25, level III]

5.3 Environmental Factors

Environmental factors such as climate and air pollution (indoor and outdoor) can trigger AE.

Warm and high sun exposures are associated with poorly controlled disease. There is no association with humidity.[28, level III]

There is an increased mean daily AE symptoms after moving into a newly painted building with natural ventilation ($p<0.001$).[29, level III]

Outdoor air pollution is significantly associated with AE symptoms ($p<0.05$).[30, level II-2]

5.4 Food

The influence of food allergy on the clinical course of AE remains unclear.[31] On the other hand, a diagnosis of food allergy should be considered in children with AE who have reacted previously to a food with immediate symptoms, or in infants and young children with moderate to severe AE that has not been controlled by optimum management.[32] Food may worsen AE in children less than two years old especially milk, egg and peanuts.

5.5 Microbial Colonisation/Infection

In AE patients, the combination of genetic predisposition for dysfunction in skin barrier and immune responses lead to higher frequency of bacterial and viral infections such as eczema herpeticum, eczema coxsackium and eczema vaccinatum. Studies have shown that the skin in AE is heavily colonised with *Staphylococcus aureus* even when the skin is not clinically infected. The degree of *S. aureus* colonisation tends to increase the AE severity.[33]

A systematic review showed that the current regular childhood vaccination did not increase the risk of atopic disorder including AE.[34, level II-2]

5.6 Patient Factors

Pregnancy has an impact on women with history of AE. Approximately 25% of patients have their pre-existing AE improve, >50% deteriorate and 10% flare during post-partum period. The hormonal changes in pregnancy results in predominant Th-2 response which is associated with atopy.[35, level III]

There is no good quality evidence to show that stress aggravates AE.

- Identification and management of aggravating factors is important in AE.

6. TOPICAL THERAPY

Topical therapy is the mainstay of treatment in AE. This includes emollient, topical anti-inflammatory agents and topical antiseptic/ antimicrobial agents. For further information on recommended medication dosing, side effects and contraindications for commonly used medications in AE, refer to **Appendix 11**.

6.1 Emollient/Moisturiser

Emollient therapy is the mainstay of management in AE. It improves the epidermal barrier function and dryness leading to reduction in pruritus. Emollients application decreases the usage of topical corticosteroids (TCS).

Emollients are available in different formulations (ointments, creams, lotions, gels and aerosol sprays). Ointments (e.g. petrolatum) are greasy in nature whereas creams and lotions contain water and are more user-friendly and acceptable cosmetically. Creams (e.g. aqueous cream and urea cream), lotions and gels contain preservatives to protect against microbial growth in the presence of water.

A Cochrane systematic review on 77 RCTs of moderate quality showed that emollients was better than no emollient:[36, level I]

- improved SCORAD (MD= -2.42, 95% CI -4.55 to -0.28)
- reduced risk of flare (RR=0.40, 95% CI 0.23 to 0.70)
- reduced rate of flare (HR=3.74, 95% CI 1.86 to 7.50)
- reduced amount of corticosteroids used at 6 - 8 weeks (MD=-9.30, 95% CI -15.33 to -3.27)

There was no reliable evidence to show that one emollient is more effective than another.

In the same systematic review, the types of emollients included were:[36, level I]

a. Atopiclair vs vehicle (Unguentum leniens)
   Atopiclair:
   - lowered EASI score (MD=-4.00, 95% CI-5.42 to -2.57)
   - reduced rate of flare (RR=0.18, 95% CI 0.11 to 0.31)
   - decreased itch score (MD=-2.65, 95% CI-4.21 to -1.09)
   - improved participant-assessed disease severity (RR=4.51, 95% CI 2.19 to 9.29)

b. Urea (4 - 5%) containing moisturisers vs vehicle
   Urea (4 - 5%) containing moisturisers:
   - improved Dyshidrotic Eczema Area and Severity Index (DASI) (RR=1.40, 95% CI 1.14 to 1.71)

- reduced rate of flare(RR=0.47, 95% CI 0.24 to 0.92)
- improved participant-assessed disease severity (RR=1.28, 95% CI 1.06 to 1.53)

c. Glycerine/glycerol 20% containing moisturisers vs vehicle/placebo
Glycerine/glycerol containing moisturisers:
   - improved SCORAD (MD= -2.20, 95% CI -3.44 to -0.96)
   - improved participant-assessed disease severity (RR=1.22, 95% CI 1.01 to 1.48)

d. Oat-containing moisturisers vs no treatment/vehicle
Oat-containing moisturisers:
   - reduced rate of flare (RR=0.31, 95% CI 0.12 to 0.70)
   - reduced amount of corticosteroids used (MD= -9.30, 95% CI -15.3 to -3.27)

Emollients have been shown to enhance the effectiveness of TCS and have steroid-sparing property. When compared topical active treatment (e.g. fluocinonide 0.05%, hydrocortisone 1%) combined with moisturiser with active treatment alone, topical active treatment combined with moisturiser:[36, level I]

- reduced investigator-assessed disease severity (SMD=-0.87, 95% CI -1.17 to -0.57)
- reduced rate of flare (RR=0.43, 95% CI 0.20 to 0.93)

There was no difference in SCORAD at 1 - 4 weeks between licochalcone-containing moisturiser and hydrocortisone acetate 1% cream with mean disease severity of 0.08 (95% CI -1.96 to 2.13).[36, level I]

In an RCT, ceramide-magnesium (Cer-Mg) treatment led to a significantly greater decrease in SCORAD and pruritus from baseline compared with unguentum leniens at three and six weeks. Similar outcomes were seen between Cer-Mg and hydrocortisone at three weeks but not at six weeks.[37, level I]

Emollients have been used in the prevention of AE in high risk infants. Daily emollient use significantly reduced the risk of AE at six months (RRR=0.50; 95% CI 0.28 to 0.90).[38, level I]

Generally, emollients/moisturisers were reported to be safe in AE.[36 - 38, level I]

- Regular use of emollients improves AE and thus reduces usage of topical corticosteroids.

Recommendation 3
- Emollient therapy is the mainstay of treatment at any stage of atopic eczema in all age groups of patients.
  - The type/formulation of emollients depends on the patient's preference.

6.2 Topical Corticosteroids

Topical corticosteroids have anti-inflammatory and immunosuppressant effects, as well as other actions relevant to their effects on skin including inhibiting fibroblast proliferation and collagen synthesis, and local vasoconstriction. The anti-inflammatory activity is through the following mechanisms:
- alteration in leukocyte number and activity
- suppression of mediator release (e.g. histamine, prostaglandins)
- enhanced response to agents that increase cyclic adenosine monophosphate (prostaglandin E2 and histamine via the histamine-2 receptor)

- TCS are classified into four classes according to their potencies (refer to **Appendix 7**):
  - Class I (very potent)
  - Class II (potent)
  - Class III (moderate)
  - Class IV (mild)

TCS is the first-line anti-inflammatory agent for AE in both children and adults. It is an established treatment in many existing guidelines. There are not many recent studies on TCS use in AE.

Fluocinonide 0.1% cream improves barrier function as measured by basal transepidermal water loss (TEWL) in active moderate to severe AE ($p<0.001$).[39, level I] It is significantly more effective than vehicle in lesions clearing or almost clearing when applied once or twice daily (57% - 59% vs 12% - 19%). Application frequency of once or twice daily are equally effective.[40, level I]

Fluticasone propionate 0.05% cream or 0.005% ointment is more effective than vehicle alone in preventing flares when applied twice weekly for 16 weeks (RR=0.46, 95% CI 0.38 to 0.55). Methylprednisolone aceponate 0.1% is also found to be more effective in similar comparison (RR=0.36, 95% CI 0.21 to 0.62).[41, level I] However, fluocinonide 0.1% and methylprednisolone aceponate 0.1% are not available in Malaysian market as of this date. The available TCS of the same potency in Malaysia are betamethasone valearate 0.1% and mometasone furoate.

Children have an increased absorption of TCS due to a greater body surface area to weight ratio. Therefore, the least-potent but effective TCS should be used. However, during acute flares, the use of short courses of moderate to very potent TCS can be considered for rapid control. For certain areas (i.e. face, neck, genitalia and skin folds), caution should be exercised with regards to choice of TCS potency due to greater penetration and higher likelihood for systemic absorption.[31]

Local adverse effects of TCS are secondary infection, skin atrophy, striae, burning, itching, folliculitis, acne-like eruptions and telangiectasia. They are related to the duration of use and potency of TCS.[42, level I] The potential systemic side effects, including hypothalamic-pituitary-adrenal (HPA) axis suppression, should be monitored particularly in children with AE on long-term potent TCS.[31] However, HPA suppression is not observed in patients treated with mild-potency TCS.[43]

Depending on the potency and site of application, patients being treated with intermittent courses of TCS should be reviewed every 3 - 6 months to ascertain response to therapy and potentially reversible atrophic changes.[14]

The fingertip unit (FTU) has been used as a method of determining the amount of TCS to apply. It should be used to guide patients on TCS quantities required.[14] Refer to **Appendix 8** on **FTU**.

