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CHILDHOOD ATOPIC ECZEMA CONSENSUS DOCUMENT

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CONSENSUS DOCUMENT

Childhood atopic eczema consensus document

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Background and prevalence

The prevalence of atopic eczema (AE) has risen over the past few decades.[1,2] There is a paucity of data on the prevalence of AE in South Africa. The ISAAC phase 1 study[2] reported a prevalence of 5 - 10% in Cape Town schoolchildren. A recent study by Todd *et al.*[3] conducted among Xhosa children demonstrated a point prevalence (dermatologist-diagnosed) of 0.7%, 1.1% and 3.7% in rural, peri-urban and urban settings respectively. AE is therefore very rare in Xhosa children in rural settlements and a clear urban/rural gradient exists for the occurrence of AE in black children. AE is frequently undertreated despite severely affecting the quality of life of patients and their families. AE also commonly predates the development of allergic rhinitis and asthma.

Nomenclature and classification of eczema

In May 2004 the World Allergy Organization (WAO) published a new report by its Nomenclature Review Committee.[1] The new WAO nomenclature is an update of the EAACI document defining terminology for skin allergies.[1]

The WAO recommends that the umbrella term for local inflammation of the skin should be 'dermatitis'. The term 'eczema' describes an aggregation of several skin diseases with clinical characteristics in common, involving a genetically determined skin barrier defect.

In children and young adults with an atopic constitution, the underlying inflammation is dominated by an immunoglobulin E (IgE) antibody-associated reaction allowing the term AE to be applied. This term should replace the term 'atopic dermatitis'. The diagnosis of AE cannot be reached without an IgE antibody determination or skin test. In other eczema cases where the inflammation is not associated with elevated IgE antibody, these patients are considered to have non-atopic eczema (Fig. 1).

AE is more common in preschool children, with a prevalence of 45 - 64%,[4] but in adults the incidence can be as high as 40%. Children with AE have a greater risk of developing asthma (approximately 30%) than children with non-atopic eczema. They also have associated food allergies and IgE-induced urticaria. Therefore the interventional, prognostic and co-morbidity implications for patients with AE are different from the implications for those with non-atopic eczema, where management is largely directed to management of the skin itself.

Diagnosis of AE

Fig. 1 in conjunction with Table I will help in the diagnosis and assessment of the severity of AE.

Pathogenesis

The pathogenesis of eczema is a complex interplay of numerous elements including immune, genetic, infection and neuroendocrine factors and their interaction with the environment.

Important immunological pathways include Langerhans cells, eosinophils, T-cells, mast cells, basophils, Fc epsilon receptors and IgE. Phosphodiesterase abnormalities and cyclic nucleotide dysregulation lead to reduced cyclic AMP modulation, and increased inflammatory activity is also present.

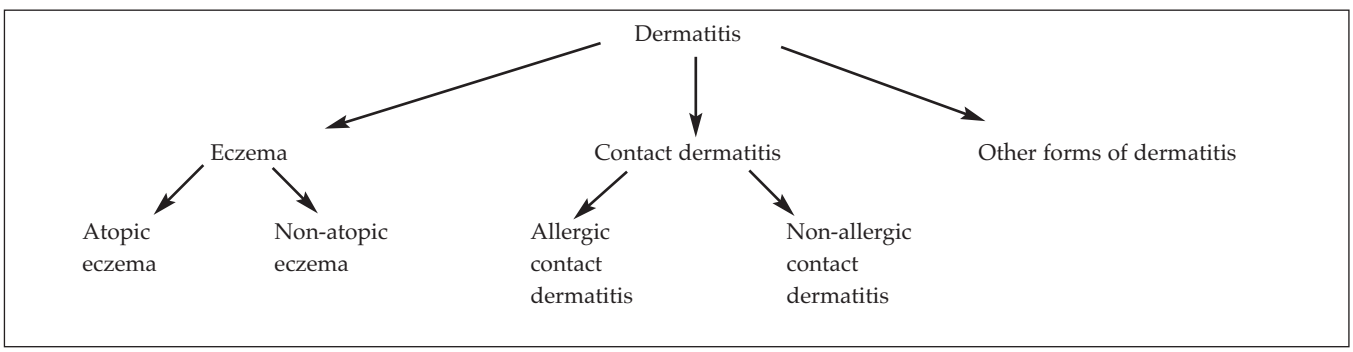

Fig 1. The new World Allergy Organization (WAO) classification of eczema/dermatitis (2004).

