

# Guidelines on the management of atopic dermatitis in South Africa

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## Objective

The guidelines for the management of atopic dermatitis have been developed in an attempt to improve the outcomes of treatment of this condition in South Africa. This condition has a major impact on the quality of life of sufferers and it is expected that these guidelines, if implemented, will play a role in achieving this.

## Recommendations

All health care workers involved in the management of atopic dermatitis should take note of these guidelines and try to implement them in clinical practice as far as possible. All treatment methods and procedures not substantiated by evidence from the literature should be discontinued and avoided to decrease the financial burden of dermatitis treatment.

## Validation

These guidelines were developed through general consensus by a panel of four dermatologists and five paediatricians from South Africa, from evidence based on extensive literature review. Draft documents were made available for comment via the internet. All input, where appropriate, was then incorporated into these guidelines.

## Guidelines sponsor

Astellas and Galderma co-sponsored the meeting of the work group and all costs generated by the meeting.

## Disclaimer

These guidelines do not represent all the possible methods of management applicable to all patients, do not exclude any other reasonable methods and will not ensure successful treatment in every situation. The unique circumstances of each patient should be taken into account by the responsible physician regarding decisions on any specific therapy.

## Introduction and methods

Atopic dermatitis (AD) is a very common, chronic, inflammatory eczematous skin disease, affecting up to 20% of children in Western Europe and Australia. The prevalence of AD in adults is less well defined, but it is believed that about 40% of childhood cases will continue into adulthood. The morbidity and impact on quality of life of these patients can be very severe<sup>1</sup> and the psychological distress suffered correlates well with the severity of the dermatitis.<sup>2</sup>

There is considerable confusion about uniform criteria for the diagnosis of AD and management is often arbitrary and empirical, often with poor outcomes. There is a need for standardised guidelines on diagnosing and managing this condition.

A panel of dermatologists and paediatricians was convened and tasked with writing and publishing these guidelines. The compilation of the panel was endorsed by the Dermatological, Paediatric (SAPA) and Allergy (ALLSA) Societies of South Africa.

The panel used an evidence-based module of evidence obtained by means of a thorough literature search published on the topic over the last 15 years. Evidence was graded according to the SIGN<sup>3</sup> grading system and recommendations and statements in the text are marked according to these levels of evidence to denote the strength of evidence and therefore the validity and weight of recommendation:

### **Levels of evidence**

- 1++ High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with very low risk of bias
- 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with low risk of bias
- 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- 2++ High quality systematic reviews of case-control or cohort studies; high quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
- 2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
- 2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.
- 3 Non-analytical studies, e.g. case reports, case series
- 4 Expert opinion

### **Grades of recommendation for interventions**

- A **Highly recommended** as method of choice, supported by at least one meta-analysis, systematic review or RCTs rated as 1++ and directly applicable to the target population; or  
A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results.
- B **Strongly recommended**, supported by a body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or  
Extrapolated evidence from studies rated as 1++ or 1+.

- C **Recommended** as possible alternative option, supported by a body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++.
- D **Weak recommendation**, supported by evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+.
- 0 **Not recommendable** due to no supporting evidence or available evidence proves lack of effectiveness.

## Scope

These guidelines were developed to address the diagnosis and management of patients who suffer from atopic dermatitis.

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## Definitions and terminology

The word “eczema” comes from the Greek for “to boil over”. In patients with eczema, the condition periodically flares up (or “boils over”). During a flare, eczema in remission or stable sub-acute or chronic eczema transforms into acute eczema. Flares may happen spontaneously or be precipitated by a number of factors.

The term “dermatitis” refers to inflammation of the skin, analogous to “appendicitis” (inflammation of the appendix), “hepatitis” (inflammation of the liver), etc. Nowadays the terms “dermatitis” and “eczema” are generally regarded as synonyms. Some authors still use the term “dermatitis” to include all types of cutaneous inflammation, so that all eczema is dermatitis, but not all dermatitis is eczema. The term “dermatitis”, however, should be used with care, as some patients regard it as implying an occupational cause. Unfortunately, there is still no international agreement on the use of these terms. Ackerman<sup>1,2</sup> has argued that, as the term eczema cannot be defined in a way that meets with universal approval, it should be dropped from the dermatological lexicon. There seems to be consensus that the term still serves a useful purpose for the clinician. Much energy has been needlessly wasted in debating which term should be used. Geographically there is unexplained preference for one or the other. The word “eczema” tends to be used more as a layman’s term and “dermatitis” more in the scientific context.

Eczema/dermatitis is not a diagnosis. The most common forms of eczema/dermatitis are atopic, seborrhoeic, primary irritant, allergic contact, photoallergic, phototoxic, nummular, asteatotic, stasis and dyshidrotic. Eczema/dermatitis associated with infection (e.g.

dermatophyte) or infestation (e.g. scabies) – the so-called “ide” reactions – are additional variants.

“Atopy” comes from the Greek “atopos” meaning strange or unusual. In 1892, Besnier was the first to describe the association of atopic dermatitis with allergic rhinitis and asthma. The term “atopy” was first coined in medicine in 1923 by two allergists, Coca and Cook. They defined atopy clinically as a proclivity to develop the triad of atopic eczema, allergic rhinitis and asthma. Patients whom they considered to be atopic possessed a distinctive antibody, which they called “regain” or “skin-sensitising antibody”, because intradermal skin tests to a variety of inhalant allergens, e.g. trees, weeds, grasses, dust, moulds and danders, elicited wheals at sites of some injections. When Hill and Sulzberger in the early 1930s encountered atopic patients with skin lesions that favoured antecubital and popliteal fossae, they initially called the disorder “neurodermatitis of atopic type”, then “atopic eczema” and finally “atopic dermatitis”.

In the 1980s, Hanifin and Rajka proposed a list of criteria, and unity in the clinical concept of atopic dermatitis was established. In 1994 the UK Working Party refined these criteria into a concise and validated set of survey-based diagnostic criteria useful for the purposes of epidemiological studies (vide infra). The word “atopy” can be defined as “a clinical hypersensitivity state that is subject to hereditary influences; included are hay fever, asthma and eczema”. These conditions develop against a complex genetic background: the so-called atopic diathesis.

The word “atopic” in the term “atopic eczema” is simply an indicator of the frequent association with atopy and the need to separate this clinical phenotype from the other forms of eczema which have other causes and distinct patterns. The terms “atopic eczema” and “atopic dermatitis” are synonymous.

According to the position paper from the Nomenclature Review Committee of the World Allergy Association<sup>3</sup> the term “atopic eczema/dermatitis syndrome” (AEDS) should be used as the umbrella term to cover the different subtypes of AD. The new nomenclature (AEDS) underlines the fact that AD is not one single disease, but rather an aggregation of several diseases with certain clinical characteristics in common.

Intrinsic AD (non-allergic AEDS = NAAEDS, a.k.a. atopiform dermatitis) fulfils the most commonly used diagnostic criteria for AD. These patients have no associated respiratory diseases, such as bronchial asthma or allergic rhinitis, show normal total serum IgE levels, no specific IgE, and negative skin-prick tests to aeroallergens or foods. In one study, intrinsic AD was more common in females and disease onset was later. Palmar hyperlinearity, pityriasis alba, recurrent conjunctivitis, and hand and/or foot eczema were uncommon. The Dennie-Morgan fold associated positively with this type of eczema. This group comprises at least 20% (up to 60%) of cases<sup>4</sup>.

Extrinsic AD (allergic AEDS = AAEDS) is commonly associated with respiratory allergies such as rhinitis and asthma, a high level of serum IgE, specific IgE and positive skin-prick tests to aeroallergens or foods. Immunological differences between NAAEDS and AAEDS can be found in the cell and cytokine pattern in peripheral blood and in the affected skin, and also by phenotyping characterisation of epidermal dendritic cells. The current explanation of this distinction is based on differences in genetics and/or environmental conditions. This group comprises 40 - 80% of patients<sup>4</sup>.

The classification into AAEDS and NAAEDS at each stage of life, i.e. infancy, childhood, teenage and adult, is essential for the allergological management of patients in respect of allergen avoidance, secondary allergy prevention, and immunotherapy. The risk of an “atopy march” is significantly lower in children with NAAEDS.<sup>5-13</sup>

This subdivision is currently controversial. Cases may transform from one type to the other. This division may not be applicable to adults. It is quite possible that there are distinct subsets of atopic eczema, e.g. those cases associated with atopy and those who have severe disease with recurrent infections. Until the exact genetic and causative agents are known, it is wiser to consider the clinical disease as one condition. Perhaps sensitivity analyses should be done within clinical trials, or among those who are thought to represent distinct subsets, e.g. those who are definitely atopic with raised circulating IgE to allergens, and those with severe disease and associated asthma.<sup>14,15</sup>

Acute eczema/dermatitis is characterised by oedema, erythema, vesiculation, exudation and crusting. Microscopy shows collections of serum in the stratum corneum, moderate to marked spongiosis, intraepidermal vesiculation, moderate to marked sub-epidermal oedema in the papillary dermis and lymphocytes in the upper dermis. Chronic eczema/dermatitis is characterised by lichenification. Lichenification refers to thickening of the skin with exaggeration of the normal markings. Flat-topped, shiny, quadrilateral coalescing papules are enclosed. Microscopy shows compact orthokeratosis, acanthosis, mild spongiosis, collagen in vertical streaks in the dermal papillae and lymphocytes in the upper dermis. Sub-acute eczema/dermatitis shows features overlapping with acute and chronic eczema/dermatitis. Lesions are commonly slightly elevated, are red, brownish or purplish in colour, and with variable scaling. Generally, physicians most commonly encounter the sub-acute presentation of eczema/dermatitis.

The morphology, distribution and evolution of eczema/dermatitis in atopic eczema/dermatitis are highly characteristic. During the infant phase (birth to 2 years) red scaly lesions develop typically on the cheeks, usually sparing the perioral and perinasal areas. The chin is typically involved and cheilitis is common. A small but significant number of infants develop a generalised eruption. Involvement of the scalp is not uncommon. The diaper area is often spared. Sometimes the cubital/popliteal fossae or other parts of the limbs are involved.

During the childhood phase (2-12 years) eczema/dermatitis involves the flexural areas (i.e. the antecubital fossae and popliteal fossae) but also the neck, wrist and ankles.

During the adult phase (12 years to adult) lesions involve similar areas to those affected during the childhood phase. Additionally, hand eczema/dermatitis, periocular eczema/dermatitis and anogenital eczema/dermatitis are common. In some cases lesions occur mostly on extensor surfaces and follicular accentuation may be prominent.