- Practical guides for TCS application are as the following.[41, level I]
  - TCS should be used concomitantly with emollients.
  - FTU can be used as a guide to the amount of TCS required for affected sites.
  - Choice of vehicle of TCS depends on the affected sites (i.e. gel for scalp; cream for face, genital and flexural areas; ointment for palm and sole).
  - Choice of potency of TCS depends on the clinical severity of eczema (i.e. potent to very potent TCS ointment for thick lesions and mild to moderate TCS cream for thin lesions).
  - After resolution of eczema flares, discontinuation of TCS application should be done gradually to avoid rebound (i.e. twice a day followed by once a day then 1 - 3 times a week before complete discontinuation).
  - After resolution of eczema flares, proactive therapy (mild TCS application intermittently once/twice a week) can be used to maintain remission.

Recommendation 4
- Topical corticosteroids (TCS) should be used to treat flares in atopic eczema (AE).
- The choice of TCS in AE depends on the:
  - age of the patient
  - site of skin lesions
  - chronicity of skin lesions
  - severity of skin inflammation
- The use of TCS should be monitored every 3 - 6 months to determine response and potential side effects.

6.3 Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (TCIs), e.g. tacrolimus and pimecrolimus, are non-steroidal immune-modulating agents for the treatment of AE. TCIs are currently licensed to be used in patients older than two years old. More safety studies are needed before recommending the use of it in patients younger than two years old.

Tacrolimus 0.1% and 0.03% ointment monotherapy is more effective than emollient in controlling pruritus in AE (MD=28.6, 95% CI 19.8 to 37.5). The median time to pruritus recurrence is longer in tacrolimus compared with the emollient (>28 days vs three days).[44, level I]

Three systematic reviews (including a Cochrane's) showed the efficacy of tacrolimus and pimecrolimus compared with various controls in AE. In the Cochrane systematic review, tacrolimus 0.1% ointment improved physician's assessment of global response, affected body surface area (BSA), EASI score and QoL significantly compared with hydrocortisone acetate 1% ointment and hydrocortisone butyrate 0.1% ointment in moderate to severe AE at six months.[45, level I]

Tacrolimus 0.1% ointment was also more effective than pimecrolimus 1% cream in AE of different severity at six weeks in terms of:
- physician's assessment of global response (RR=1.80, 95% CI 1.34 to 2.42)[45, level I]
- investigators' global assessment (RR=0.58, 95% CI 0.46 to 0.74) [46, level I]
- BSA and EASI ($p< 0.001$)[45, level I]

In another analysis, tacrolimus 0.03% ointment was more effective than hydrocortisone acetate 1% in physician's global assessment (RR=2.58, 95% CI 1.96 to 3.38). However, there was no difference between tacrolimus 0.03% ointment and mid-potency corticosteroids (RR=0.45, 95% CI 0.13 to 1.57). There was insufficient data on the affected BSA and EASI. When compared with pimecrolimus 1% cream, tacrolimus

0.03% ointment was also more effective in physician's assessment of global response (RR=1.42, 95% CI 1.02 to 1.98).[45, level I]

Between different concentrations, tacrolimus 0.1% was more effective than tacrolimus 0.03% in improving:[45, level I]

- physician's assessment of global response (RR=0.82, 95% CI 0.72 to 0.92)
- EASI (p=0.006 in children and p<0.001 in adults)

Proactive treatment with tacrolimus 0.1% and 0.03% used 2 - 3 times weekly for 40 - 52 weeks as maintenance therapy significantly prevented, delayed and reduced mild to severe AE flares.[41, level I]

Pimecrolimus 1% cream was significantly more effective in improving flares and QoL when compared with vehicle at six weeks. However, it was less effective than triamcinolone acetonide 0.1% on similar outcomes at six months (RR=0.89, 95% CI 0.83 to 0.96).[46, level I]

The most common adverse events in TCIs are burning, pruritus and skin infection.[44 - 46, level I]

- Proactive treatment with TCIs 2 - 3 times weekly may be considered for maintenance therapy in AE.

Recommendation 5

- Topical calcineurin inhibitors may be considered to treat flares in atopic eczema for patients aged two years and above.

6.4 Wet Wrap Therapy

Wet wrap therapy (WWT) consists of two layers of tubular bandage or garments with inner wet and outer dry layers, applied over moisturiser alone or in combination with TCS (refer to **Appendix 9**). WWT can be used continuously for 24 hours.

In a systematic review of six RCTs, four studies showed improvement in AE clinical severity with WWT and TCS compared with TCS alone. A non-significant tendency to increased risk of mild skin infections was observed in WWT group. However, the studies used in the review were of low quality and heterogenous.[47, level I]

WWT with TCS should only be used to treat AE in children for 7 - 14 days. However, WWT with emollients alone can be continued until the AE is controlled.[32] In the local setting, WWT in combination with emollients and mild to moderate potency TCS has been used to treat non-infected moderate to severe AE.

Recommendation 6

- Wet wrap therapy (WWT) with moisturiser alone or in combination with mild to moderate potency topical corticosteroids (TCS) may be used in non-infected moderate to severe atopic eczema.
  - The use of TCS in WWT should not exceed 14 days.

6.5 Other Topical Therapy

There is a new effective non-steroidal anti-inflammatory topical treatment i.e. phosphodiesterase 4 (PDE4) inhibitor (crisaborole ointment).[48, level I] However, the cost is likely to be prohibitive and more long-term safety study is required.

There are also other emerging topical therapies which are currently undergoing clinical trials at the time of the CPG development (e.g. Janus kinase (JAK) inhibitors).

7. PHOTOTHERAPY

Phototherapy is a therapeutic option for patients with severe AE who do not respond or develop side effects to conventional treatment. It may improve disease severity, pruritus and sleeplessness in these patients.

In a systematic review of moderate quality RCTs on phototherapy in moderate to severe AE:[49, level I]

- narrow band ultraviolet B (NB-UVB) was more effective than visible light (mean reduction in total disease activity score=9.4 points, 95% CI 3.6 to 15.2) at 12 weeks
- ultraviolet A (UVA) showed non-significant improvement compared with visible light (mean reduction in total disease activity score=4.4 points, 95% CI -1.0 to 9.8) at 12 weeks
- ultraviolet A1 (UVA1) was more effective than ultraviolet AB in reducing SCORAD in acute flares of AE after 15 days ($p<0.05$)
- UVA1 was as effective as NB-UVB in improving disease activity at 6 - 8 weeks and persisted four weeks after cessation of treatment

Frequently reported adverse events were xerosis, treatment-induced erythema and burning, pruritus, worsening of AE and folliculitis. However, there was no documented short-term serious adverse event.[49, level I]

In the local settings NB-UVB is widely available; hence it is more commonly used.

There is no retrievable evidence on the effectiveness and safety of light-emitting diode and laser therapies in the management of AE.

Recommendation 7

- Ultraviolet A1 may be used to control acute flares in atopic eczema (AE).
- Narrow-band ultraviolet B may be offered in moderate to severe chronic AE.

8. SYSTEMIC THERAPY

Systemic therapy includes adjunctive treatment (e.g. antihistamines and systemic antibiotics) and specific treatment of AE (e.g. immunomodulating agent and biologics). Specific systemic treatments should be used only in severe cases of AE in patients where other management options have failed or are not appropriate, and where the AE has a significant impact on quality of life. For further information on recommended medication dosing, side effects and contraindications for commonly used medications in atopic eczema, refer to **Appendix 11**.

8.1 Antihistamines

Itch is a common symptom in AE and antihistamines are frequently prescribed to relieve it. Based on a Cochrane systematic review, there was no high-level evidence to support the use of antihistamines as monotherapy in AE.[50, level I] Antihistamines should not substitute topical therapy in the management of AE.[51]

In AE patients with sleep disturbance due to itch, sedating antihistamines should be considered as a short-term measure at bedtime.[14, 31] In the absence of urticaria and other atopic conditions, non-sedating antihistamines are not recommended as a treatment for AE.[31]

Recommendation 8
- Antihistamines should not be used as monotherapy or to substitute topical therapy in atopic eczema (AE).
- Sedating antihistamines may be considered as a short-term measure at bedtime in AE patients with sleep disturbance.