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Table I. Assessment and stepwise diagnosis of atopic eczema

Step 1	Step 2	Step 3	Step 4
Must have:	**Need 3 or more:**	**Can do as necessary (not essential):**	**Classify:**
Pruritus	• Flexural eczema • Previous flexural eczema • Dry skin • Other atopic disease • Onset before age 2	Evaluate and manage: • Rhinitis • Asthma • Food allergy • Environmental allergy	Mild Moderate Severe

Furthermore, neural mediators such as substance P, acetylcholine, calcitonin, gene-related peptide and neurokinin A are also important. Decreased barrier function leads to increased transepidermal loss, decreased water content of the stratum corneum, increased permeability to hydrophilic substances, decreased ceramides in the skin and decreased barrier to infectious agents.

Provoking factors for eczema exacerbations include the following: (*i*) microbial colonisation (*Staphylococcus aureus*); (*ii*) stress; (*iii*) barrier disruption; (*iv*) environmental exposure; (*v*) contact, inhalant and ingestant allergens; (*vi*) sweating; (*vii*) pollutants; (*viii*) sensory irritants (wool); (*ix*) chemical irritants; and (*x*) maternal ingestants (in breast-milk).

Implications for identifiable allergic pathogenetic factors

Since a number of environmental factors are known to trigger eczema flare-ups, these must be identified and avoided. In those patients with AE specific sensitivity to an environmental factor can be confirmed and specific avoidance implemented. Nonspecific irritants and other factors appear to aggravate both the atopic and non-atopic forms of eczema (e.g. wool, chemicals in soaps, etc.).

In patients with AE who are sensitive to house-dust mites, intensive house-dust mite avoidance measures, including hot washing of the bedding at 60°C and mite-impermeable mattress covers and bedding covers play an important role in reducing the severity of the symptoms.[2]

In young patients with specific IgE to foods, the significance in a given patient must be assessed either from the level of specific IgE or the size of the skin-prick wheal. Certain cut-off values have a 95% predictive value for clinical sensitivity to such foods.[5]

Prevention of AE – evidence

The cumulative evidence of studies has proven that intervention is worthwhile in high-risk families. There is now sufficient evidence that exclusive breast-feeding of high-risk infants for at least 4 months prevents the development of AE.[6] If mothers are unable to breast-feed, a hypoallergenic extensively hydrolysed formula is given to the infant (e.g. Alfare, Nutramigen). If this is not possible a partially hydrolysed formula such as Nan-HA may be tried.

There is no good evidence that the automatic substitution of breast-milk with soya formula will prevent allergic diseases, although soya milk may be used as an alternative in infants who have confirmed cow's milk allergy.[7]

Food testing in established AE

The importance of food allergy in the development and aggravation of the symptoms of atopic dermatitis in infants and young children is now well established. In contrast, food allergy is much less common and appears to play a far less important role in teenagers and adults with atopic dermatitis. Food allergy in the general paediatric population has a prevalence of 4 - 5%, whereas up to 80% of infants with atopic dermatitis will have positive food allergy tests.[8]

Because of the high prevalence of food allergy in infants and young children with atopic dermatitis, testing for food allergy is an essential part of the management of the infant.

Paediatric food allergy screening

IgE testing is cost-effective. The foods most commonly implicated in allergy in young infants are egg, milk, peanut, wheat, fish and soya. These can be screened by performing a Fx5e CAP paediatric screening test and if positive, specific IgE CAP RAST for the individual allergens can be requested.

Skin-prick tests

Skin-prick tests (SPTs) are inexpensive and provide quick results. SPTs have been found to be a highly sensitive but moderately specific indicator of an immediate reaction to food. They require co-operation in young children. A wheal of greater than 3 mm with a visible red flare constitutes a positive result provided that the saline control is non-reactive and that the histamine-positive control gives at least a 3 mm wheal-and-flare response.