Morphologically, lesions may be acute, sub-acute or chronic. Importantly for the clinician, the diagnosis of atopic eczema/dermatitis is based on the aforementioned criteria, namely age of the patient, distribution of the rash and morphology of the rash. Atopic eczema is a difficult disease to define, as the clinical features are highly variable in morphology, body site and time.

There is no specific diagnostic test that encompasses all people with typical eczema that can serve as a reference standard. Diagnosis is, therefore, essentially a clinical one.<sup>16,17,18</sup>

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## **Aetiopathogenesis of atopic dermatitis**

This is probably multifactorial. Current thinking favours a skin barrier defect as the most significant predisposing factor where mutations in the filaggrin gene feature strongly.<sup>1-8</sup> Most studies investigating the causes of atopic dermatitis deal with children. There is little to suggest that adult atopic dermatitis should have a different aetiopathogenesis apart from some clinical features that differ, such as the predominant involvement of the hands and the head and neck.<sup>9</sup>

### **Genetics**

Population-based family studies in Europe suggest that in atopic families, up to 50% of offspring will have atopic dermatitis.<sup>10</sup> Twin studies showing a concordance rate for atopic dermatitis of 0.75 for monozygotic twins compared to 0.20 for dizygotic twins support a genetic basis for atopic dermatitis.<sup>10,11,12</sup> Further evidence for a genetic predisposition to atopic dermatitis is the finding of candidate genes.<sup>1,10,12</sup>

### **Allergic sensitisation**

The predisposition for IgE hyper-responsiveness to allergens defines the term atopy.<sup>13</sup> A systematic review of the published evidence for allergic sensitisation and dermatitis in 12 population studies from around the world has shown that IgE hyper-responsiveness does not necessarily equate to atopic dermatitis, even though it may be associated with the disease phenotype, especially those with severe disease.<sup>14,15</sup> Amongst those with atopic dermatitis, up to 20 - 60% were not atopic per definition. Geographic location was associated with the risk of being atopic, amongst those with atopic dermatitis as compared to normal healthy controls.

In five studies that included adolescents and adults, the findings were essentially similar. In a cross-sectional household survey from Ethiopia, which included adults and children, 15% of those with atopic dermatitis and 8% of those without atopic dermatitis were atopic by skin-prick testing.<sup>16</sup> This lack of association between atopic dermatitis and allergen sensitisation in that setting was confirmed in a cross-sectional survey and nested case controlled study of children.<sup>17</sup>

## **Environment**

A documented increasing prevalence of atopic dermatitis over the last 50 years is not consistent with genetic drift alone,<sup>18,19,20</sup> but supports a strong environmental influence as evidenced by population migration studies.<sup>21,22</sup> These environmental influences, which affect initial disease expression or aggravation of established disease, are summarised in Table 1. Population studies from Africa seldom confirm a role for these environmental factors.<sup>16,17,23</sup> Interestingly, many are surrogate markers of urbanisation<sup>21,22</sup> and increased socio-economic status,<sup>24</sup> which appear to be the only fairly consistent association across all population groups\*. More detailed information can be obtained from published reviews on gene-environment interactions.<sup>1,10,12,21,25-40</sup>

The aetiopathogenesis of atopic dermatitis is best explained by the concept of a damaged barrier function, whether intrinsically normal or dysfunctional, that induces a state of epidermal repair, coupled with aberrant responses to epidermal insults in the affected skin.<sup>2,3,4,8,10,12,24,27,41,42,43</sup> In Africa this hypothesis has still not been validated. A novel filaggrin gene defect has been documented in a single Ethiopian case of atopic dermatitis<sup>44</sup>. What evolutionary advantage the skin barrier defect conveyed to the populations now exposed to environmental influences precipitating atopic disease is unknown.

**Table 1: Environmental influences on atopic dermatitis**

\* Possible surrogate markers of urbanisation and increased socio-economic status.

<b>Environmental factor</b>	<b>Effect on atopic dermatitis</b>	<b>References</b>
Rural compared to urban living (hygiene hypothesis)	Increased risk with urbanisation	21, 22, 24, 25, 38
*Socioeconomic status	Increased risk with higher socio-economic status	16, 17, 24, 28, 45
*Education level of parents	Increased risk with higher level of education	29
*Family size (hygiene hypothesis)	Increased risk with decreasing family size	25, 29
*Day-care attendance (hygiene hypothesis)	Decreased risk with day-care attendance in infancy	25

Animal exposure in early life (hygiene hypothesis)	May be protective with specific pet exposure in early life	25, 36, 37, 41, 46
*Endotoxin exposure in early infancy (hygiene hypothesis)	Decreased risk of dermatitis development with early life exposure	25
*Basic hygiene (hygiene hypothesis)	Increased risk with improved personal hygiene	25
*Early life infections (hygiene hypothesis)	No clear evidence for protection from specific organism exposure Protection may be related to microbial burden in early life	25
*Parasite exposure in early life (hygiene hypothesis)	Little evidence for a protective effect on atopic dermatitis development Exposure reduces IgE sensitisation	25, 41, 45, 47, 48
Vaccination (hygiene hypothesis)	Protective effect suggested but association with vaccination type unclear.	25, 30, 49, 50
Early life antibiotic use (hygiene hypothesis)	Increased risk with increasing antibiotic prescribing in infants	25, 36
*Mode of delivery	Increased risk with caesarean section	37, 51
*Maternal age	Increased risk with increased age	30, 33
<u>Maternal diet:</u> - Probiotics  - Food avoidance  - Specific foods	Possible decreased risk with probiotic use  Little evidence for decreased risk with food avoidance if applied in pregnancy or while breast feeding  Evidence for decreased risk if fish consumed during pregnancy and breast feeding	30, 34, 35, 36  30, 34, 35, 36, 40  38, 40, 52
Environmental tobacco smoke	Major risk factor for development of atopic dermatitis	70, 71
Maternal risk (parent-of-origin effect)	Increased risk if mother had atopic dermatitis	12, 30, 38
<u>Diet:</u> - Formulae  - Solid food introduction - Inclusion – specific food  - Exclusion – specific food  - Diet restriction - Elemental diet - Organic food	Fully hydrolysed formula – decreased risk Partially hydrolysed formula – no clear evidence for role in control or prevention No clear evidence for role in control or prevention Evidence for delayed onset with fish in early life Decreased risk with maternal probiotic use Disease control in children <2years age with documented allergy or intolerance only No clear evidence for role in control or prevention No clear evidence for role in control or prevention No clear evidence for role in control or prevention	36, 39, 40, 53, 54 36, 39, 54, 55 40 40 35, 36 30, 35, 36 36, 39, 53 36, 39, 53 38, 56
<u>Diet supplementation:</u> - Anti-oxidants  - Essential fatty acids  - Early fish as solid food - Probiotics	Vitamin E, zinc, selenium – no effect in dermatitis control Borage, fish, evening primrose oils – no effect in dermatitis control Evidence for delayed onset of dermatitis No clear role in established dermatitis	35 35  38, 52 35, 36, 39, 40, 57
Breastfeeding	Some evidence for decreased risk in breastfed infants with a family history of atopic dermatitis	30, 39, 40, 58, 59



<u>Allergen exposure:</u>		
- House dust mite	Decreased exposure/load – no effect prevention but may have an effect on control in severe cases	32, 35, 36, 38
- Super-antigen	Staphylococcal control – no effect control	35, 36, 38, 60
- Type IV allergens	Contact dermatitis – increased association	61, 62
<u>Irritant exposure:</u>		
- Climate	Increased risk in cooler climates Unclear risk in climate extremes	21 21, 36
- Hard water	Hard water – no effect if calcium carbonate removed	28, 63
- Clothing	Disease aggravation by fibre roughness Disease aggravation by heavy textiles Silk clothing – no clear evidence for role in control	35 35 38, 64
- Occlusive wraps	Wet or dry – no clear evidence for role in control	38, 65
- Clothes softeners	No clear evidence for role in control	35
<u>Bath additives:</u>		
- Emollients	No clear evidence for role in control	38, 66
- Antiseptics	No clear evidence for role in control	35, 36, 38, 60
- Salt	No clear evidence for role in control	35
<u>Pollution:</u>		
- Urbanisation	Increased risk with urbanisation	21, 31
- Smoking	Increased risk in adults linked to lifetime exposure	67
- Solvents	Increased risk in established dermatitis	31
<u>Co-morbidities:</u>		
- HIV	No increased risk	68
- BMI	Increased risk in prevention and dermatitis control	24
- Smoking	Increased risk in adults linked to lifetime exposure	67
- Psychosocial stress	Increased risk in prevention (episodes in early life) and dermatitis control	36, 37, 69
- Malaria	Increased risk in Africa	17

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## Epidemiology of atopic dermatitis

### How common is atopic dermatitis and who gets it?

Much of the published work on the epidemiology of atopic dermatitis has been done on children<sup>1,2,3,4,5</sup> and a variety of prevalence measures have been used, including lifetime prevalence, point prevalence and one-year prevalence rates. The International Study of Asthma and Allergies in Childhood ISAAC Phases I and III<sup>6,7</sup> have documented that the one-year prevalence rate for atopic dermatitis symptoms varies worldwide dependent on the population and geographic area studied (globally, nationally or locally). A comparison of the two studies documents a general decline or plateau one-year prevalence rate in the developed world, but an increasing prevalence in the developing world.<sup>8</sup>

There are few studies addressing the prevalence of atopic dermatitis in South African populations. The Phase I ISAAC study<sup>6</sup> of 13- to 14-year-old school children in Cape Town showed a 8.3% one-year prevalence rate of atopic dermatitis symptoms, with 2,3% having severe disease (sleep disturbance for >1 night per week). The Phase III follow-up study<sup>7</sup> documented an increased one-year prevalence of 13.3% amongst children of the same age. No children 6 to 7 years of age were included for South Africa in either study. In 3- to 11-year-old normal children, the one-year prevalence rate was 1-2.5% in amaXhosa children, depending on the methodology used to define atopic dermatitis and whether the children came from urban or rural environments.<sup>9</sup>

While it is accepted that atopic dermatitis is a particular problem in children, the burden of disease is significant in adults. A study in adults in Scotland document a 0,2% one-year point

prevalence for atopic dermatitis in those over 40 years of age. Adults accounted for 38% of the atopic dermatitis population.<sup>10</sup> African studies from Nigeria and Ethiopia have documented that 40% to 60% of patients with atopic dermatitis were older than 19 years of age.<sup>11,12</sup>

Few incidence studies have been done and these are in cohorts of children in Europe.<sup>5,13</sup>

### **What is the natural history and severity of atopic dermatitis?**

Studies on the natural history of atopic dermatitis document up to 60% spontaneous clearing by puberty.<sup>3,5,10,13,14,15</sup> Atopic dermatitis may recur in adults and the risk is associated with a family history, early onset, severity and persistence of childhood atopic dermatitis and the presence of mucosal atopy.<sup>10</sup> In adults the clinical picture may be altered: patients presenting with hand dermatitis caused by exposure to additional insults such as irritants like wet work, detergents, chemicals and solvents or head and neck involvement.<sup>16</sup>

The concept of the “atopic march”, where children with atopic dermatitis evolve into mucosal forms of atopic disease,<sup>17,18</sup> has been challenged by some cohort studies<sup>19,20</sup>. Early wheeze and specific sensitisation pattern (wheat, cat, mite, soy and birch) were predictors of wheezing at school age, irrespective of the presence of atopic dermatitis in a German-birth cohort study.<sup>15</sup> The development of rhinoconjunctivitis is more strongly associated with atopic dermatitis than is asthma.<sup>21</sup> It is probable that there are many subsets of the atopic dermatitis phenotype.