8.2 Immunomodulating Agents

Corticosteroids, cyclosporin A, methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), intravenous immunoglobulin (IVIG) and interferon gamma (IFN-γ) are some of the immunomodulating agents used in AE. These agents are used in moderate to severe AE which are uncontrolled after optimisation of topical treatment and/or phototherapy. They are also considered in chronic AE where QoL is substantially impacted.[51]

a. Systemic Corticosteroids

Systemic corticosteroids is a common immunosuppressive agent used in various inflammatory conditions. They have been shown to be rapidly effective, but had unfavourable long-term risk/benefit ratio.[52]

In a systematic review on children with severe AE:[53, level I]
- combination of oral and intranasal beclomethasone diproprionate was more effective than placebo at four weeks
- intranasal flunisolide was more effective than placebo at two weeks

Another systematic review showed that prednisolone was less effective than cyclosporin A for adults with severe AE:[54, level I]
- less stable remission (≥SCORAD 50) (p=0.031) at six weeks
- higher incidence of relapse (p=0.04) at 12 weeks

Both systematic reviews showed no serious adverse event when steroids were used for 2 - 4 weeks. Common adverse events were hypertension and exacerbations of AE after termination of treatment.[53 - 54, level I]

b. Azathioprine

AZA is a purine analogue that inhibits deoxyribonucleic acid (DNA) production. It reduces inflammation by its antiproliferative effect on B-lymphocytes and T-lymphocytes. Thiopurine methyltransferase (TPMT) is an enzyme required in the metabolism of AZA. Monitoring TPMT levels or genotyping can help to identify patients with low or absent TPMT activity who are at increased risk for severe, life-threatening myelosuppression from AZA. Overall concordance between genotype and phenotype in healthy volunteers is 98.4%.[55]

AZA is more effective compared with placebo in the treatment of AE at 12 weeks:
- improved SASSAD (MD=5.4%, 95% CI 1.4 to 9.3)[56, level I]
- improved SASSAD ranged from 26% to 37%[54, level I]
- mean reduction of disease activity by 27%[53, level I]
- improved DLQI (MD=3.5, 95% CI 0.3 to 6.7)[56, level I]

When compared to MTX, AZA was equally effective in reduction of disease activity and improvement in QoL at 12 and 24 weeks in AE.[54, level I]

Adverse event was generally mild in AZA and common side effects observed were nausea, minor haematological and biochemical abnormalities.[54, level I; 56, level I]

- Baseline TPMT testing is advised prior to AZA initiation, with avoidance of use in those with very low or absent enzyme activity.

c. Cyclosporin A

Cyclosporin A is an oral calcineurin inhibitor. It reduces inflammation by immunosuppressive effect on T-lymphocytes and reduction of interleukin-2 production. Cyclosporin A is the only approved systemic treatment for adults with severe AE.[52]

In two systematic reviews of moderate quality RCTs, cyclosporin A was more effective than placebo in moderate to severe AE in terms of: [53 - 54, level I]

- reduction in SCORAD, Costa index, SASSAD after treatment with doses ranging between 2.5 and 5 mg/kg body weight for 4 - 52 weeks
- reduction in AE severity of about 50% (range 29 - 90%) at 6 - 8 weeks
- improvement in disease severity in both short- and long-term follow-up
- improvement in quality of life based on DLQI

In a meta-analysis, high dose cyclosporin A (4 - 5 mg/kg) was more effective in reducing disease severity compared with low dose cyclosporin A (2.5 - 3 mg/kg) at two weeks (mean relative change of 40% vs 20%). Relapse (increase in disease severity to >75% of the patient's baseline score) after discontinuation of cyclosporin A was observed in 50% of patients within two weeks and up to 86% of patients within six weeks to nine months.[53, level I]

An RCT showed that continuous therapy (one year) was more effective than short intermittent therapy (12 weeks) of cyclosporin A in improvement of:[57, level I]

- disease severity maintained beyond eight weeks
- QoL at 12 months (p=0·01).

In head-to-head comparison with other immunosuppressive agents:

- cyclosporin A is more effective than prednisolone in adults with severe AE at six weeks and followed-up for another 12 weeks (p=0.031)[54, level I]
- cyclosporin A and MMF are equally effective as maintenance treatment of AE at 10 weeks (MD=0.8, 95% CI -4.4 to 6.0)[54, level I]
- cyclosporin A shows faster clinical improvement compared with enteric-coated mycophenolate sodium (EC-MPS) at three weeks (MD=6.6, 95% CI 1.5 to 11.7) and at six weeks (MD=7.1, 95% CI 2.1 to 12.2) in severe AE. However, clinical remission is longer in EC-MPS after discontinuation of medication at 33 weeks.[58, level I]
- cyclosporin A and MTX are equally effective in reducing SCORAD in children with severe AE at 12 and 24 weeks.[59, level I]

Adverse events reported are mild (57%), moderate (37%) and severe (6%) at 1-year treatment.[57, level I] Common adverse events are hypertension, gastrointestinal symptoms, hypertrichosis, fatigue, flu-like symptoms, headache, paraesthesia, haematological and biochemical abnormalities (increased creatinine level >30% from baseline). [53, level I] Severe adverse events include infections, abdominal pain, acute cholecystitis and basal cell carcinoma.[53, level I; 57, level I]

d. Methotrexate

MTX is an anti-folate metabolite that inhibits T-lymphocytes function by blocking the synthesis of DNA, ribonucleic acid (RNA) and purine.

There was no retrievable placebo-controlled efficacy study for MTX. In a systematic review of systemic therapies for management of AE, an RCT showed MTX was as effective as AZA in reducing SCORAD at 12 and 24 weeks (p=0.89 and p=0.58 respectively) and improving QoL at 12 weeks (p=0.46).[54, level I]

MTX and cyclosporin A are equally effective in the reduction of SCORAD in children with severe AE at 12 and 24 weeks (p=0.93 and p=0.29 respectively).[59, level I]

Common adverse events observed in MTX are haematological abnormalities, gastrointestinal disturbances and infection. However, there is no severe and serious adverse events.[54, level I; 59, level I]

e. Mycophenolate Mofetil and Enteric-coated Mycophenolate Sodium

MMF and EC-MPS contain active metabolite mycophenolic acid (MPA). MPA arrests the synthesis of DNA and RNA in B- and T-cell development via inhibition of inosine monophosphate dehydrogenase, and therefore prevents immune cell proliferation.[58, level I]

There is no retrievable evidence comparing MMF to placebo. A systematic review showed that:[54, level I]

- MMF was as effective as cyclosporin A in maintenance treatment of AE at 10 week (MD in SCORAD=0.8, 95% CI -4.4 to 6.0)
- EC-MPS had longer clinical remission compared with cyclosporin A after discontinuation of medication at 33 weeks.

Commonly reported adverse events are fatigue, headache, gastrointestinal disturbance, flu-like symptom and viral infection.[58, level I]

Recommendation 9

- Systemic corticosteroids may be considered for short-term control of severe acute exacerbation of atopic eczema (AE).
- Azathioprine, cyclosporin A, methotrexate or mycophenolate may be used in the treatment of severe AE after optimisation of topical treatment.

8.3 Biologics

Biologics are therapeutic proteins specifically designed to block the activity of bioactive mediators of immune responses. AE is an inflammatory skin condition orchestrated by multiple cytokines,

chemokines and immunoglobulins. Therefore, usage of biologics is a reasonable therapeutic option.

a. Dupilumab

Dupilumab is a monoclonal antibody that blocks interleukin-4 (IL-4) and interleukin-13 (IL-13) receptors.

In recent RCTs, dupilumab showed rapid improvement in AE severity compared with placebo in adults with moderate to severe AE. It had higher proportion of patients with an IGA score of zero or one (clear or almost clear) or reduction from baseline of at least two points in the score and improvement in EASI >75% at week 16 ($p< 0.001$)[60 - 61, level I] and up to 52 weeks ($p<0.001$).[61, level I]

Adverse events commonly reported are nasopharyngitis, headache and skin infection.[60 - 61, level I]

b. Omalizumab

Omalizumab is a recombinant human monoclonal antibody that binds to free human IgE in the blood and IgE receptor on the surface of B-lymphocytes.

In two RCTs, omalizumab showed no significant difference in EASI and pruritic score at 20 weeks[62, level I] and comparable reduction in SCORAD at 24 weeks[63, level I] when compared with placebo in AE.

Minor adverse events with omalizumab are injection site reaction, mild infection, headache, vertigo, migraine and pruritus.[62, level I]

c. Infliximab

Infliximab is a chimeric monoclonal antibody that works against Tumour Necrosis Factor Alpha (TNF-α).