The predictive values of SPTs have been published and can be used as a guide to determine sensitivity.

Table II. Treatment and management of atopic eczema

	Clear	Mild	Moderate	Severe
Basic treatment	Emollients	Emollients	Emollients	Emollient
Maintenance		TCI (pimecrolimus) Mild TCS	TCI (pimecrolimus) Mild/moderate TCS	Consider referral Moderate/potent TCS Consider treatment as for flare
Flare		As above	Temporarily replace maintenance treatment with moderate/potent TCS	Consider referral Cyclosporine Azathioprine Phototherapy Oral steroids Methotrexate
Adjuvant treatment (optional, not routinely needed)		Antibiotics Search for and avoid trigger factors	Antibiotics Antihistamines Search for and avoid trigger factors	Antibiotics Antihistamines Search for and avoid trigger factors
Always treat	Herpetic infections Bacterial infections	Herpetic infections Bacterial infections	Herpetic infections Bacterial infections	Herpetic infections Bacterial infections

TCI = topical calcineurin inhibitors (pimecrolimus (Elidel)); TCS: topical cortisone preparations (see Table III for guideline to potency).

CAP RAST blood tests

The concept of a cut-off value above which a test has a very high positive predictive value for allergy is not entirely clear. Using specific IgE values generated by the Pharmacia CAP system, Sampson and Ho[9] have correlated the results of IgE values with the results of double-blinded food challenges. Specific IgE values giving positive predictive values of at least 95% were egg (6 kμ/l), milk (32 kμ/l), peanuts (15 kμ/l) and fish (20 kμ/l). Importantly, the negative predictive value of both blood and skin tests is greater than 95%.

Other tests

'Atopy patch testing' is being explored as an alternative test for detecting food sensitivities.[10] Its role is still currently regarded as experimental.

Management

Management of atopic dermatitis should comprise: (*i*) general measures – avoidance of trigger factors; (*ii*) adjuvant measures; and (*iii*) anti-inflammatory therapy.

Table II is a summary of the management of AE.

Role of general measures

There is consensus that the following may be beneficial in management of AD: (*i*) avoid overheating and external irritants; (*ii*) keep the skin covered with clothing as this may reduce exposure to irritants and trauma from scratching; (*iii*) avoid skin care products that cause irritation, e.g. astringents and soaps; (*iv*) avoid wool clothing (or fabrics with rough texture or occlusive properties) – cotton is preferable; and (*v*) advise on hobbies, occupational exposure and potentially harmful habits, e.g. excessive hand washing.

Role of bathing

Further study is required to determine the efficacy of various cleansers used in bathing, the role of bathing as a steroid-sparing modality, and the optimal duration of bathing. Emollients applied during or after bathing provide a surface lipid film retarding evaporative water loss from the epidermis.

The current recommendations are:[11,12] (*i*) regular bathing to hydrate the skin and debride crust – useful for most patients for both cleansing and hydrating the skin; (*ii*) bathe once daily for several minutes in warm (not hot) water; (*iii*) use a moisturising cleanser; (*iv*) avoid antibacterial cleansers (may lead to bacterial resistance); (*v*) after bathing, pat dry; and (*vi*) emollients should be applied immediately after bathing.

Role of emollients

Skin dryness is a very common feature of AE and is a diagnostic criterion for the disease. Emollients are universally recommended as first-line therapy; however, despite this there is a paucity of studies to justify their use, and in fact the quality and quantity of evidence is inversely proportional to the frequency of use.[13,14]

The consequences of dry skin include: (*i*) inflammation;[15] (*ii*) loss of suppleness leading to fissuring; (*iii*) impaired barrier function; and (*iv*) increased adherence of *S. aureus*.

Use of emollients

Emollients are effective as first-line agents and may be steroid-sparing.

Ointments and creams provide better barrier function than lotions. In general, oilier preparations are better emollients but these may be too messy for routine use. Different preparations may be needed for the face and body. Patients should be allowed to decide on the most suitable emollient for their skin, i.e. an emollient that is effective and cosmetically acceptable. Emollients must be applied frequently. The maximum duration of any emollient is 6 hours. They should be applied regularly, at least twice during the day, even if there are no symptoms, and after swimming or bathing. This cleanses the skin and reduces the bacterial load. Best results are seen if emollients and medications are applied within 3 minutes of bathing to retain hydration.[16] Sufficient quantities must be prescribed, viz. 250 g/week for children and 500 g/week for adults for the whole body.