Studies assessing the severity of atopic dermatitis in Europe revealed that in children, 84% have mild, 14% moderate and 2% severe disease.<sup>22,23</sup> In adult cohorts, those that had severe disease accounted for 12%, using the SCORAD scoring system.<sup>16</sup> In a Japanese population survey, 70 to 90% of cases were mild dependent on age group. Moderate to severe atopic dermatitis was found predominantly in early adolescence and adulthood.<sup>24</sup>

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## Atopic dermatitis and food allergy

The relationship between atopic dermatitis and food allergy is complex<sup>1</sup>. Many patients believe that atopic dermatitis is caused by diet, but the majority of atopic dermatitis is not triggered by foods. In some patients with food allergy and atopic dermatitis, dietary modification may help atopic dermatitis, but they will still need to use a good skin care routine and pharmacological measures to maintain skin integrity.<sup>2,3</sup> Investigations for food allergy are not routine in all cases of atopic dermatitis. Concomitant or causative food allergy should be considered in those patients with a convincing history of food allergy and those with moderate to severe eczema that does not respond to appropriate and adequate topical treatment.

### Food allergy in atopic dermatitis:

Sensitisation to foods (presence of raised ImmunoCAP or positive skin-prick tests (SPT)) is common in atopic dermatitis, but is not synonymous with clinically relevant food allergy.

About 40-60% of patients with moderate to severe atopic dermatitis are sensitised to food allergens,<sup>4,5,6,7,8,9</sup> which is much greater than the overall prevalence of food sensitisation in the general population of around 5-15%<sup>10,11,12</sup> In 2009, South African infants with atopic

dermatitis were shown to have frequent sensitisation to foods, most commonly egg white (47.1%), cow's milk (28.4%) and peanuts (26.8%).<sup>13</sup> In 2011, infants attending a tertiary dermatology clinic for atopic dermatitis were shown to have even higher sensitisation rates (66% to at least one food), most commonly to egg (54%), peanuts (42%) and cow's milk (26%).<sup>1,14,15</sup>

Approximately 30-40% of children with moderate to severe atopic dermatitis seen at specialised units have co-existing food allergy,<sup>4,5,6,7,16,17,18,19,20,21</sup> but this is less common in less selected populations<sup>9</sup> and in adults. In 50% of these patients the reaction is an immediate hypersensitivity reaction coexisting with atopic dermatitis. These immediate concomitant food allergy reactions usually have non-eczematous cutaneous features<sup>5</sup> with or without gastrointestinal reactions, respiratory symptoms or anaphylaxis and occur within two hours of food ingestion. South African data in children attending a tertiary dermatology clinic for atopic dermatitis (selected and severe cases) show 42% of patients have a concomitant immediate type food allergy.<sup>14,15</sup> There is no data on delayed reactions in the South African setting. International literature on food reactions in children with moderate to severe disease shows isolated eczematous reactions occur in 10% of reactions (3-4% of such children) and are usually delayed >6 hours after food ingestion.<sup>2,17,18,21</sup> A combination of non-eczematous and eczematous reactions occurs in 40% of cases (12-16% of such children).<sup>2,17,18</sup>

The same food allergens that cause reactions in the general population are responsible for the majority of reactions in children with atopic dermatitis. Egg, milk, peanut, wheat and soy cause 90% of food reactions in children with AD.<sup>22,23</sup>

There is no specific diet for the treatment of unselected patients with atopic dermatitis so patients should not routinely be placed on exclusion diets.<sup>25</sup> Elimination diets are potentially harmful. Food allergy should only be considered in specific cases, and elimination diets reserved for those children who have been proven to be allergic and tailored to the individual after appropriate investigations, including challenge tests where necessary, have been performed to assess possible food triggers. They must be done under the supervision of a dietician and should always be combined with atopic skincare. In birth cohort studies, severity of eczema is associated with increased sensitisation to foods<sup>16</sup> as well as increased risk of food allergy<sup>16,26</sup>. Food allergy is more common in those with a very early onset of atopic dermatitis.<sup>27</sup>

### **Testing for food allergy**

Routine testing for food allergy is not recommended. Only patients who fulfil the following criteria for evaluation for food allergy should be tested.

- A history of an immediate non-eczematous reaction to food
- A convincing history of food-induced flares of atopic dermatitis
- Cases of moderate to severe AD in an infant or child which is resistant to adequate and appropriate atopic skin care
- Cases of severe AD in teenagers or adults which is resistant to adequate and appropriate atopic skin care.

An accurate diary of what the patient eats and of the condition of the skin, both atopic dermatitis and acute reactions, can be useful to guide food related investigations.

Tests for IgE sensitisation (SPT and specific IgE ImmunoCAP tests) are useful in the investigation of food allergy but there is no 100% reliable test for identifying which foods trigger atopic dermatitis<sup>1</sup>. The aims of food allergy testing in a patient with atopic dermatitis may be to prove that a food allergy results in a non-eczematous immediate hypersensitivity reaction. Such food allergy testing is done in a similar way in patients with or without atopic dermatitis. An additional aim of testing may be to prove that a food allergy results in direct exacerbation of atopic dermatitis. This is much more challenging. Tests with no or poor evidence to support their use include IgG testing, ELISA/ACT, applied kinesiology, ALCAT testing, analysis of hair samples, Vega testing, cytotoxic testing and others.

### **Immediate (IgE mediated) hypersensitivity food reactions**

The diagnosis of immediate type (IgE mediated) food allergy is made by taking a thorough history, performing tests, looking for specific IgE sensitisation (SPT and ImmunoCAP), and performing oral food challenges if indicated<sup>1</sup>. Negative skin and ImmunoCAP tests are good for excluding an immediate type reaction, but cannot exclude a delayed type reaction. The presence of “positive” tests indicating sensitisation is not synonymous with food allergy. The predictive values for a history of a food reaction, positive SPT and positive food specific IgE in isolation are all poor for diagnosing food allergy in AD. The level of sensitisation must be interpreted in conjunction with the history, and in many cases where uncertainty remains, a food challenge test will be the best means to definitively prove food allergy or food tolerance.

Skin-prick tests have high negative predictive values and are a good predictor that subjects will not have an immediate type reaction on exposure but cannot exclude a delayed type reaction. However, positive predictive values are low,<sup>28,29</sup> hence a “positive” result does not equal clinical reactivity. Published “cut-off levels” for clinical relevance have been studied for selected allergens (child >2 years: milk  $\geq 8\text{mm}$ , egg  $\geq 7\text{mm}$ , peanuts  $\geq 8\text{mm}$ ; child <2 years: milk  $\geq 6\text{mm}$ , egg  $\geq 5\text{mm}$ , peanuts  $\geq 4\text{mm}$ ).<sup>29</sup> However, these values may not be applicable in South Africa, especially in black African subjects where patients may be clinically tolerant despite high levels of skin prick reactivity.<sup>14</sup> As patients develop tolerance, heightened SPT reactivity may lag behind reductions in specific IgE levels and may remain positive for years after a food has been successfully reintroduced into the diet.

ImmunoCAP testing for food specific IgE has high negative predictive values, but positive predictive values are low.<sup>17,29,31</sup> Published “cut-off levels” for clinical relevance<sup>31</sup> have been studied for selected allergens. The values that achieved a 95% PPV are known for milk ( $\geq 15\text{kU/L}$ ;  $\geq 5\text{kU/L}$  if age <2), egg ( $\geq 7\text{kU/L}$ ;  $\geq 2\text{kU/L}$  if age <2), peanuts ( $\geq 14\text{kU/L}$ ) and fish ( $\geq 20\text{kU/L}$ ). It is not currently known whether these results are applicable in South Africa.

Atopy Patch Testing has not been shown to add significant information to a skin test as a diagnostic test for food triggers of acute or delayed reactions to foods.<sup>33,34</sup> A much less time-consuming diagnostic tool with similar sensitivity and specificity is the recently described SAFT (Skin Application Food Test).<sup>34</sup> Here, patch tests with fresh food are applied, but read after 30 minutes for urticarial test reactions. This test is, however, not in routine clinical practice and is not in any of the international guidelines.

If the diagnosis of food allergy or tolerance is not absolutely clear or the clinical relevance of a positive food allergy test is not certain, a food challenge should be performed. The gold standard is the double-blind placebo-controlled food challenge. This requires two separate challenges with a suitable vehicle, one with and one without the food under consideration, to avoid the patient and the operator from knowing which of the challenges contains the active food. For an open challenge the food is given in its usual form and therefore both the observer and the patient know the food is being ingested. Although this may be associated



with false positive reactions it is acceptable in infants and young children with objective symptoms and as a preliminary screening of foods that are at a low level of suspicion as a negative challenge is definitive.