There is no strong retrievable evidence on the effectiveness of infliximab in AE.[53, level I]

d. Intravenous Immunoglobulin

A systematic review showed IVIG was less effective in reduction of SCORAD at 12 weeks compared with placebo and cyclosporin A in AE.[54, level I]

Most common adverse effects reported are headache, nausea, vomiting and low-grade fever. They are transient and self-limiting, and usually happen during the first few hours after injection.[54, level I]

- Dupilumab is a potential biologic therapy in adult patients with moderate to severe AE after optimisation of conventional therapy.

8.4 Other Systemic Agents

a. Leukotriene Antagonist

There is no significant difference in reduction of SASSAD in AE between montelukast and placebo at eight weeks follow-up (MD=0.35, 95% CI -6.1 to 6.8).[53, level I]

b. Interferon Gamma

There is no strong retrievable evidence on the effectiveness of IFN-γ in AE.[54, level I]

9. ANTIMICROBIALS

9.1 Topical Antibiotics Combined with Corticosteroids

A systematic review using a combination of TCS and topical antibiotics (fusidic acid, mupirocin, neomycin, gentamicin or tetracycline) compared with TCS alone showed no difference in global outcome for clinically infected eczema (RR=0.52, 95% CI 0.23 to 1.16).[64, level I]

One RCT demonstrated improvement in SCORAD and EASI for both hydrocortisone ointment with mupirocin and hydrocortisone ointment alone by 74% (p=0.012) and 65% (p=0.019) respectively compared with emollient at eight weeks but there was no significant difference between the hydrocortisone groups.[65, level I]

9.2 Systemic Antibiotics

Staphylococcus aureus colonisation of the skin in patients with moderate to severe AE is common. The degree of colonisation significantly correlates with AE clinical severity and disease exacerbation. Anti-staphylococcal treatment is widely practised in the management of AE.

In a Cochrane systematic review, oral antibiotics showed no long-term benefits in patients with non-infected AE. Improvement in global outcome was observed among those treated with flucloxacillin at day 28 (RR=2.49, 95% CI 1.27 to 4.89), but no further improvement at day 56 post-treatment (MD= -0.10, 95% CI -0.59 to 0.39).[66, level I]

Routine use of systemic antimicrobials among patients with non-infected AE is not recommended. Systemic antimicrobial agents should be reserved for patients with signs of secondary infections.[14] Refer to Malaysian National Antibiotic Guidelines 2014 for choices of antibiotic in skin and soft tissue infection.

Recommendation 10
- Systemic antibiotics may be considered when there is clinical evidence of infection in patients with atopic eczema.

9.3 Sodium Hypochlorite 0.005% (Bleach Bath)

Staphylococcus aureus infection is a common complication in AE and can worsen the disease. Bleach bath has been used as an antiseptic bath to reduce colonisation of bacteria including *Methicillin-resistant Staphylococcus aureus (MRSA)*.[31, 51]

Bleach bath significantly reduces EASI score, affected BSA, itch score, and the use of TCS and antibiotics compared with water bath at 1 - 3 months in AE.[67 - 68, level I] However, water bath results in better SCORAD reduction.[68, level I]

Combined use of bleach bath and intranasal mupirocin ointment improves EASI score and affected BSA at one and three months compared with combination of water bath and intranasal petrolatum ointment in moderate to severe AE ($p<0.05$).[64, level I; 69, level I]

A recent meta-analysis showed that bleach baths were effective in decreasing AE severity, but not more effective than water baths alone.[70, level I]

Bleach bath is well tolerated with similar incidence of mild adverse events compared to water bath.[68, level I] Adverse events reported are stinging, burning, itch, xerosis, erythema, urticaria and oozing.[70, level I]

9.4 Other Antiseptics

Antiseptics at appropriate dilutions, e.g. triclosan or chlorhexidine, should be used as an adjunct therapy to decrease bacterial load in children who have recurrent infected AE.[32] In local setting, short-term antiseptic agents may be used for weepy lesions in AE:

- diluted potassium permanganate solution as bath/soak over the limbs and trunk
- normal saline daps/wash over the face

Long-term continuous use of antiseptics should be avoided.

A Cochrane review found no benefit of antibacterial soaps and bath additives in AE.[64, level I]

- Bleach bath has been shown to improve severity of AE.
- Other antiseptic baths (e.g. potassium permanganate, triclosan, chlorhexidine) may be helpful in reducing bacterial colonisation of the skin.

10. SPECIFIC ALLERGEN IMMUNOTHERAPY

Specific allergen immunotherapy (SIT) is also known as desensitisation or hyposensitisation which involves the administration (sublingual or subcutaneous) of specifically relevant allergen(s) in the treatment of IgE-mediated allergic disease. SIT works by inhibiting abnormal immune responses to the relevant allergen thus reducing symptoms in patients with AE.

A recent Cochrane meta-analysis did not show conclusive evidence on the effectiveness of SIT in treating patients with AE. The allergens included in the study were:[71, level I]

- *Dermatophagoides pterionyssinus*
- *Dermatophagoides farinae*
- Grass pollen

- There is insufficient evidence to recommend specific allergen immunotherapy in the management of AE patients without other atopic conditions.

11. NON-PHARMACOLOGICAL INTERVENTIONS

11.1 Bathing Practices

Longer duration of bathing (>10 minutes) may be associated with risk of greater AE severity (p=0.0562).[72, level III] However, frequency of bathing is not associated with the severity.[73, level I] There is no evidence on clinical benefit of emollient bath additives in AE.

There is no retrievable evidence with regards to appropriate water temperature. However, the CPG development group advices against the use of extreme temperatures (too hot or too cold) during bathing to avoid worsening of AE.

11.2 Dietary Interventions

a. Food Avoidance

- **Maternal dietary avoidance**

A Cochrane systematic review showed no significant protective effect of maternal dietary antigen avoidance (e.g. cow's milk, egg, peanuts, fish and chocolate) during pregnancy and lactation on incidence of AE during first 18 months of life. The review also found no significant reduction in eczema severity in infants with established AE with maternal dietary antigen avoidance during lactation.[74, level I]

- **Food avoidance in established eczema**

In another Cochrane systematic review, there was no significant beneficial effect in elimination of food in mother's diet (e.g. wheat, fish, beef, chicken, nuts, chocolate, citrus food, colouring and preservatives) or use of few foods diet which only includes 5 - 6 foods (lamb, potato, rice, one of the brassicas, pear and tap water) and elemental diet in AE. The RCTs in the review were of poor quality.[75, level I]

There may be some benefits in using an egg-free diet in infants with positive specific IgE to eggs. However, there was little evidence to support the use of various exclusion diets in unselected patients with AE.[75, level I]

b. Breastfeeding

Exclusive breastfeeding for three months or more may help to prevent the development of AE in infants with family history of atopy.[14]

However, a meta-analysis showed that there was no evidence on protective effect of exclusive breastfeeding for at least 3 months against AE, even among children with a positive family history.[76, level II-2]

A Cochrane systematic review on breastfeeding duration showed no significant difference in the reduction of AE risk in the first 12 months of life and at 5 - 7 years of age when infants exclusively breastfed for 3 - 4 months compared with 6 - 7 months.[74, level I]

c. Soy Formula

A Cochrane systematic review showed no significant difference between soy and cow's milk formulas in prevention of childhood AE.[77, level I]

d. Hydrolysed Formula

A systematic review showed some evidences that partially hydrolysed 100% whey protein infant formula (pHF-W) reduced risk of AE compared with intact protein cow's milk formula among infants with risk of atopy.[78, level I]

This is supported by a recent meta-analysis of moderate quality RCTs demonstrating a trend in reduction of eczema in infants with high risk of developing allergy fed with pHF-W compared with cow's milk formula.[79, level I]

In the prevention of AE, hydrolysed formulas should not be offered to infants in preference to breast milk.[14]

e. Complementary Feeding

The AE risk is reduced with early introduction of complementary food at the age of four and/or five months compared to those on exclusive breastfeeding (up to six months). However, stronger evidence is required.[80, level II-2]

f. Probiotic and Prebiotic

Probiotic and prebiotic are food supplements/food that modify and reinstate the pre-existing intestinal flora. Probiotics are live 'good' bacteria which include *lactobacilli sp*. and *bifidobacteria*. Prebiotics are dietary fibre (non-digestible oligosaccharides and fructooligosaccharides) which stimulates the growth or activity of bacteria in the colon.