Adverse effects

No adverse effects are reported other than mild transient burning with oil-in-water emollients[17] or with urea-containing products.[18]

Topical steroids

Although topical steroids have been the cornerstone of AE treatment for the last 40 years, there is surprisingly little consensus on the most effective way in which to use them. Steroid phobia, i.e. an unwillingness to use topical steroids because of exaggerated perception of side-effects, has emerged as a significant problem, especially in affluent countries. Caregivers should reinforce the positive benefits of topical steroids.

In the most extensive systematic review of treatments for AE,[14] it was found that an analysis of randomised controlled trials confirmed a significant benefit of topical steroids over placebo. There are many different strengths of steroids and formulations on the market; however it is difficult to assess the best products owing to inadequate supporting evidence.

Table III. Table of potency of topical cortisone preparations

Mild strength	Moderate strength	Potent strength
Procutan	Advantan	Dermovate
Mylocort	Elocon	Diprolene
Stopitch	Locoid	Nerisone Forte
	Synalar	
	Betnovate	
	Persivate	
	Diprosone	
	Nerisone	

It is possible to make a few general claims for topical steroids: (*i*) there is no evidence that antibiotic/corticosteroid combinations are more effective than steroids alone; (*ii*) the type of vehicle used for a topical steroid may enhance its efficacy; (*iii*) patients prefer cosmetically acceptable topical steroid creams; (*iv*) there is no evidence to support the use of once-daily versus twice-daily topical corticosteroid administration; (*v*) there is no evidence to suggest that skin thinning is a problem with correct use of topical corticosteroids; and (*vi*) dilution of topical steroids does not necessarily reduce adverse effects – this could affect stability, compatibility and microbiological purity.

Intermittent use of mild to mid-potency topical steroids in conjunction with emollients has been standard disease management (Table III).[16] Reactive treatment with more potent steroids may be needed for relief of acute flares. Short-burst treatment with a potent topical steroid (0.1% betamethasone-valerate) had better results than long term use of 1% hydrocortisone in an 18-week trial.[19]

Recommendations for use of topical steroid management in AE are as follows.[20]

1. Most AE requires initial use of mid-strength steroids. However, 1% hydrocortisone is advised in children with mild to moderate eczema unless under specialist care.

2. Most topical steroids are applied either once or twice daily (as specified by the manufacturers) to induce remission. Thereafter intermittent use, typically twice weekly, may be continued to maintain control. The least potent preparation that adequately controls the disease process should be selected.[11]

3. High-potency topical steroids may be needed for short bursts in areas of lichenification or thick skin.

4. The vehicle base influences the potency, with ointments more potent than creams. Wet wraps and occlusion increase potency and less potent topical steroids should be used when this modality is used.

5. As inflammation subsides, use less topical steroids and more moisturiser.

6. Mid-strength topical steroids used immediately after bathing can be used intermittently in conjunction with emollients.[21]

Adverse events

These are well documented, and occur primarily when applied continuously especially on delicate skin areas such as the face, neck and skin folds.

Cutaneous effects are skin atrophy, telangiectasia, hypopigmentation, steroid acne, increased hair growth, and

rosacea-like reactions. Systemic effects are uncommon such as suppression of the hypothalamic-pituitary-adrenal (HPA) axis, growth retardation, and increased risk of glaucoma, cataract and Cushing's syndrome.

Antihistamines in atopic dermatitis

Evidence-based studies on the effectiveness of oral antihistamines in the management of atopic dermatitis are conflicting and their value is often disputed. First-generation sedating antihistamines have traditionally been prescribed for the treatment of pruritus and for sedation.[11]

Systemic antihistamines act primarily by blocking the H1 receptors in the dermis and thereby ameliorate histamine-induced pruritus. However, histamines are only one of many agents that produce pruritus and many patients may receive only minimal benefit from antihistamines.[22-24]

It has been found that even if there is benefit to some individual patients, the effectiveness of antihistamines is often short lived because of tachyphylaxis; increasing doses may be required and antihistamines are therefore contraindicated for long-term therapy.[12,25,26] They may be useful adjuncts to therapy during acute flares especially for sedation and for their anxiolytic effects.[23,27]

As pruritus is worse at night the sedating antihistamines may be used at bedtime.