### **Delayed eczematous food allergy reactions**

The diagnosis of delayed eczematous reactions is more difficult than the diagnosis of immediate reactions<sup>1</sup>. In such cases specific IgE and skin prick tests may not correlate with the presence or absence of a delayed food reaction. In these cases an elimination-reintroduction diet is the only reliable way of determining whether or not a food is a trigger. Such diets must be done under supervision of a dietician. If patients respond to any dietary intervention, it is highly recommended that the food should be reintroduced to confirm the diagnosis. This may be a formal food challenge in hospital in the presence of any sensitisation or history of immediate reactions to the food(s), or a home challenge/reintroduction in the absence of sensitisation or a history of only delayed symptoms. If a formal food challenge is performed for atopic dermatitis, the schedule may need to be prolonged to observe the patient for up to six hours after the maximum dose for immediate and intermediate reactions. It is important to review the patient at 24 hours for scoring to formally document delayed-type worsening of atopic dermatitis. In cases of prolonged avoidance of a food, it is recommended to perform SPT or ImmunoCAP tests in patients prior to reintroduction of the food – even in cases where there has not been a history of any immediate reactions and such a challenge should be performed under controlled circumstances.

The process of elimination-rechallenge testing involves:<sup>1,25</sup>

- Removing all sources of the suspected food or foods for four to six weeks to bring about an improvement in the atopic dermatitis. If the atopic dermatitis does not improve within four weeks, it is unlikely that food allergy is a relevant trigger and oral food challenges are not necessary. In this case a normal diet should resume immediately.
- Even if the atopic dermatitis has resolved, foods should be reintroduced sequentially to assess for a return (or worsening) of the atopic dermatitis, prior to ascribing the improvement to the exclusion diet. This is because the improvement may be coincidental or reflect a placebo effect. Concomitant therapies and other environmental factors should not be changed during the period of assessment for food allergies. In addition, if multiple foods have been excluded it is imperative to see which of these foods is truly responsible and exclude only those foods, while allowing the return of non-contributory foods into the diet.
- Food reintroduction may be performed as a standard food challenge with a single food in incremental doses. If there is no immediate reaction, then give the food for three to four days successively and monitor atopic dermatitis scores daily. In selected cases where there has not been prolonged exclusion of the food and there was no immediate type reaction, a home challenge may be performed.
- Should the skin not react to the introduction of this food, challenge with a new food every three to four days.
- However, should the food exacerbate the atopic dermatitis, it may be considered a causal food allergen and be removed from the diet to bring about the improvement in the symptoms for the second time. Where doubt still exists, a second re-challenge may be necessary.

Removing foods from one's diet requires support and education, especially in cases where the food is common and present in many hidden sources. A dietician must be consulted to

ensure the allergen is completely eliminated from the diet, as well as to provide alternatives to ensure nutritional adequacy of the residual diet.

The natural history of food allergy resolution is variable and may differ in those with and without atopic dermatitis. It varies between allergens, with milk, egg, soy and wheat resolving earlier, and more commonly than allergies to peanuts or tree nuts.<sup>36</sup> Allergy to fish and shellfish, which more commonly develops later, may be life-long. In atopic dermatitis, approximately 25% of patients will outgrow their food allergy after one year.<sup>37</sup> Patients with severe concomitant IgE mediated food allergy/anaphylaxis should be followed up very frequently, but all patients should be reassessed after 12 months. Repeat testing should be followed by food reintroduction in the form of a formal food challenge to reduce the risk of immediate reactions that may be present or may have developed, in order to restore a normal diet wherever possible.

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## Diagnosis of atopic dermatitis

The diagnosis of this condition is often not straightforward, especially in adults. Several other conditions have to be considered in the differential diagnosis (vide infra). Where the disease represents mere continuation of atopic dermatitis from childhood, the diagnosis is usually easy and the clinical picture also typical. Difficulty arises where onset occurs after the age of 18 years (adult-onset atopic dermatitis) and in these cases the disease pattern is often not obvious, although it may still present with the usual flexural dermatitis seen in children. Non-typical morphology and localisation are common with nummular, prurigo-like, follicular and seborrhoeic patterns often seen<sup>1</sup>. Erythroderma is a rare manifestation of atopic dermatitis in adults<sup>2</sup>. The physical and environmental factors at play in adults differ from that in children and this is responsible for the different patterns of involvement.

The traditional criteria set out by Hanifin and Rajka<sup>3</sup> are used less than before. Williams et al developed a revised set of criteria<sup>4</sup> (as the “UK Workng Party”) and this was validated in the hospital setting<sup>5</sup> and in the community<sup>6</sup>. It is the opinion of this work group that these criteria

should be adopted for the diagnosis of atopic dermatitis, even though a recent study<sup>7</sup> done on children has shown that these criteria are not reliable when applied to low-prevalence populations such as the amaXhosa of South Africa.

These criteria are set out as follows in **Table 2**:

The diagnosis of atopic dermatitis is primarily clinical; special investigations only contribute in identifying external aggravating factors.

**Revised criteria for the diagnosis of atopic dermatitis<sup>4</sup>:**

- a. Must have:
  - Pruritus / Itching
- b. Plus three or more of the following:
  - History of flexural dermatitis (front of elbows, back of knees, front of ankles, neck, around the eyes) or involvement of cheeks and/or extensor surfaces in children aged up to 18 months
  - Visible flexural dermatitis involving the skin creases (or involvement of cheeks and/or extensor surfaces in children aged up to 18 months)
  - History of a generally dry skin in the past year
  - Personal history of asthma or hay fever (or history of atopic disease in a first degree relative in children aged under four years)
  - Onset under the age of two years (used only for children aged four years or older at time of diagnosis)

The histological findings on skin biopsy can be suggestive of the diagnosis, but on the whole it is not helpful and cannot be relied upon to make the diagnosis.<sup>4</sup>

Total IgE-levels are significantly raised in about 80% of cases, being normal in the rest, therefore reducing the value thereof in the diagnosis. The level of IgE does not correlate with severity of the dermatitis and 15% of non-atopic individuals have raised IgE levels.

Several conditions have to be considered in the differential diagnosis of AD, as listed below. These have to be excluded on clinical grounds and by employing appropriate investigations.

**Table 3: Differential diagnosis of atopic dermatitis in adults:**

- Seborrhoeic dermatitis
- Discoid (nummular) dermatitis
- Irritant contact dermatitis (especially of the hands)
- Allergic contact dermatitis and airborne contact dermatitis
- Photo-allergic and photo-irritant dermatitis
- “HIV-dermatitis”
- Drug-induced dermatitis
- Cutaneous T-cell lymphoma
- Psoriasis, especially the erythrodermic type
- Scabies
- Insect bites
- Filariasis

## **Measuring the severity of atopic dermatitis**

The severity of dermatitis in individual cases can be measured and monitored in several ways. The SCORAD index (SCORing Atopic Dermatitis),<sup>8</sup> the Objective Severity Assessment of Atopic Dermatitis (OSAAD)<sup>9,10,11,12</sup> and the Three Item Severity Score<sup>13</sup> all have merit in research context, but are not practical for daily clinical use.

It is the opinion of this work group that the severity assessment should be simplified to make it easy to use in practice. The aim is to stratify treatment accordingly in individual patients. We propose:

1. A measurement of the area involved in percentage of body surface, where 1% body surface is equal to the size of one hand (including the fingers) of the patient.
2. Acute, sub-acute or chronic changes, where acute changes would imply more severe dermatitis. These changes have been explained under the heading of definitions.
3. Impact on the quality of life of the patient as measured by sleep disturbance, absenteeism, visible scratching, social withdrawal, etc., according to the judgment of the clinician managing the case.

Dermatitis can then be classified as mild, moderate or severe as outlined below. Stratification of treatment according to this scheme will also be explained.

A flare of dermatitis can be defined as any episode of “upgrading” of the dermatitis from one group to the next, e.g. mild to moderate.

**Table 4: Assessing the severity of atopic dermatitis:**

- Mild: Less than 5% body surface involved
  - No acute changes
  - No significant impact on quality of life
- Moderate: 5-30% body surface involved
  - Mild dermatitis with acute changes
  - Mild dermatitis with significant impact on quality of life
- Severe: More than 30% body surface involved
  - Moderate dermatitis with acute changes
  - Moderate dermatitis with significant impact on quality of life

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### **Special investigations in atopic dermatitis**

To make a diagnosis of atopic dermatitis, special investigations are rarely necessary. The investigations are done mainly to identify trigger factors that flare up or aggravate dermatitis

so that patients may be advised to avoid these. However, these investigations are useful in the management of atopic dermatitis, mainly in children.<sup>1,2</sup>

A **skin biopsy** is done occasionally and may be useful if an adult presents with generalised exfoliative erythroderma to differentiate it from other causes of erythroderma.<sup>1</sup>

Estimation of **total serum IgE, ImmunoCAP assays** for specific IgE and skin-prick tests (**SPTs**) may be done to confirm the atopic nature of the individual patient's condition. It may be of value occasionally to confirm the atopic nature of the rash in adult-onset dermatitis. However it must be remembered that 20 - 60% of patients with atopic dermatitis have normal total serum IgE levels and negative ImmunoCAP assay, whereas 15% of apparently healthy people have raised IgE<sup>3</sup>.

The skin-prick test is the most common procedure used to confirm food and inhaled aeroallergens sensitisation. Either commercially available extracts or fresh foods may be used, most commonly cow's milk, hen's egg, wheat, soy, fish and peanuts. Aeroallergens (mites, pollens, moulds, and animal dander) can be tested in the same way. Commercial extracts are placed directly on the skin and the skin is pricked through the liquid. Aqueous fresh foods (or solid native foods crushed with saline) may be tested in the same way. Solid native foods such as fruit may also be tested by pricking the food with the lancet and then pricking the skin, the "prick-prick test." A new lancet should be used for each skin-prick. The test site is observed for 15-20 minutes and the mean wheal reaction (largest diameter + 90 degrees to this divided by 2) is measured and recorded in millimetres. A positive control with histamine should be 3mm or more; a negative control with saline is also done.<sup>4,5,6,7</sup>

Variants of SPT include the **scratch patch test** where the skin is scratched and the food applied under an occlusive patch, and the **skin application test** where the food is applied to the skin without scratching and examined at 10 minute intervals for a reaction. These tests are not commonly used as no additional value is added to the routine SPT.<sup>6,7</sup>

The indications for and interpretation of these investigations are discussed fully in the section concerning diet in atopic dermatitis.