- **Probiotic**

A meta-analysis on probiotics (e.g. non-spore lactobacillicus, bifidobacterium and mixed lactobacilli) given to healthy infants (<2 years old) and pregnant women found a reduction in the incidence of AE (RRR=0.69, 95% CI 0.62 to 0.78). However, the primary papers used were of poor quality with significant heterogeneity.[81, level I]

- **Prebiotic**

Two systematic reviews on the prevention of AE using supplementation of expressed breast milk or infant formula with prebiotics showed reduction in incidence of AE but the results were not significant.[81 - 82, level I]

There is insufficient evidence to recommend probiotic and prebiotic in the management of AE. Limitations of the included studies in the above reviews are heterogeneity in the strains used, dose and duration of intervention.

g. Other Dietary Intervention

- **Fish Oil**

Fish oils are rich in omega-3 fatty acids namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These may reduce the inflammatory components of AE. Two small studies in a Cochrane systematic review showed that fish oil improved symptoms and quality of life at 12 - 16 weeks when compared with placebo in adults with AE.[83, level I]

- **Mineral**

Minerals such as zinc and selenium show no significant difference in reducing disease severity in AE.[83, level I]

- **Vitamins**

There is insufficient evidence to suggest the use of vitamin B6, D and E in AE.[83, level I]

- **Maternal dietary supplementation**

Two systematic reviews showed no significant association between maternal intake of vitamins and nutrients during pregnancy, lactation or both pregnancy and lactation, and reduction of incidence of childhood AE.[84 - 85, level I]

- There is insufficient evidence to recommend dietary supplements in the management of AE.

11.3 Educational and Psychological Interventions

Educational and psychological interventions are used as an adjunct to conventional therapy in the management of AE.

In a Cochrane systematic review of 10 RCTs, psychological techniques are used to manage itching and scratching or sleep disturbance. Educational interventions are also used to help parents and children to understand the condition and their role in managing it successfully. However, there was lack of rigorously designed trials on effectiveness of educational and psychological interventions in the management of AE in children.[86, level I]

In the guidelines of care for the management of AE, educational programmes and eczema workshops are recommended as adjunct to the conventional therapy in the management of AE.[87]
A major challenge in AE management is its complex treatment,

which must be tailored for both acute exacerbations and long-term maintenance. Patient education plays an important role in the self-management of AE. The addition of a written eczema action plan (WEAP) to the routine verbal instruction may enhance patients' understanding and empower patients/caregivers to better manage their condition thus reducing the frequency and severity of flares, and frequency of clinical encounters (refer to **Appendix 10**).

Recommendation 11

- Educational interventions should be considered as part of the management of atopic eczema.

12. TRADITIONAL AND COMPLEMENTARY MEDICINE

Traditional and complementary medicine (TCM) refers to the broad set of health practices that are not part of conventional medicine or practice and are not fully integrated into the dominant health care system. In some instances, TCM is often interchangeable with traditional medicine.

12.1 Herbal and Food Supplementation

a. Chinese Herbal Medicine

Based on a Cochrane systematic review of 28 RCTs of moderate quality, topical or oral chinese herbal medicine (CHM) was found to be better than placebo in AE for:[88, level I]

- overall severity score (EASI, SASSAD and SCORAD) (SMD= -0.88, 95% CI -1.67 to -0.09)
- severity of itch score measured by Visual Analogue Score (VAS) (SMD= -1.53, 95% CI -2.64 to -0.41)
- improvement of QoL at 12-week (MD= -2.50, 95% CI -4.77 to -0.23)

Two meta-analyses on RCTs of moderate quality showed that topical or oral CHM was better compared with 'conventional treatments' (e.g. econazole nitrate cream, calamine lotion, zinc oxide cream and topical corticosteroids) in AE, for the following outcomes:

- erythema (SMD=-0.76; 95% CI -1.05 to -0.47) and surface damage scores (SMD= -1.08; 95% CI, -1.59 to -0.56)[89, level I]
- total effectiveness rate (RR=1.19, 95% CI 1.04 to 1.36); However, sub-group analysis showed no difference between topical CHM and topical corticosteroids (RR=1.04, 95% CI 0.93 to 1.16)[90, level I]

CHM in combination with conventional therapy is more effective than conventional therapy alone in AE for overall clinical score, MD= -2.56; 95% CI -3.46 to -1.66.[89, level I]

Topical or oral CHM is generally safe compared with placebo or conventional therapy.[89 - 91, level I]

- It is important to note that the above-mentioned effectiveness of CHM in AE is pertaining to specific preparations and hence, should not be generalised to other CHM preparations.
- Some traditional medicine (not limited to CHM) contain prohibited substances (e.g. dexamethasone, mercury). Refer to http://npra.moh.gov.my for further information.

b. Evening Primrose Oil

Evening primrose oil (EPO) is the oil from the seeds of evening primrose plant and contains 8 - 10% gamma-linolenic acid (GLA).

In a Cochrane systematic review, EPO did not show significant differences in improvement of symptoms and QoL compared with placebo in AE.[92, level I]

c. Borage Oil

Borage oil is obtained from the seeds of *Borago officinalis* and contains at least 23% GLA.

In a Cochrane systematic review, there was no significant differences in improvement of symptoms in AE with borage oil 1500 mg twice a day compared with placebo.[92, level I]

12.2 Topical Oils and Massage Therapy

Virgin coconut oil (VCO) applied topically is more effective than mineral oil (paraffin oil) in improving mean SCORAD ($p<0.001$) in AE. There is no difference in side effects when comparing between the two ($p=0.089$).[93, level I]

Olive oil applied topically causes reduced stratum corneum integrity and induces more erythema compared with sunflower seed oil in AE.[91, level I]

Based on a systematic review, there was no difference in general improvement at eight weeks between massage therapy alone and in combination with essential oil in AE. However there was worsening of symptoms in massage therapy with essential oil group beyond eight weeks.[91, level I]

12.3 Acupuncture

There is insufficient evidence to recommend the use of acupuncture in AE.[89, level I; 91, level I;]

12.4 Balneotherapy

Balneotherapy is the practice of full body immersion in mineral water or mineral-laden mud (i.e. hot springs, cold springs or other sources of such water like the Dead Sea).

An RCT showed synchronous balneophototherapy (immersion in mineral water with phototherapy) was better than NBUVB monotherapy in improving SCORAD ($p<0.05$) in AE.[94, level I]

12.5 Homeopathy

There is insufficient evidence to recommend the use of homeopathic remedies in AE.[95, level I]

Recommendation 12
- Traditional and complementary medicine should not replace conventional therapy in atopic eczema.

13. REFERRAL

Referral to a dermatology service may be needed in the management of AE. The urgency of referral is dependent upon various factors. The referral section is adapted from existing guidelines and expert opinions of the CPG development group.[14, 32, 96]

The urgency for referral to a dermatologist is divided into the following categories:

1. Urgent referral (within 24 hours)
   - AE with clinical suspicion of eczema herpeticum (eczema with widespread herpes simplex infection)
   - AE with severe skin bacterial infection that requires intravenous antibiotics
   - AE with acute erythroderma where the eczema is affecting more than 80% body surface area

2. Non-urgent referral
   - Diagnostic uncertainty
   - Severe or uncontrolled eczema:
     - requirement of potent and very potent TCS
     - frequent infections
     - poor sleep or excessive scratching
     - treatment failure with appropriate topical therapy regimen
   - Parental concern
   - Need for treatment demonstration/education
   - Involvement of sites that are difficult to treat
   - Psychological disturbance on the patient or family

14. IMPLEMENTING THE GUIDELINES

The management of AE should be guided by evidence-based approach in order to provide quality care to the patients. Several factors may affect the implementation of recommendations in the CPG.

14.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:

- wide dissemination of the CPG (soft- and hardcopies) to healthcare providers
- regular training on common dermatoses

Existing barriers for application of the recommendations of the CPG are:

- limited exposure on management of AE
- cost and availability of treatment
- variation in practice of healthcare providers

14.2 Potential Resource Implications

To implement the CPG, there must be strong commitment to:

- ensure widespread distribution of the CPG to healthcare providers via printed and electronic copies
- reinforce regular trainings with adequate funding for healthcare providers
- ensure widespread distribution of updated patient education materials

The following is proposed as clinical audit indicator for quality management of AE:

$$\text{Percentage of patients treated for AE with improvement (based on IGA) (target ≥70\%)} = \frac{\text{Number of patients treated for AE with improvement (based on IGA) in a period}}{\text{Total number of patients treated for AE in the same period}} \times 100\%$$

Implementation strategies will be developed following the approval of the CPG by MoH which include launching of the CPG, Quick Reference and Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

The following Medical Subject Heading terms or free text terms were used either singly or in combination, search was limit to English, human and last 10 years:

Clinical Question: Is biologics effective and safe in atopic eczema?