Topical antihistamine applications may be of use for very short periods but should not be used chronically as they may cause sensitisation and should be avoided if possible.[23]

New non-steroidal topical immuno-modulators (calcineurin inhibitors)

New therapies such as the topical calcineurin inhibitor pimecrolimus represent major advances in the management of AE. They complement existing treatment options and also overcome some of the drawbacks of topical steroid therapy. They have a specific mechanism of action, inhibiting inflammatory cytokine transcription in activated T-cells and other inflammatory cells through inhibition of calcineurin.[28,29] They selectively target the inflammatory cells involved in AE without suppressing the Langerhans cells. They are therefore extremely safe and can be used for long-term treatment and prevention of AE.

Pimecrolimus cream has been approved in South Africa for the treatment of mild to moderate AE in children 2 years and older. It is indicated for acute as well as long-term management of mild to moderate AE. It can alleviate the symptoms and prevent flare progression in children.

Pimecrolimus can be used safely on sensitive areas including the face, neck and flexures. It is also indicated in children where the parents may have reservations about using topical steroids (steroid phobia). Kapp *et al.*[30] have shown that pimecrolimus can be used safely in infants as young as 3 years of age.

The results of short- and long-term clinical trials on pimecrolimus demonstrate a rapid and sustained effect in controlling pruritus, which is the primary complaint of patients with AE.

Patients treated with pimecrolimus should be counselled on the use of appropriate sun protection, including the application of sunscreen. This is because of concern regarding the potential for development of cutaneous malignancy.

Tacrolimus, a topical immunomodulator, is not available in South Africa at present.

Use of phototherapy, tar and systemic immunomodulators

Phototherapy

The following forms of phototherapy have been used in the management of AE:[31] (*i*) conventional UVA/UVB combination therapy; (*ii*) UVA1 therapy; (*iii*) photochemotherapy with methoxsalen plus UVA (PUVA); and (*iv*) narrow-band UVB (312 nm).

High-dose UVA1 has strong immunomodulating properties. However, there is ongoing discussion on the risk of long-term carcinogenicity associated with its use.

PUVA therapy may be associated with severe side-effects, including the development of cutaneous neoplasms.

Tar preparations

In selected patients tar preparations may be effective, administered topically or in the bathtub.[11] The cosmetic disadvantages of coal tar make it unacceptable to many patients and may affect compliance.[32] There are few scientific studies focusing on the clinical efficacy of tar in the treatment of AE.[33]

Systemic immunomodulators

Oral immunomodulators have been used predominantly for severe AE, including ciclosporin, azathioprine and myco-phenolic acid, among others.[32]

Ciclosporin

Ciclosporin is effective in the treatment of severe AE, but its usefulness may be limited by side-effects.[32] Trials have demonstrated prompt relief of symptoms with rapid relapse after cessation of therapy. Long-term maintenance therapy provides satisfactory freedom from remissions. In one group of children, short-course ciclosporin treatment given in 12-week cycles, with at least 7 days between each course, resulted in a lower cumulative dose of ciclosporin compared with children on continuous therapy.[33]

Interferon-gamma

Three randomised controlled clinical trials reported that interferon-gamma provided significant relief from AD symptoms. However, evidence is limited to a subset of patients and there was a high overall rate of side-effects.[34-36]

Systemic corticosteroids

Systemic corticosteroids are known to be effective in the short-term treatment of AD, but no evidence exists to support their use. They are not routinely recommended as rebound flaring and long-term side-effects limit their use.[32] Their use should be confined to specialists.

Azathioprine

A randomised, double-blind, placebo-controlled trial[37] examined the use of azathioprine 2.5 mg/kg per day in the treatment of AD, but conclusions were limited by a high drop-out rate. In another study,[38] azathioprine was shown to be effective but potential toxicities limited its use.