In adults with head and neck dermatitis a positive ImmunoCAP assay to *Malassezia* species may be useful as such patients may benefit from treatment with oral anti-yeast treatment.<sup>1,2</sup>

**Patch tests** involve formal patch testing to diagnose superimposed allergic contact dermatitis, e.g. in adult patients with chronic hand dermatitis. The aetiology of the continuing dermatitis is elucidated.<sup>1</sup> Formal patch tests are also useful for deteriorating dermatitis that is being intensively treated. The patient may have an allergic contact dermatitis to one of the components of the current topical treatment.<sup>1</sup>

The **Atopy Patch Test** (APT) is used to diagnose type IV hypersensitivity reactions and is used to determine food and aeroallergen triggers for dermatitis. It is a specialised, time-consuming procedure that is highly specific. but has lower levels of sensitivity.<sup>6</sup> It is not often used in adults with atopic dermatitis.<sup>1,2,5,6</sup>

If immunodeficiency is suspected with atopic dermatitis, tests like **HTLV-1, HIV, immunoglobulin subtypes, T and B cell numbers and functions** will need to be done. If secondary bacterial infections are suspected, pus swabs will be necessary. For suspected herpes infection a **Tzanck smear, rapid PCR test done on a dry swab** or **electron microscopy** will give a quick confirmation.<sup>1</sup>

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## Prevention of atopic dermatitis

Prevention of atopic dermatitis, next to a cure for the condition, would be first prize for practitioners treating and researching this condition. Many exciting strategies for prevention are being investigated, but need further research. Our existing advice has not met with much progress in the last decade of investigation.

### Primary prevention

Attempts to provide allergen-free diets to pregnant mothers, so popular in the early 1990s, have failed to prevent the development of allergy or atopic dermatitis. Food allergen avoidance during pregnancy and early life is unhelpful; in fact, it may even promote atopy.<sup>1</sup> Allergen avoidance in breastfeeding mothers (avoiding potentially allergenic foods), even in the case of high-risk infants, is unhelpful.<sup>2</sup> **[1+;A]** Cigarette exposure is now conclusively linked to atopic aetiology and it is a major factor in cause of flares of dermatitis.<sup>3,4</sup> **[1-;B]** Whilst all components of the “hygiene hypothesis” may contribute to a rising prevalence of allergic disorders, it must be remembered that they are epidemiologically linked to atopy, but would certainly not be important or useful in individual families. Such factors include birth by vaginal delivery, living on a farm, reduced consumption of antibiotics in infants, living in less hygienic circumstances, day-care attendance and living within the context of more siblings.<sup>5</sup>

The current role of probiotic supplementation is unclear. **[1++; 0]** Unfortunately, there are studies supporting benefit of probiotics in prevention,<sup>6,7,8</sup> and studies that fail to support benefit.<sup>9,10,11</sup> The ultimate answer to the probiotic strategy may well depend on actual bacterial strains (not all organisms have equal benefit), dose, viability and timing of intervention. There is insufficient evidence at present to give a clear recommendation.

The role of breastfeeding is also unclear. Studies of exclusive breastfeeding are equivocal in their findings.<sup>12,13,14</sup> There is now mounting evidence that the most valuable allergy prevention strategy is four months of exclusive breastfeeding, followed by weaning between four and six months of age, to a diet that incorporates gradual and consistent introduction of a wide range of foods – even those known to be allergenic (cow's milk, egg, peanuts, wheat and fish).<sup>15,16</sup> **[1+++; A]** In high-risk infants who cannot be breastfed, there is evidence that hypo-allergenic milk formulae may be beneficial.<sup>17,18</sup> **[2+; B]** These include partially hydrolysed whey formulae and extensively hydrolysed casein- and whey-based formulae. Where cost is an important consideration, there is one study that has documented the



benefit of partially hydrolysed whey milk.<sup>18</sup> There is evidence that omega-3 polyunsaturated fatty acids (n-3 PUFA) supplementation during pregnancy will reduce some food allergy sensitivities,<sup>19</sup> however, this effect was not seen for supplementation of maternal diet during lactation.<sup>19</sup>**[2+; C]** There is no clear evidence for prevention of atopic dermatitis by supplementing the neonatal or infant diet with n-3 PUFA.<sup>20</sup>

### **Primary Prevention of Atopy:**

The only practical advice that can be given to the parents of soon-to-be born or new-born high-risk infants is to exclusively breastfeed for the first four months of life and not to smoke during pregnancy or around young children.

### **Secondary prevention – prevention of the atopic march**

The administration of newer anti-histamines to clearly atopic infants with dermatitis had initially shown some promise in the overall prevention of asthma, but this is no longer the case. The ETAC study found that a sub-set of atopic infants had a reduced prevalence of wheeze after receiving cetirizine<sup>21</sup>. A study of levocetirizine for asthma prevention, however, failed to provide benefit.<sup>22</sup>**[2+; B]** Specific immunotherapy shows promise, but is clearly impractical unless orally available.<sup>23</sup> Newer immunotherapy vaccines, and especially those that include bacterial products, are showing promise.<sup>23</sup>**[3; C]** The role of probiotics in secondary or tertiary prevention is unclear.<sup>24</sup> The use of aqueous creams on the skin of new-born infants has been linked to an increased rate of dermatitis in children.<sup>25</sup>**[3; B]**

### **Tertiary prevention**

The avoidance of allergens, irritants and triggers in the established dermatitis patient is an important adjunct to treatment and prevention of acute flares. Flares of atopic dermatitis, together with uncontrolled symptoms, are the main cost drivers in this disease and certainly impact significantly on the quality of life of the patient.<sup>2</sup> It should be stated that the successful treatment of dermatitis could improve the outcome of other atopic conditions such as asthma.<sup>26</sup>**[2+; B]**

Avoidance of the following trigger factors is important in atopic dermatitis patients: **[1+; A]**

- Exposure to personal and/or second-hand tobacco smoke;
- Irritants and sensitisers in the home or in the workplace; and
- Proven allergens.

Since varicella infection is more common and more severe in eczematous skin, varicella vaccine seems a prudent strategy in children with AD.<sup>27</sup>**[2+; B]**

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## Patient education in atopic dermatitis

Education of patients with atopic dermatitis is an essential and unavoidable component of management.<sup>1</sup> Where the disease involves young children, education of parents is mandatory. Without adequate attention to education, all therapies are futile and the patient is doomed to an impaired quality of life. Practitioners treating individuals with atopic dermatitis must be aware that the disease is one of the most important medical conditions to affect quality of life.<sup>2</sup> Quality of life impairment usually involves the entire family.<sup>3</sup> Whilst much of the educational principles centre on an adequate explanation of the therapies and their appropriate application and timing, there are a number of messages that must be mentioned independently.<sup>4</sup>

These include:

- An explanation of the disease process, its aetiology and its pathology.
- Avoidance of generic (cigarette smoke, irritants) and individual specific (allergens) trigger factors.
- Attention to skin hygiene and care.
- Attention to itch prevention (avoiding hot bedrooms, cutting of nails, avoidance of woollen and other rough, scratchy clothing, avoidance of overdressing, avoidance of soaps and adequate moisturisation).
- An explanation of the chronic and relapsing nature of the disease.
- An explanation that all therapies are able only to treat the condition but not cure it.
- A discussion about the scientific basis of alternative therapies (homeopathy, reflexology, naturopathy, acupuncture and herbal therapy). Such discussion should suggest that whilst such therapies are not grounded by the same evidence required for allopathic medicine, many individuals feel compelled to try them when desperate. Such desperation can usually be overcome by careful attention to skin care and medicine use.
- Honest discussion about medication side effects.

Educational messages need to be frequently repeated. Patients and parents must be given adequate opportunity to raise concerns and ask questions. Atopic dermatitis consultations – even follow-up visits – usually require a long consultation.

Education is greatly aided by information leaflets, reputable website addresses and contact details for support groups<sup>5</sup>.

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## **Non-pharmacological treatment modalities for atopic dermatitis**

These non-pharmacological interventions are used together with standard treatments to prevent or improve control of atopic dermatitis. Most of the studies involve children; a few include adolescents and occasionally adults.

### **Occlusive dressings [1-; B]**

A critical review of wet wraps as an intervention for severe and refractory atopic dermatitis<sup>1</sup> found that the wet wrap method varied widely between studies, making comparisons difficult. Their findings suggest that wet wraps (cream or ointment applied to the skin then covered by a double layer of cotton bandages, with a moist first layer and a dry second layer and kept in place for 24 hours) were safe short-term interventions. They were more efficacious when used together with topical steroids and reduced the absolute amount of topical steroid required – thus it could be recommended as a second-line short-term (14 days) intervention to limit systemic absorption. The number of adolescents and adults included in the review was small and the authors raise the concern of possible increased risk of striae if wet wraps were to be used with topical steroids during puberty.

Studies in mild to moderate dermatitis comparing the addition of wet wraps to standard therapy showed no additional benefit from wet wraps in children.<sup>2</sup>

A more recent review on the use of occlusive dressing (wet or dry) found little evidence for their use, but noted that the studies were of poor quality.<sup>3</sup>

No such studies have been done in South Africa.

### **Bathing practices [1+; A]**

Although salt has been used for centuries for treating skin diseases – including dermatitis – according to a systematic review<sup>5</sup> there is little evidence to support the use of salt baths for treating atopic dermatitis. Contrary to this practice, hard water has been thought to play a role in triggering atopic dermatitis. In a randomised controlled study done in the United Kingdom, there were no benefits demonstrated when ion exchange water softeners were used.<sup>6</sup> These softeners removed predominantly calcium, but not other contaminants.

The use of emollients is a cornerstone of atopic dermatitis management, but in a systematic review of randomised controlled studies, Tarr et al reported little evidence for the addition of emollients to the bath water.<sup>7</sup>

Infections are accepted as triggers for atopic dermatitis and have been implicated as the cause in those with poor control. Previous reviews have shown no benefit<sup>5</sup> and an updated Cochrane systematic review confirmed lack of benefit for the use of bath antiseptics for infected or non-infected atopic dermatitis patients.<sup>8</sup>

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.

**Table 5: The current recommendations for bathing:**

- Regular bathing to hydrate the skin and debride crust – useful for most patients for both cleansing and hydrating the skin;
- Bathe once daily for several minutes in warm (not hot) water;
- Use a moisturising cleanser;
- Avoid antibacterial cleansers (may lead to bacterial resistance);
- After bathing, pat dry; and
- Emollients should be applied immediately after bathing.

### **Antiseptics and antimicrobials [1+; A]**

Although secondary infection and colonisation of damaged skin by bacteria is understandable, the role of bacteria in the pathogenesis of atopic dermatitis is not clear.<sup>9</sup>

Evidence for the regular use of antimicrobial and antiseptic agents in the control of uninfected dermatitis has been reported in a systematic review<sup>5</sup> of trials that included children, adolescents and adults. There was little evidence to support the use of antiseptics in either bath water or if applied directly to the skin. The intermittent use of short-term mupirocin was of benefit for relapsing atopic dermatitis that was not overtly infected, but there is concern for emerging resistant organisms. There were no randomised control trials supporting the use of oral antibiotics.