1. ECZEMA/
2. eczema*.tw.
3. eczematous dermati*.tw.
4. DERMATITIS, ATOPIC/
5. (atopic adj1 (eczema or dermati*)).tw.
6. (infantile adj1 eczema).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. BIOLOGICAL PRODUCTS/
9. biologics.tw.
10. (product* adj1 (biologic* or natural)).tw.
11. OMALIZUMAB/
12. omalizumab.tw.
13. xolair.tw.
14. RITUXIMAB/
15. antibody, rituximab cd20.tw.
16. cd20 antibody, rituximab.tw.
17. gp2013.tw.
18. idec c2b8.tw.
19. idec-c2b8.tw.
20. idecc2b8.tw.
21. ((idec c2b8 or idec-c2b8 or idecc2b8) adj1 antibody).tw.
22. mabthera.tw.
23. rituxan.tw.
24. rituximab.tw.
25. rituximab cd20 antibody.tw.
26. RECOMBINANT FUSION PROTEINS/
27. ((chimeric or fusion or hybrid) adj1 proteins, recombinant).tw.
28. (recombinant adj1 (chimeric proteins or fusion proteins or hybrid proteins)).tw.
29. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 7 and 29

Appendix 2

CLINICAL QUESTIONS

1. What are the reliable diagnostic criteria of atopic eczema?
2. What are the supportive investigations in atopic eczema?
3. What are the effective scoring tools in the assessment of atopic eczema?
4. What are the co-morbidities associated with atopic eczema?
5. What are the aggravating factors of atopic eczema?
6. Are the following topical treatments effective and safe in atopic eczema?
   - Emollient
   - Topical corticosteroids
   - Topical calcineurin inhibitors
   - Topical antibiotics and antiseptics
   - Dressing
   - Others
7. Are the following photo/light therapies effective and safe in atopic eczema?
   - Ultraviolet A
   - Ultraviolet B
   - Light-emitting diode
   - Laser
8. Are the following systemic therapies effective and safe in atopic eczema?
   - Systemic immunomodulators (e.g systemic corticosteroids, methotrexate (MTX), azathioprine (AZA), cyclosporin (CsA), mycophenolate mofetil (MMF), leukotrine inhibitors, alitretonoin, interferon gamma)
   - Biologics
   - Allergen specific immunotherapy
   - Antimicrobials (e.g. antibiotics, antivirals, antifungals)
   - Antihistamines
9. Is food antigen elimination diet during pregnancy and lactation effective and safe to prevent atopic eczema in babies with family history of atopy?
10. Are the following dietary interventions effective and safe in treatment /prevention of atopic eczema?
    - Food antigen elimination (e.g. cow's milk/partially hydrolysed/ elements formula/soy milk/goat's milk/egg/wheat/chicken/fish/ peanuts)
    - Breastfeeding
    - Prebiotics and probiotics
    - Vitamins and minerals
    - Delayed introduction of complementary foods

11. Are the following traditional and complementary medicines effective and safe in the treatment of atopic eczema?
    - Herbal supplement
    - Acupuncture
    - Aromatherapy
    - Bath therapy
    - Chromotherapy
    - Autologous blood injection
    - Massage
    - Homeopathy
12. Are psychosocial and counselling interventions (patient's education) effective in atopic eczema?
13. What are the referral criteria for atopic eczema?
    - Urgent referral
    - Non-urgent referral

Appendix 3

GUIDELINES FOR THE DIAGNOSIS OF ATOPIC DERMATITIS (HANIFIN AND RAJKA CRITERIA)

Must have 3 or more basic features:

1. Pruritus
2. Typical morphology and distribution:
   - ○ Flexural lichenification or linearity in adults
   - ○ Facial and extensor involvement in infants and children
3. Chronic or chronically-relapsing dermatitis
4. Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Plus 3 or more minor features:

1. Xerosis
2. Ichthyosis/palmar hyperlinearity/keratosis pilaris
3. Immediate (type 1) skin test reactivity
4. Elevated serum IgE
5. Early age of onset
6. Tendency toward cutaneous infections (especially *Staphylococcus aureus and Herpes simplex*)/impaired cell-mediated immunity
7. Tendency toward non-specific hand or foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Dennie-Morgan infraorbital fold
12. Keratoconus
13. Anterior subcapsular cataracts
14. Orbital darkening
15. Facial pallor/facial erythema
16. Pityriasis alba
17. Anterior neck folds
18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Course influenced by environmental/emotional factors
23. White dermographism/delayed blanch

Source: Hanifin JM. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Suppl). 1980; 92:44-7.

Appendix 4

INVESTIGATOR'S GLOBAL ASSESSMENT (IGA)

Score	Description
0 = Clear	No inflammatory signs of atopic eczema
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration
2 = Mild disease	Mild erythema, and mild papulation/infiltration
3 = Moderate disease	Moderate erythema, and moderate papulation/infiltration
4 = Severe disease	Severe erythema, and severe papulation/infiltration
5 = Very severe disease	Severe erythema, and severe papulation/infiltration with oozing/crusting

Modified: Eichenfield LF, Lucky AW, Boguniewicz M, et al. Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. J Am Acad Dermatol. 2002;46(4):495-504.

Appendix 5

DERMATOLOGY LIFE QUALITY INDEX

Hospital:
Name: Date: DLQI
Age:
Address: Diagnosis: Score:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1. Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐

2. Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐

3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

4. Over the last week, how much has your skin influenced the **clothes** you wear?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

5. Over the last week, how much has your skin affected any **social** or **leisure** activities?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

6. Over the last week, how much has your skin made it difficult for you to do any **sport**?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

7. Over the last week, has your skin prevented you from **working** or **studying**?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

   If "No", over the last week how much has your skin been a problem at **work** or **studying**?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐

8. Over the last week, how much has your skin created problems with your partner or any of your **close friends** or **relatives**?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

9. Over the last week, how much has your skin caused any **sexual difficulties**?
   Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

10. Over the last week, how much of a Problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?
    Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

Please check you have answered EVERY question. Thank you.

Source: Department of Dermatology, Cardiff University. Quality of Life Questionnaires. (Available at: http://sites.cardiff.ac.uk/dermatology/quality-of-life/)

Appendix 6

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Hospital:
Name: Date: CDLQI
Age:
Address: Diagnosis: Score:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1. Over the last week, how **itchy, "scratchy"**, **sore** or **painful** has your skin been?

   Very much ☐
   A lot ☐
   A little ☐
   Not at all ☐

2. Over the last week, **how embarrassed** or **self-conscious**, **upset** or **sad** have you been because of your skin?

   Very much ☐
   A lot ☐
   A little ☐
   Not at all ☐

3. Over the last week, how much has your skin affected your **friendships**?

   Very much ☐
   A lot ☐
   A little ☐
   Not at all ☐

4. Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?

   Very much ☐
   A lot ☐
   A little ☐
   Not at all ☐

5. Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?

   Very much ☐
   A lot ☐
   A little ☐
   Not at all ☐

6. Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?

   Very much ☐
   A lot ☐
   A little ☐
   Not at all ☐

7. Last week was it **school time**? ⇨ **If school time**: Over the last week, how much did your skin problem affect your **school work**?

   Very much ☐
   A lot ☐
   A little ☐
   Not at all ☐

   OR

   was it **holiday time**? ⇨ **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday?**

   Very much ☐
   A lot ☐
   A little ☐
   Not at all ☐

8. Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding** you?

   Very much ☐
   A lot ☐
   A little ☐
   Not at all ☐

9. Over the last week, how much has your **sleep** been affected by your skin problem?

   Very much ☐
   A lot ☐
   A little ☐
   Not at all ☐

10. Over the last week, how much of a problem has the **treatment** for your skin been?

    Very much ☐
    A lot ☐
    A little ☐
    Not at all ☐

Please check you have answered EVERY question. Thank you.

Source: Department of Dermatology, Cardiff University. Quality of Life Questionnaires. (Available at: http://sites.cardiff.ac.uk/dermatology/quality-of-life/)

Appendix 7

TOPICAL CORTICOSTEROIDS CLASS AND POTENCY (UK CLASSIFICATION)

Class & Potency	Drug (Generic Name)
Class I (Very Potent)	• Clobetasol propionate 0.05% cream/ointment
Class II (Potent)	• Betamethasone dipropionate 0.05% cream/ointment • Betamethasone valerate 0.1% cream/ointment • Diflucortolone valerate 0.1% cream • Fluocinolone acetonide 0.025% cream • Fluticasone propionate 0.05% cream • Mometasone furoate 0.1% cream/ointment • Triamcinolone acetonide 0.1% cream
Class III (Moderate)	• Betamethasone valerate 1 in 2 dilution (0.05%) cream/ointment • Betamethasone valerate 1 in 4 dilution (0.025%) cream/ointment • Clobetasone butyrate 0.05% cream/ointment
Class IV (Mild)	• Betamethasone valerate 1 in 8 dilution (0.0125%) cream/ointment • Betamethasone valerate 1 in 10 dilution (0.01%) cream/ointment • Hydrocortisone acetate 1% cream/ointment

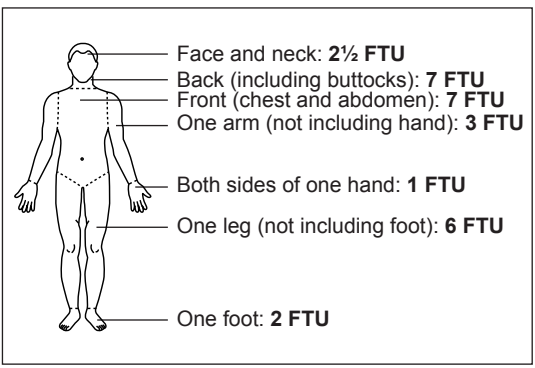
Adapted: British National Formulary (BNF). 69th edition. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2015.