Mycophenolate mofetil and intravenous immunoglobulin

Conflicting data exist on the efficacy of mycophenolate mofetil and intravenous immunoglobulin.[11]

Others

There is insufficient evidence to support the role of leukotriene inhibitors, thymopentin (TP-5), allergen-antibody complexes of house-dust mites, desensitisation injections, theophylline, and papaverine in the treatment of AE.[32]

There is recent evidence that probiotics with *Lactobacillus rhamnosis* (ATCC 53103) administered to at-risk infants in the first 2 years of life reduces the risk of the development of AE.[32]

Complementary therapy

Complementary therapies include Chinese herbal medicine, herbal medicine, homeopathy, aromatherapy, massage therapy, acupuncture, climatotherapy, and African traditional medicine.

Studies have failed to show any convincing benefit with Chinese herbal medicine and aromatherapy. A worsening of the eczema was noted with prolonged aromatherapy.

There are few or no studies evaluating the safety and efficacy of the other treatment modalities involving complementary medicine.

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References

1. Johansson SGO, Bieber B, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TAE, Ring J, Thien F, van Cauwenberge P, Williams HC. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; **113:** 832-836.
2. Williams H, Robertson C, Stewart A, *et al.* Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood. *J Allergy Clin Immunol* 1999; **103:** 125-138.
3. Todd G, Saxe N, Milne J, Tolosana S, Williams H. Prevalence of atopic dermatitis in Xhosa children living in rural, peri-urban, and urban areas. *Curr Allergy Clin Immunol* 2004; **17:** 140.
4. Sugiura H, Umemotoa N, Deguchi H, *et al.* Prevalence of childhood and adolescent atopic dermatitis in a Japanese population: comparison with the disease frequency examined 20 years ago. *Acta Derm Venereol* 1998; **78:** 293.
5. Sporik R, Hill D, Hosking CS. Specificity of allergen skin prick testing in predicting positive open food challenges to milk, egg, and peanut in children. *Clin Exp Allergy* 2000; **30:** 1540-1546.
6. Gdalevich M, Robin G, Mimouni D, Grotto I, Shpilberg O, Ashkenazi I. Breastfeeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001; **45:** 520-527.
7. Businco L. Is soya allergy overestimated? *Paediatr Asthma Allergy Immunol* 1993; **7:** 73-76.
8. Sampson HA. Food sensitivity and the pathogenesis of atopic dermatitis. *J R Soc Med* 1997; **90:** 3-9.
9. Sampson HA, Ho DG. Relationship between food specific IgE concentrations and risk of positive food challenges in children and adolescents. *J Allergy Clin Immunology* 1997; **100:** 444-451.
10. Vanto T, Juntunen Backman K, Kalimo K, Klemola T, Varjonen E. The patch tests, skin prick test and serum IgE as diagnostic tools in cow milk allergy in infants. *Allergy* 1999; **54:** 837-842.
11. Eichenfield LF, Hanifin JM, Luger TA, Stevens SR, Pride HB. Consensus conference on paediatric atopic dermatitis. *J Acad Dermatol* 2003; **49:** 1088-1095.
12. McHenry PM, Williams HC, Bingham EA. Fortnightly review: Management of atopic eczema. *BMJ* 1995; **310:** 843-847.
13. Williams HC. In: Stevens ARJ, ed. *Dermatology. Health Care Needs Assessment.* Oxford: Radcliffe Medical Press, 1997: 261-348.
14. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; **4:** 1-191.
15. Marks R. How to measure the effects of emollients. *J Dermatol Treat* 1997; **8:** 125-118.
16. Ellis C, Luger T, Abeck D, Allen R, Graham-Brown RA, De Prost Y. International consensus conference on atopic dermatitis 11 (ACCAD11). *Br J Dermatol* 2003; **148:** suppl. 63, 3-10.