No benefits for the regular use of topical antifungals in addition to topical steroids were found for 60 adult patients with head and neck involvement, although yeast colonisation fell significantly.

In a more recent review of the subject of antimicrobial use in atopic dermatitis control, no benefit when used as a topical agent or bath additive was found.<sup>8</sup>

### **Laundry practices**

Patients are often advised to avoid certain products based on reported cases of skin irritation or allergy after exposure. Evidence for this advice is scarce.<sup>10,11</sup>

#### **Enzyme-containing washing powders [1-; C]**

One randomised double-blind crossover study in adults failed to show any benefit from avoiding enzyme containing washing powders for laundry.

#### **Fabric softeners [1-; C]**

For both the irritated and normal skin, the “softened” fabric was less irritating by all measured parameters, in a right/left comparison study of atopic dermatitis volunteers with no active dermatitis.

There is limited evidence suggesting that laundry practices have effect on atopic dermatitis control. Logic would support adopting practices that are simple and reduce undue exposure to potential allergens and irritants in those with impaired skin barrier function. The benefit of using fabric softeners that reduce fabric roughness is indirectly supported by evidence relating to clothing choices (see below). The development of fabric softeners free of perfumes would be in keeping with the simple approach alluded to above.

### **Clothing [1-; C]**

Wool intolerance is a minor criterion for diagnosis in atopic dermatitis, according to Hannifin. Despite this there are few studies on the benefits of specific clothing in atopic dermatitis. In a systemic review<sup>5</sup> two small, randomised controlled trials were reported. Itching and discomfort caused by garments made of various fibres, including cotton, and of different weave, weight and roughness were related to fibre weight and roughness only. Sweating increased discomfort for all tested fibres.

Fabric roughness determines skin irritation, and not the type of textile. This is indirectly supported by the finding that cloth washed with fabric “softeners” causes less irritation than control cloth.

There is little evidence to support the recent fashion for silk clothing use in atopic dermatitis control according to a systemic review based on poor quality studies.<sup>4</sup>

As these studies were done in Europe, they may have no bearing to the South African climate where the more occlusive synthetic materials may provoke sweating and itch.

### **Allergen avoidance**

Recent evidence has demonstrated that up to two-thirds of those with the atopic dermatitis phenotype do not show IgE hyper-responsiveness and are thus not atopic by definition.<sup>12,13</sup> Despite this, it remains fashionable for patients with atopic dermatitis to be treated with allergen avoidance, with or without supporting evidence of allergy despite increasing support for a primary skin barrier defect underlying atopic dermatitis.<sup>14-21</sup>

Avoidance of allergen exposure can be associated with prevention of atopic disease or aggravation of established disease.<sup>22,23</sup> Once sensitised, desensitising therapeutic interventions can be attempted. Only the evidence for a role of allergen avoidance in established atopic dermatitis will be addressed here.

#### **A. Inhalant allergy**

##### **House dust mite [1+; B]**

Circumstantial evidence suggests an important precipitating role for house dust mite allergens in patients with atopic dermatitis. Reducing exposure to the allergen should theoretically be beneficial for cases of established dermatitis.

A review of the evidence for house dust mite reduction revealed that there is little evidence to support a clinical benefit from house dust mite allergen reduction in preventing atopic dermatitis or controlling established disease, although it may help to reduce severity in severe atopic dermatitis.<sup>5,10</sup>

### Pollens [1-; C]

Seasonal variations in atopic dermatitis could be related to exposure to pollens.<sup>9</sup>

### Animals [1+; B]

There is currently conflicting evidence for the role of pet allergens in atopic dermatitis.<sup>9,24,25,26</sup> In a systematic review of cohort, case-controlled and cross-sectional studies, Langan et al found no good evidence for a protective effect of furry pet avoidance.<sup>33</sup> In African studies of atopic dermatitis there is no association with animals in the home and atopic dermatitis.<sup>27-30</sup>

## **B. Ingestant allergy [1+; B]**

### **Diet manipulation other than food avoidance:**

Diet supplementation with a variety of products has been suggested both for prevention of atopic dermatitis (maternal manipulation) and control of existing disease. These aspects are dealt with fully under the section concerning food allergies and the section on prevention of atopic dermatitis.

## **C. Contact allergy [1-; C]**

Increasing evidence is being found for the role of contact allergens in atopic patients. It is well known that atopic dermatitis is a risk factor for developing contact allergies, but the precise role of contact reactions (irritant and allergic) in atopic dermatitis pathogenesis is not clear.<sup>9</sup>

In a prospective subgroup analysis of 143 Polish children and adolescents classified as having atopic dermatitis by the ISAAC criteria, the authors found considerable overlap between atopic and allergic contact dermatitis (55.4% and 30% in children and 38.6% and 51.7% in adolescents respectively). Of those diagnosed with atopic dermatitis based on a history of an itchy flexural rash, 19.5% (9/46) children and 52% (13/25) adolescent were found to be due to allergic contact dermatitis and lacked sufficient features for a diagnosis of atopic dermatitis by Hanifin and Rajka's criteria.<sup>31</sup>

A systematic review and meta-analysis of allergens responsible for allergic contact dermatitis found that the top five allergens in children and adolescents included nickel, ammonium persulfate, gold sodium thiosulfate, thimerosal and p-toluenediamine.<sup>32</sup> Most studies were from Europe and the United States and the proportion of positive reactions increased from 1995.

### **Psychosocial factors [1+; B]**

Although stress and psychological factors appear to influence atopic dermatitis, evidence of their impact is limited.<sup>12</sup>

Chida et al undertook a systemic review and meta-analysis of cohort studies of psychosocial factors and atopic disorders. They reported a bidirectional relationship between the two and noted that early childhood adverse psychosocial episodes were associated with an increased risk of developing atopic disease. Most studies dealt with asthma.<sup>33</sup>

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## Emollients in atopic dermatitis

### Role of emollients

Skin dryness is a very common feature of atopic dermatitis and is a diagnostic criterion for the disease. The consequences of dry skin include:

- Inflammation;
- Loss of suppleness leading to fissuring;
- Impaired barrier function; and
- Increased adherence of *Staphylococcus aureus*.

Emollients (or moisturisers) act by occluding water loss from outer layers of the skin and by directly adding water to the dry outer layers of the skin, thereby providing a protective film over the skin to keep moisture in and irritants out. Emollients are classified according to their mechanism of action as occlusive (prevent water loss from the skin) or humectant (improve water binding in the skin). They are widely used to relieve symptoms in many skin diseases and may also reduce pruritus through an unknown mechanism<sup>1</sup>. They can be applied directly to the skin or used as a bath additive.

### Use of emollients [1-; B]

Emollients are universally recommended as first-line therapy; however, despite this there is a paucity of studies to justify their use – in fact, the quality and quantity of evidence is inversely proportional to the frequency of their use.<sup>3</sup> There are very few RCTs evaluating the effectiveness and safety of emollients.<sup>7,8,9</sup> There was a lack of studies of any design that evaluated the effectiveness of emollients in children with atopic dermatitis. The available data consisted of isolated case series and case reports, with no controlled studies comparing emollients to placebo/no active intervention. With no control groups, it is not possible to quantify the benefits or harms of emollient therapy. One RCT evaluated the use of emollients for the treatment of atopic dermatitis in children, in which emollients gave positive results, in particular on xerosis, pruritus and improvement of the quality of life, but no overall improvement in SCORAD counts<sup>9</sup>. Evidence from studies of various designs were identified for aqueous cream, emollients containing urea<sup>6</sup> or ceramide,<sup>11,12,13,25</sup> an antimicrobial emollient,<sup>14</sup> and bath emollient preparations.<sup>15</sup> These are discussed below.

Emollients are available in a variety of formulations (ointments, creams, lotions, gels and aerosol sprays). Ointments such as white soft paraffin are greasy in nature, whereas creams and lotions contain water and are more acceptable cosmetically. Creams, lotions and gels contain preservatives to protect against microbial growth in the presence of water.

Antiseptics added to emollients include triclosan, chlorhexidine hydrochloride and benzalkonium chloride.<sup>14,15</sup>

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.<sup>3</sup> The maximum duration of effect of any emollient is six 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 three minutes of bathing to retain hydration.<sup>4</sup> Sufficient quantities must be prescribed, viz. 250g/week for children and 500g/week for adults for the whole body.

Generally, emollients are free of side-effects, but they can cause contact dermatitis. There is little basis for suggesting the use of one moisturiser as opposed to another.

Thus, complete emollient treatment should be in place, ranging from the bath preparations which are “wash-off” emollients, to the “leave-on” emollients.<sup>21</sup>

Aqueous cream is not a suitable emollient, since the preservative sodium lauryl sulphate (unbuffered) can aggravate the dermatitis. It has been found in studies to increase transepithelial water loss and disruption of the skin barrier function. Many studies have now confirmed this finding.<sup>10,27</sup> Aqueous cream or any product using unbuffered sodium lauryl sulphate emulsifier should therefore not be used as a leave on emollient.

### **Newer emollients [1-; C]**

There are now many new emollients available in South Africa, many of which have ingredients that are conducive to restoring the skin barrier function.

A randomised controlled trial examined the effects of an emollients containing evening primrose oil and oat extract, compared to no emollient.<sup>9</sup> There was no significant difference between the two groups. Studies examining the role of emollients containing urea failed to show any benefit.<sup>6,11,12,13</sup>

A study examining the role of ceramide-containing emollients showed some improvements, however, the results were not properly evaluated.<sup>25</sup> The latest addition to these products contain, in addition to ceramides, filaggrin breakdown products to replace the “missing” molecules in the atopic skin – the result of the filaggrin mutations is reputed to form a very important part of the aetiology of atopic dermatitis. Early results are very promising and these products compare favourably to existing ceramide-containing moisturisers.<sup>26</sup>

Two studies evaluated preparations containing antimicrobials.<sup>14,17</sup> The results did not show any significant improvement. However, topical irritant reactions were common in these patients.<sup>17</sup>

### **Bath emollients [1-; C]**

Four studies considered the use of bath oil preparations.<sup>15,16,17,18</sup> These studies showed a modest improvement in symptoms with bath emollients and three of the four studies supported the use of bath emollients. The evidence is, however, not really conclusive and no

strong recommendation can be made at this stage. Frequent bathing did not demonstrate any advantage over less frequent bathing.