Appendix 8

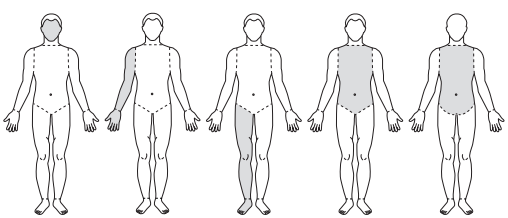
FINGERTIP UNIT

HOW MUCH CREAM/OINTMENT SHOULD BE USED?
Use index finger (first finger) to measure. One fingertip unit (FTU) is the amount of cream squeezed along index finger from tip to the first joint (as shown in picture).
1 FTU = 0.5 g (covers the size of two palms of adult)

For adults
The diagram shows the amount of cream needed to cover different areas of the body (this is only a general guide).



For children
The amount of cream needed depends on the age of the child (this is only a general guide).



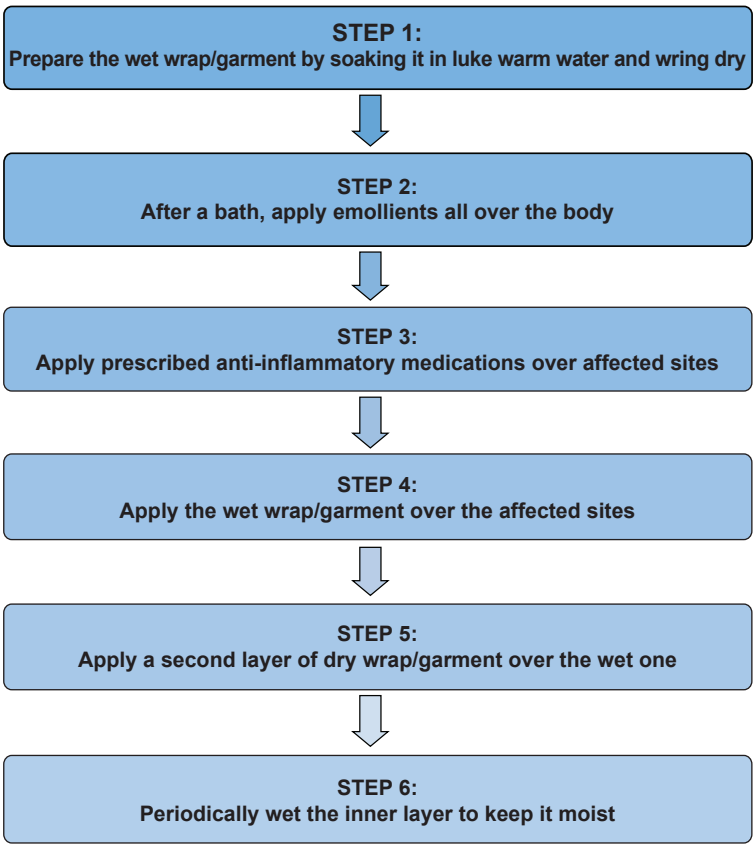
Child's Age	Face and neck	Arm and hand	Leg and foot	Front	Back
	Number of FTU needed				
3 - 12 months	1	1	1½	1	1½
1 - 3 years	1½	1½	2	2	3
1 - 6 years	1½	2	3	3	3½
6 - 10 years	2	2½	4½	3½	5
>10 years	2½	2	7	7	7

Modified: Bewley A; Dermatology Working Group. Expert consensus: time for a change in the way we advise our patients to use topical corticosteroids. Br J Dermatol. 2008;158(5):917-920.

Mooney E, Rademaker M, Dailey R, et al. Adverse effects of topical corticosteroids in paediatric eczema: Australasian consensus statement. Australas J Dermatol. 2015;56(4):241-251.

Appendix 9

SIX STEPS OF WET WRAP THERAPY



Source: Paediatric Dermatology Unit, Paediatric Department, Hospital Kuala Lumpur. Six Steps of Wet Wrap Therapy. HKL. (unpublished document)

Appendix 10

WRITTEN ECZEMA ACTION PLAN

NAME:	**GREEN = GO : Use preventive measures** **YELLOW = CAUTION: Use lower strength medications** **RED = FLARE : Use higher strength medications and consult your doctor**
GREEN 	**ECZEMA UNDER CONTROL** **REGULAR DAILY SKIN CARE** 1. Bath twice a day with gentle cleanser less than 10 minutes. 2. Apply moisturiser to all body parts immediately after bath. 3. Apply moisturiser to all body parts minimum thrice a day. 4. Bath and moisturise your skin before bed. 5. Wear suitable cloth/pyjamas, preferably cotton, to bed.
YELLOW 	**ECZEMA WORSENING** **SKIN CARE DURING WORSENING** 1. Continue regular skin care from GREEN phase. 2. Apply anti-inflammatory creams till eczema clears. 2a. Face: Apply hydrocortisone 1% twice a day for 5 - 7 days, then once a day for 5 - 7 days till eczema clears. 2b. Body: Apply betamethasone (1:4) twice a day for 5 - 7 days, then once a day for 5 - 7 days till eczema clears. 3. Take antihistamine (anti-itch), prescribed by doctor, half an hour before bed. 4. If eczema gets better, revert back to GREEN phase. 5. If eczema not responding within 3 days or eczema and itch worsens, move to RED phase.
RED 	**UNCONTROLLED ECZEMA** **SKIN CARE DURING UNCONTROLLED ECZEMA** 1. Continue regular skin care form GREEN phase. 2. Bath daily with antiseptic wash for 5 - 7 days. 3. Apply anti-inflammatory creams till eczema clears. 3a. Face: Apply betamethasone (1:8) twice a day for 5 - 7 days, then once a day for 5 - 7 days till eczema clears. 3b. Body: Apply betamethasone (1:2) twice a day for 5 - 7 days, then once a day for 5 - 7 days till eczema clears. 4. Take antihistamine (anti-itch), prescribed by doctor, half an hour before bed. 5. If eczema gets better revert back to YELLOW phase, then subsequently to GREEN phase. 6. If eczema not responding within 3 days or eczema and itch worsens, consult your doctor.

Source: Paediatric Dermatology Unit, Paediatric Department, Hospital Kuala Lumpur. Written Eczema Plan. HKL. (unpublished document)

RECOMMENDED MEDICATION DOSING, SIDE EFFECTS AND CONTRAINDICATIONS FOR COMMONLY USED MEDICATIONS IN ATOPIC ECZEMA

DRUG	RECOMMENDED DOSAGE	POSSIBLE SIDE EFFECTS	CONTRAINDICATIONS	SPECIAL PRECAUTIONS
TOPICAL CORTICOSTEROIDS				
Mild Betamethasone Valerate 1 in 10 dilution (0.01%) Cream/Ointment Betamethasone Valerate 1 in 8 dilution (0.0125%) Cream/Ointment Hydrocortisone Acetate 1% Cream/Ointment	1 - 2 times daily	Worsening of untreated infection, contact dermatitis, perioral dermatitis, acne, depigmentation, dryness, hypertrichosis, secondary infection, skin atrophy, pruritus, tingling/stinging, rosacea, folliculitis, photosensitivity	Untreated bacterial, fungal or viral skin lesions in rosacea and perioral dermatitis	Avoid prolonged use Caution when used on face or intertriginous and flexor areas
Moderate Betamethasone Valerate 1 in 2 dilution (0.05%) Cream/Ointment Betamethasone Valerate 1 in 4 dilution (0.025%) Cream/Ointment Clobetasone Butyrate 0.05% Cream/Ointment	1 - 2 times daily			

RECOMMENDED MEDICATION DOSING, SIDE EFFECTS AND CONTRAINDICATIONS FOR COMMONLY USED MEDICATIONS IN ATOPIC ECZEMA (CONT.)