17. Abeck D, Atrom K. Optimal management of atopic dermatitis. *Am Clin Dermatol* 2000; **1:** 41-46.
18. Wilhelm KP, Scholerman A. Efficay and tolerability of a topical preparations containing 10% urea in patients with atopic dermatitis. *Acta Dermatol* 1998; **24**(1-2): 26-30.
19. Thomas KS, Armstrong S, Avery A, *et al.* Randomised controlled trial of short bursts of potent topical corticosteroids. Prolonged use of a mild topical steroid in children with mild or moderate atopic eczema. *BMJ* 2002; **324:** 768-771.
20. Sidbury R, Hanifin JM. Old, new, and emerging therapies for topic dermatitis. *Dermatol Clin* 2000; **18:** 1-11.
21. Tofte SJ, Hanifin JM. Current management and therapy of atopic dermatitis. *J Am Acad Dermatol* 2001; **44:** S13-16.
22. Munday J, Bloomfield R, Goldman M, *et al*. Chlorpheneramine is no more effective than placebo in relieving the symptoms of childhood atopic dermatitis. *Dermatology* 2002; **205**(1): 40-45.
23. Leung DYM. Atopic dermatitis. In: Leung DYM, Sampson HA, Geha RS, Szefler SJ, eds. *Pediatric Allergy.* St Louis: Mosby, 2003: 569-570.
24. Wahlgren CF, Hagermark O. Bergstrom R. The antipruritic effect of a sedative and a non sedative anthistamine in atopic dermatitis. *Br J Dermatol* 1990; **122:** 545-551.
25. Holgate ST, Church MK. Eczema and contact dermatitis. In: *Allergy.* Mosby Wolfe, 1995. Chapter 23, 23.1 - 24.10.
26. Kemp JP. Tolerance to antihistamine is it a problem? *Ann Allergy* 1989; **63:** 621-623.
27. Prose NS. Atopic dermatitis. In: Rudolph CD, Rudolph AM, Hostetter MK, eds. *Pediatrics.* 21st ed. McGraw Hill, 2000: 1177 - 1179.
28. Grassberger M, Baumruker T, Enz A, *et al.* A novel anti-inflammatory drug, SDZ ASM 981, for the treatment of skin diseases: *in vitro* pharmacology. *Br J Dermatol* 1999; **141:** 264-273.
29. Zuberbier T, Chong S. The ascomycin macrolactam pimecrolimus (Elidel, SDZ ASM 981) is a potent inhibitor of mediator release from human dermal mast cells and peripheral blood basophils. *J Allergy Clin Immunol* 2001; **108:** 275-280.
30. Kapp A, Papp K, Bingham A, *et al.* Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. *J Allergy Clin Immunol* 2002; **110:** 279-284.
31. Grundmann-Kollmann M, Behrens S, Podda M, *et al.* Phototherapy for atopic eczema with narrow-band UVB. *J Am Acad Dermatol* 1999; **40:** 995-997.
32. Hanifin JM, Cooper KD, Ho VC, *et al.* Guidelines of care for atopic dermatitis. *J Am Acad Dermatol* 2004; **50:** 391-404.
33. Harper JI, Ahmed I, Barclay G, Lacour M, Hoeger P, Cork MJ. Cyclosporin for severe childhood atopic dermatitis. Short course versus continuous therapy. *Br J Dermatol* 2000; **142:** 52-58.
34. Hanifin JM, Schneider LC, Leung DY, Ellis CN, Jaffe HS, Izu AE.. Systemic interferon-gamma therapy for atopic dermatitis. *J Am Acad Dermatol* 1993; **28:** 189-197.
35. Reinhold U, Kukel S, Brzoska J, Kreysel HW. Systemic interferon-gamma treatment in severe atopic dermatitis. *J Am Acad Dermatol* 1993; **29:** 58-63.
36. Musial J, Milewski M, Undas A, Kopinski P, Duplaga M, Szczeklik A. Interferon-gamma in the treatment of atopic dermatitis: influence on T-cell activation. *Allergy* 1995; **50:** 520-523.
37. Meggit SJ, Reynolds NJ. Azathioprine for atopic dermatitis. *Clin Exp Dermatol* 2001; **26:** 369-375.
38. Berth-Jones J, Takwale A, Tan E, *et al.* Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, cross over trial. *Br J Dermatol* 2002; **147:** 324-330.
39. Kalilmaki M, Salminen S, Poussa T, Isolauri E. Probiotics and the prevention of atopic disease: a 4 year placebo controlled study. *Lancet* 2003, **361:** 1869-1871.