### **Steroid-sparing effects of emollients**

Emollients are commonly described as having a steroid-sparing effect, however, no robust evidence supports this view.<sup>19,20,22</sup> Studies have not found emollients to convincingly produce a steroid sparing effect.

### **Wet wraps [2-; D]**

Studies evaluating emollients in conjunction with and without topical corticosteroid wet wrap therapies have also been evaluated.<sup>23,24</sup> Many of these studies were poorly designed and the conclusion from these studies was that wet wraps did not offer significant symptom relief compared to conventional therapy. Wet wraps can, however, be used in severe recalcitrant atopic dermatitis when conventional treatments have failed. (See also the section on non-pharmacological treatment.)

### **Recommendations from NICE guidelines in Children<sup>28</sup>**

Healthcare professionals should:

- Offer children with atopic dermatitis a choice of unscented emollients to use every day for moisturising, washing and bathing. This should be suited to the child's needs and preferences, and may include a combination of products or one product for all purposes. Leave-on emollients should be prescribed in large quantities, as mentioned and easily available to use at nursery, pre-school or school.
- Inform children with atopic dermatitis and their parents or carers that they should use emollients in larger amounts and more often than other treatments. Emollients should be used on the whole body both when the atopic dermatitis is clear and while using all other treatments.
- Inform children with atopic dermatitis and their parents or carers that they should use emollients and/or emollient wash products instead of soaps and detergent-based wash products.
- Advise parents or carers of children aged under 12 months with atopic dermatitis to use emollients and/or emollient wash products instead of shampoos for the child. If shampoo is used for older children with atopic dermatitis it should be unscented and ideally labelled as being suitable for eczema; washing the hair in bath water should be avoided.
- Show children with atopic dermatitis and their parents or carers how to apply emollients, including how to smooth emollients onto the skin rather than rubbing them in. Healthcare professionals should offer an alternative emollient if a particular emollient causes irritation or is not acceptable to a child with atopic dermatitis.
- Review repeat prescriptions of individual products and combinations of products with children with atopic dermatitis and their parents or carers at least once a year to ensure that therapy remains optimal.

Where emollients (excluding bath emollients) and other topical products are used at the same time of day to treat atopic dermatitis in children, the different products should ideally be applied one at a time with several minutes between applications where practical. The

preferences of the child and parents or carers should determine which product should be applied first.

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## Topical pharmacological treatment of atopic dermatitis

### **Topical corticosteroids (TCS) [1++; A]**

Topical corticosteroids continue to be the mainstay of atopic dermatitis treatment.<sup>1,2</sup> For more than four decades TCSs have provided effective flare control through their anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive actions.<sup>3</sup> They suppress the release of inflammatory cytokines, and they act on a variety of immune cells, including T lymphocytes, monocytes, macrophages, dendritic cells and their precursors.<sup>4</sup> Various strengths and formulations of TCS are available. The extent to which they induce cutaneous vasoconstriction and inhibit inflammation corresponds with their potency. There are no adequate trials to suggest superiority of one corticosteroid within a potency group over another.

The extensive use of topical corticosteroids in clinical practice is supported by an ever-expanding body of clinical trial data, which helps to provide physicians with sensible recommendations for the quantity, frequency, and duration of topical corticosteroid therapy.<sup>5,6</sup> Guidelines for prescribing TCS are well described.<sup>7,8</sup> Preparations of very weak or moderate strength are used on the face and genital area, whereas those of moderate or potent strength are used on other areas of the body.<sup>9</sup> Patients should be educated about the different steroid potencies in order to minimise untoward side-effects.<sup>10</sup>

Better absorption of topical corticosteroids is observed in areas of inflammation and desquamation compared to normal skin, and absorption occurs more readily through the outer dermis in infants than through the skin of adults.<sup>11</sup>

The vehicle through which the active steroid is delivered plays an important role in absorption and can enhance its efficacy. Generally ointments are more effective than creams, as the emollient action and occlusive effect result in better penetration. Ointments also require fewer preservatives so the potential for irritant and allergic reactions is lower. Wet wraps and application under occlusion enhance absorption of topical steroids.

**Table 6: The available TCS formulations:**

- Water-based lotions: To be used on acute, wet dermatitis or the scalps of babies<sup>12</sup> and hairy skin areas in adults.
  - Alcohol-based lotions: To be used on scalps of older patients.
- Shampoo: In short contact applications for resistant scalp dermatitis in adults.
- Creams: For thin, subacute lesions, thin skin areas, skin folds, under occlusion like diapers and the face.
  - Ointments: For dryer subacute lesions.
- Fatty ointments: For thick, chronic, lichenified lesions and on thick skin areas.

The corticosteroid preparations available in South Africa at present are listed below according to potency, with the different available formulations shown:

**Table 7: Topical corticosteroids available in South Africa:**

<b>a) Lowest potency</b>	
0,5% Hydrocortisone:	Cream, Ointment
<b>b) Low potency</b>	
1% Hydrocortisone:	Cream, Ointment.
<b>c) Moderate potency</b>	
Beclomethasone dipropionate:	Cream
Clobestone butyrate:	Cream
Fluticasone propionate:	Cream, Ointment.
Hydrocortisone 17-butyrate:	Cream, Lipocream, Ointment, Lotion, Emulsifying Lotion
Methylprednisolone aceponate 1%:	Milk, Scalp solution, Cream, Ointment, fatty ointment
Momethasone furoate:	Cream, Ointment, Lotion.
<b>d) Potent</b>	
Betamethasone valerate:	Cream, Ointment, Solution, Scalp Solution
Fluocinolone acetonide:	Cream, Ointment, Gel.
Diflucortolone valerate:	Cream, Fatty Ointment, Forte Ointment.
<b>e) Very potent</b>	
Clobetasol propionate:	Cream, Ointment, Shampoo, Scalp Solution.
Bethametasone dipropionate:	Cream, Ointment.

Topical steroids can be used for 10-14 days when the dermatitis is active, followed by “holidays” with just emollients. TCS can also be used in bursts of 3-7 days to treat exacerbations. This rationale can be extended to using potent TCS for a few days to initiate control, followed by the use of a milder potency TCS and/or emollient.<sup>8</sup> For chronic lichenified eczema, frequent applications of potent steroids are required for much longer periods. A possible regimen in the use of TCS as maintenance treatment for stable disease is “weekend use”, where the product is applied on weekend days only, combined with emollients, while emollients continue alone during the rest of the week. This has been shown to provide excellent control with minimal side-effects and much reduced cost.<sup>13</sup>

The amount of TCS to use is a common practical problem for patients. The fingertip unit is useful: Index finger from distal crease to fingertip equals 0.5g. This aids monitoring compliance and use. There is no clear evidence to suggest that twice-daily application of TCS is better than a once-daily application. It would be justifiable to use once-daily corticosteroids as a first step in all patients with atopic dermatitis, thus reducing cost, improving compliance and reducing side-effects.

No convincing evidence is available to demonstrate superior clinical efficacy of corticosteroid-antibiotic combination products to corticosteroids alone. When efficacy of TCS is reduced, this is thought to be related to disease severity rather than corticosteroid resistance.<sup>14</sup>

There are many challenges on the subject of TCS use, especially in the light of steroid abuse, steroid misuse, steroid phobia and side-effects. Adverse effects are well documented and it is important to recognise the side-effects of skin atrophy, telangiectasia, hypopigmentation, steroid acne, hirsutism, rosacea and contact sensitisation to the steroid itself. Skin thinning is not a problem when topical steroids are used correctly.

Uncommon systemic effects are the suppression of the hypothalamic-pituitary-adrenal axis, growth retardation, tachyphylaxis, glaucoma, cataract formation and Cushing's syndrome.<sup>15</sup> Over recent years the risk of adverse effects of TCS has been reduced by optimising application protocols and using newer steroid preparations with improved risk/benefit ratios, e.g. prednicarbate, mometasone furoate, fluticasone and methylprednisolone aceponate.<sup>9,10</sup> This improved risk/benefit ratio means that the products may be used at a younger age (from the age of four months) and for longer periods (for four weeks continuously in babies and three months in older children and adults).<sup>16</sup> Should these drugs be required at a younger age and for longer periods, as is often the case, the benefit versus risk should be evaluated in each individual case and the appropriate formulation carefully selected. Intermittent dosing should be used as far as possible.

The judicious use of TCS would include short-term appropriate applications as initial monotherapy or in combination with other therapeutic agents that ideally possess complementing mechanisms of action. These drugs could be either systemic agents or topical agents such as the topical calcineurin inhibitors.<sup>17</sup>

### **Topical calcineurin inhibitors (TCIs) [1++; A]**

TCIs (pimecrolimus and tacrolimus) are complex macrocyclic compounds that result in selective inhibition of cytokine transcription in activated T-cells. Pimecrolimus selectively targets T cells and mast cells. In contrast to tacrolimus, pimecrolimus has no effects on the differentiation, maturation and function of dendritic cells. In contrast to corticosteroids, TCIs do not affect endothelial cells and fibroblasts and thus do not induce skin atrophy.

TCIs are registered for short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in immunocompetent patients aged two years or older.<sup>18,19</sup> Clinical trial data have proven that pimecrolimus<sup>20,21</sup> and tacrolimus<sup>22</sup> reduces the incidence of flares and has a significant effect on reducing pruritus.

Pimecrolimus and tacrolimus are safe and effective in reducing the severity of atopic dermatitis symptoms in children and adults. In South Africa, pimecrolimus 10mg/1gm and tacrolimus 0.03% are registered for use from two years of age. Tacrolimus 0.1% is registered for use in patients older than 15 years.