DRUG	RECOMMENDED DOSAGE	POSSIBLE SIDE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
TOPICAL CORTICOSTEROIDS (continued)				
Potent Betamethasone Dipropionate 0.05% Cream/Ointment Betamethasone Valerate 0.1% Cream/Ointment Fluocinolone Acetonide 0.025% Cream Fluticasone Propionate 0.05% Cream Triamcinolone Acetonide 0.1% Cream	1 - 2 times daily	Worsening of untreated infection, contact dermatitis, perioral dermatitis, acne, depigmentation, dryness, hypertrichosis, secondary infection, skin atrophy, pruritus, tingling/stinging, rosacea, folliculitis, photosensitivity	Untreated bacterial, fungal or viral skin lesions, in rosacea and perioral dermatitis	Avoid prolonged use. Caution when used on face or intertriginous and flexor areas
Mometasone Furoate 0.1% Cream/Ointment	Once daily			
Very Potent Clobetasol Propionate 0.05% Cream/Ointment	1 - 2 times daily			

RECOMMENDED MEDICATION DOSING, SIDE EFFECTS AND CONTRAINDICATIONS FOR COMMONLY USED MEDICATIONS IN ATOPIC ECZEMA (CONT.)

DRUG	RECOMMENDED DOSAGE	POSSIBLE SIDE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
TOPICAL CALCINEURIN INHIBITORS				
Tacrolimus 0.03% - 0.1% Ointment	Twice daily	Burning, stinging, soreness, pruritus, skin disorders, headache, flu-like symptoms	Hypersensitivity to tacrolimus.	Use in patients with Netherton's syndrome or other skin diseases with barrier defect is not recommended
Pimecrolimus 1% Cream	Twice daily	Application site reactions, risk for infections, headache, fever	Hypersensitivity to pimecrolimus.	Only to be used in children age two years and older
SYSTEMIC (ORAL) IMMUNOMODULATING AGENTS				
Azathioprine	1 - 3 mg/kg daily (Off-label use)	Nausea, vomiting, pancreatitis, pericarditis, bone marrow depression (dose-related) characterised by anaemia, leukopenia, thrombocytopenia and rarely, aplastic anaemia, acute myeloid leukaemia, hematological toxicity, hypersensitivity reaction (Stevens-Johnson's syndrome, toxic epidermal necrolysis), hepatotoxicity	Hypersensitivity to azathioprine, history of treatment with alkylating agents (e.g. chlorambucil, cyclophosphamide)	Thiopurine methyltransferase (TPMT) enzyme deficiency Women of childbearing age Screen for Hepatitis B, C and HIV before commencement Monitor FBC, RP and LFT two weeks after commencement and as needed subsequently

RECOMMENDED MEDICATION DOSING, SIDE EFFECTS AND CONTRAINDICATIONS FOR COMMONLY USED MEDICATIONS IN ATOPIC ECZEMA (CONT.)

DRUG	RECOMMENDED DOSAGE	POSSIBLE SIDE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
SYSTEMIC (ORAL) IMMUNOMODULATING AGENTS (continued)				
Cyclosporine A/Ciclosporin	2.5 - 5 mg/kg daily in two divided doses	Hypertension, hepatoxicity, tremor, paraesthesia, hypertrichosis, oedema, acne, gingival hypertrophy, hyperkalaemia, increased susceptibility to infections, nephrotoxicity, seizures	Hypersensitivity to cyclosporine, concomitant phototherapy	Limit use to two years to prevent increased risk of malignancy Avoid excessive sunlight exposure Pregnancy and breast feeding Screen for Hepatitis B, C and HIV before commencement Monitor FBC, RP and LFT two weeks after commencement and as needed subsequently
Methotrexate	10 - 25 mg weekly (0.2 - 0.5 mg/kg); not to exceed 30mg weekly (Off-label use)	Gastrointestinal disturbances (e.g. diarrhoea, nausea, vomiting), bone marrow depression, aplastic anaemia, hepatotoxicity, renal failure, skin reactions (e.g. photosensitivity, toxic epidermal necrolysis) alopecia, dizziness, neurotoxicity, encephalopathy, seizure, infections	Chronic liver disease, alcoholic liver disease, breast-feeding, hypersensitivity to methotrexate, evidence of immunodeficiency syndrome, pre-existing blood dyscrasias, pregnancy in patients with non-malignant disease	Pre-existing peptic ulcer disease or ulcerative colitis Nephrotoxicity may occur especially at high doses Monitoring and dose adjustment for elderly Screen for Hepatitis B, C and HIV before commencement Monitor FBC, RP and LFT two weeks after commencement and as needed subsequently

RECOMMENDED MEDICATION DOSING, SIDE EFFECTS AND CONTRAINDICATIONS FOR COMMONLY USED MEDICATIONS IN ATOPIC ECZEMA (CONT.)

DRUG	RECOMMENDED DOSAGE	POSSIBLE SIDE EFFECTS	CONTRAINDICATION	SPECIAL PRECAUTIONS
SYSTEMIC (ORAL) IMMUNOMODULATING AGENTS (continued)				
Mycophenolate Mofetil	1.5 - 2 g daily in two divided doses (Off-label use)	Diarrhoea, dyspepsia, vomiting, abnormal liver function test, acne, leukopenia, sepsis, certain infections	Hypersensitivity to mycophenolate	Avoid use of concomitant live vaccines Pregnancy and women of childbearing age Screen for Hepatitis B, C and HIV before commencement Monitor FBC, RP and LFT two weeks after commencement and as needed subsequently
Mycophenolate Sodium	720 mg twice daily in two divided doses (Off-label use)			
Prednisolone	*Adults:* 5 - 60 mg daily in 2 - 4 divided doses *Children:* 1 - 2 mg/kg daily in 2 - 4 divided doses *Maximum: 60 mg*	Fluid retention, hypertension, acne, Cushing's syndrome and growth retardation in children, hyperglycaemia, increased appetite, obesity, peptic ulcer, pancreatitis, osteoporosis, headache, seizure, psychotic disorder, glaucoma, drug-induced myopathy, drug-induced adrenocortical insufficiency, superinfection	Systemic fungal infections	May exacerbate conditions of patients with hypothyroidism, cirrhosis, ulcerative colitis, hypertension, diabetes, peptic ulcer, osteoporosis, psychological disturbances, on-going or latent infection Use lowest effective dose; taper dose when necessary

Source: MIMS Drug Monograph, MIMS Product Monograph, and Truven Health Analytics Micromedex® Solutions 2018 at MIMS Gateway (Available at: https://online1.mimsgateway.com.my/)

LIST OF ABBREVIATIONS

AE	atopic eczema
AZA	azathioprine
BSA	body surface area
CAM	complementary and alternatives medicine
Cer-Mg	ceramide-magnesium
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
CPG(s)	clinical practice guidelines
DASI	Dyshidrotic Eczema Area and Severity Index
DFI	Dermatitis Family Impact
DG	Development Group
DHA	docosahexaenoic acid
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EC-MPS	enteric-coated mycophenolate sodium
EPA	eicosapentaenoic acid
EPO	evening primrose oil
FTU	fingertip unit
GLA	gamma-linolenic acid
HPA	hypothalamic-pituitary-adrenal
HR	hazard ratio
IDQOL	Infant's Dermatology Quality of Life Index
IFN-γ	interferon gamma
IgE	immunoglobulin E
IGA	Investigators' Global Assessment
IL-4	interleukin-4
IL-13	interleukin-13
ISAAC	International Study of Asthma and Allergies in Childhood
IVIG	intravenous immunoglobulin
kg	kilogramme
MaHTAS	Malaysian Health Technology Assessment Section
MD	mean difference
mg	milligramme
MoH	Ministry of Health
MMF	mycophenolate mofetil
MRSA	*Methicillin-resistant staphylococcus aureus*
MTX	methotrexate
NB-UVB	narrow band ultraviolet B
OR(s)	odds ratio(s)
pHF-W	partially-hydrolysed formula 100% whey
POEM	Patient-Orientated Eczema Measure
PO-SCORAD	Patient-Oriented Severity Scoring of Atopic Dermatitis
QoL	quality of life
RC	Review Committee
RCT(s)	randomised controlled trial(s)
RNA	ribonucleic acid
RR	relative risk
RRR	relative risk reduction
SASSAD	Six Area, Six Signs Atopic Dermatitis

SCORAD	Severity Scoring of Atopic Dermatitis
SIT	specific allergen immunotherapy
SMD	standardised mean difference
TCIs	topical calcineurin inhibitors
TCM	traditional and complementary medicine
TCS	topical corticosteroids
TEWL	transepidermal water loss
TNF-α	Tumour Necrosis Factor Alpha
TPMT	thiopurine methyltransferase
UVA	ultraviolet A
UVA1	ultraviolet A1
VAS	Visual Analogue Score
VCO	virgin coconut oil
vs	versus
WEAP	Written Eczema Action Plan
WWT	wet wrap therapy

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