In South Africa, tacrolimus is registered for use in children from the age of two years (0.03% strength), as well as in adults and adolescents from the age of 16 years (both 0.03% and 0.1% strengths). The 0.03% strength is to be applied initially as a thin layer twice daily to affected skin until the lesion clears. If this fails or results are inadequate, then the 0.1% preparation should be applied. If there is no improvement after three weeks, treatment should be stopped. In patients aged two to 15, the 0.03% strength may be applied twice daily for up to three weeks, and then the application reduced to once daily until the lesion clears.<sup>23</sup>

TCIs provide a steroid-free, anti-inflammatory topical therapy for atopic dermatitis. The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a corticosteroid with moderate potency, whereas 1% pimecrolimus cream is less active.<sup>24</sup> Both agents proved to be

effective with a good safety profile for a period of up to two years with pimecrolimus and up to four years with tacrolimus.<sup>21,22</sup>

TCIs are frequently associated with a transient burning sensation of the skin, less so with pimecrolimus than tacrolimus.<sup>25</sup> TCIs are not associated with skin atrophy and are therefore useful for the face and intertriginous areas.<sup>26</sup> This property can be an advantage of long-term use and tacrolimus ointment therapy additionally reverses corticosteroid-induced skin atrophy.<sup>27</sup>

Pimecrolimus was found to be a safe drug with none of the side-effects seen with topical steroids, and was also found to reduce the dependency of patients on topical steroids.<sup>28</sup> The percutaneous absorption of TCIs was found to be low. A significant proportion of patients could also be maintained without topical steroids for a year. A 12-month vehicle controlled study of children showed that early use of pimecrolimus reduced the frequency of flares, although early use of topical steroids might have shown similar benefits.<sup>29</sup> Similar results have been published for the use of tacrolimus<sup>22</sup>.

In January 2006, the FDA added a boxed warning to TCI labels noting that the long-term safety of these agents has not been established. The warning was added in response to widespread off-label use in the infant population (under two years of age) and concerns about a potential cancer risk based on three factors:

- A shared mechanism of action with systemic calcineurin inhibitors;
- Animal toxicology studies; and
- Rare post marketing case reports of malignancy (skin cancer and lymphomas).<sup>30</sup>

A recent, large review publication critically evaluated the preclinical, clinical, and epidemiological evidence that has thus far failed to substantiate a relationship between TCI use and malignancy, making the boxed warning probably inappropriate<sup>31</sup>.

In the UK the National Institute of Clinical Excellence approves the use of topical tacrolimus for children older than two years of age with moderate to severe dermatitis not controlled by TCS, and of topical pimecrolimus as a second-line option for resistant dermatitis of the head and neck.<sup>32</sup> In the USA both of these agents are approved as second-line treatments, and the site of application is not restricted for pimecrolimus. Tacrolimus has a favourable safety profile for up to four years. Generalised herpetic and molluscum infection has been observed with TCIs, but it is unclear whether there is an increased susceptibility to viral infections with TCIs. TCIs are not safe to use in pregnancy or during breastfeeding.

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## Use of phototherapy in atopic dermatitis [1+; A]

When topical modalities fail to control atopic dermatitis, phototherapy is the next option. Narrow band UVB (NB-UVB) is highly effective and has replaced broadband UVB for treating atopic dermatitis. Acutely inflamed atopic dermatitis patients do not tolerate UV well. Therefore the initial treatment will include immunomodulators like ciclosporin or mycophenylate mofetil or immunosuppressives like azathioprine or methotrexate. Once the acute inflammation has settled, UVB can be instituted.<sup>1,2,4,5,6,7</sup>

If there is significant erythroderma, UVL in very low doses has to be introduced to prevent nonspecific irritancy and flaring of the atopic dermatitis. The dose escalation is much slower than in patients with psoriasis.<sup>1,2</sup>

In patients with acute flares of atopic dermatitis, UVA-1 can be used.<sup>1,2</sup>

In patients in whom NB-UVB fails, photochemotherapy (PUVA) can be effective.<sup>2</sup> This can be given topically (soak/bath PUVA) or systemically (oral PUVA).<sup>1,2,6</sup> Goeckerman therapy with tar and UVB in a “day treatment” setting will improve more than 90% of patients with refractory atopic dermatitis, and prolonged remission can be induced.<sup>1,2,3,4,5</sup>

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## Systemic therapy in atopic dermatitis

Narrowband UVB, methotrexate and ciclosporin remain reasonable first-line systemic treatments for atopic dermatitis, with mycophenylate and azathioprine as second line options.<sup>1</sup>

### Ciclosporin [1+; A]

Atopic dermatitis symptoms respond to ciclosporin because the disease is mediated by activated T cells and thus is sensitive to a reduction in IL-2 expression. The role of ciclosporin in severe, refractory atopic dermatitis is well established.

Consistent evidence was found that short-term use of the drug effectively decreased atopic dermatitis severity.<sup>2</sup>

In patients in whom atopic dermatitis cannot be controlled by standard topical therapies, ciclosporin significantly decreases symptom scores, disease extent, pruritus and sleep deprivation, and has also been shown to improve QOL. Ciclosporin is used as an additional therapy. Topical therapies should not be discontinued while systemic treatment is administered.

Exclusion criteria for the use of the drug are: Renal or liver impairment, hypertension, previous or current malignancies, epilepsy primary or secondary immunodeficiency.<sup>3</sup>

#### Drugs to avoid while treating with Ciclosporin:<sup>2</sup>

Erythromycin, Clarithromycin, itraconazole and non-steroidal anti-inflammatory drugs.

#### Dosages, side-effects and monitoring

The recommended starting dosage, in children is 5mg/kg daily in divided dosages for the first two weeks, by which time a clinical improvement should be observed. The dosage can then be reduced to 1.5-3 mg/kg/day, according to clinical response and the patient's serum creatinine levels. If a clinical response is observed, the ciclosporin dose can be tapered slowly over the next 2-3 months. The total length of treatment is usually 6-12 months.

The most common adverse effects may include hypertension, renal dysfunction, headache, hypertrichosis, gingival hyperplasia and paraesthesia. Renal toxicity, which is dose and time related, can be acute or chronic, but usually responds rapidly to either reduction in dose or cessation of the drug.

Paediatric trials indicate that renal toxicity and hypertension are rare in children.

#### **Azathioprine [1+; A]**

It has several adverse effects, including myelosuppression, hepatotoxicity and susceptibility for infection, and the recommended dosage (1-3mg/kg/day) should be determined on the basis of individual thiopurinemethyltransferase (TPMT) levels.<sup>4</sup>

In the absence of defined protocols for the use of azathioprine in childhood atopic dermatitis, patients were treated for up to two years and then treatment was discontinued.<sup>4</sup>

Azathioprine could be used for short-term treatment in patients who are not eligible for, or are unresponsive to, ciclosporin.<sup>2</sup> The risk of developing hepatosplenic T-cell lymphoma and other lymphomas has put a damper on the enthusiasm to use this drug.<sup>5</sup>

#### **Systemic Corticosteroids [1+; A]**

Systemic corticosteroids are frequently used for short-term therapy of severe atopic dermatitis, but their use is controversial.<sup>4</sup>

The 2006 Practical Allergy (PRACTALL) consensus group guidelines suggest that in the case of acute flare-ups, patients might benefit from a short course of systemic corticosteroids, but long-term use and use in children should be avoided.<sup>4,6</sup>

The use of systemic corticosteroids should be restricted to the management of severe, acute and recalcitrant flares, and that its use should be limited to short courses of a few weeks. In the rare instances when these agents are prescribed, we prefer the use of prednisolone or prednisone at between 1 and 2 mg/kg/day. To minimise rebound flares or recrudescence of disease following discontinuation, we favour tapering after initial control or improvement is seen after the first 1-3 weeks, typically tapering over a period of 1-4 weeks depending on the severity and course of disease.<sup>7</sup>

### **Methotrexate [1+; B]**

Methotrexate is a folic acid antagonist that prevents the production of tetrahydrofolic acid by binding to dihydrofolate reductase. It should be considered a second line drug and is being used widely in the treatment of atopic dermatitis. Several studies proved efficacy in adults.<sup>8,9</sup> A study comparing methotrexate to azathioprine showed similar efficacy and safety, with methotrexate having a slight advantage.<sup>10</sup> The onset of action may be slow (up to eight weeks), liver and bone marrow functions have to be monitored according to established protocols and females have to use reliable contraception for up to three months after discontinuation of treatment.<sup>11,12</sup>

### **Mycophenolate mofetil (MMF) [2+; C]**

Severe refractory atopic dermatitis was documented to be responsive to MMF in adults<sup>13</sup> and children<sup>14</sup>. Trials comparing MMF with azathioprine<sup>15</sup> and ciclosporin<sup>16</sup> showed similar efficacy to these more established drugs, but the onset of action was slightly slower.

The standard dosage in adults appears to be 1g orally twice daily, on an empty stomach. It is available as a 250mg capsule. The safety profile concerning neutropenia and the development of lymphomas and other malignancies in long-term use of MMF also needs to be evaluated.

### **Antibiotics [1+; D]**

Oral antibiotics have no benefit on atopic dermatitis when used for skin that is not clinically infected, but infected dermatitis should be treated with penicillinase-resistant penicillins, cephalosporins or clindamycin.<sup>17,18</sup> Long term systemic antibiotics are contraindicated. Intranasal mupirocin combined with sodium hypochlorite (bleach) baths showed promise in a recent RCT in children.<sup>19</sup>

### **Anti-fungals [1+; A]**

*Malassezia sympodialis* sensitisation plays an important role in atopic dermatitis in adults, especially in patients with head and neck dermatitis.<sup>20</sup> IgE-mediated reactions to the fungus can be demonstrated in such patients and RCTs with systemic itraconazole<sup>21</sup> and ketoconazole<sup>22</sup> showed significant benefit in such patients. These drugs represent effective treatment options for this group of patients.

## **Intravenous immunoglobulin [1; B]**

This modality can be used as a last resort in children with severe, refractory atopic dermatitis, supported by at least one RCT.<sup>23</sup>

## **Interferon-gamma**

This expensive treatment may be a useful modality for moderate to severe atopic dermatitis in children and adults who have a history of recurrent skin infections with herpes simplex, human papilloma virus or molluscum contagiosum.<sup>24</sup>

## **Biological drugs**

Infliximab, efalizumab, tocilizumab and rituximab have been studied in this regard, but no firm recommendations can be provided at this stage.

## **PPAR-gamma antagonists (thiazolidinediones)**

These anti-diabetic drugs are also anti-inflammatory and (rosiglitazone) have been retrospectively shown<sup>25</sup> to be beneficial in atopic dermatitis. It also acts by improving skin barrier function and thus may be more effective as preventative treatment.<sup>26</sup>

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## Specialist referral of patients with atopic dermatitis

The majority of patients with atopic dermatitis respond to dedicated conservative treatment. Indications for referral to a specialist are listed in Table 2. There are additional indications.

**Table 8: Indications for referral for specialist dermatological advice**

**Immediate (same-day) referral:**

- If eczema herpeticum (KVE) is suspected\*

**Urgent referral (seen within two weeks):**

- If the AE is severe and has not responded to optimal topical therapy after one week
- If treatment of bacterially infected AE has failed

**Routine (non-urgent) referral: If any of the following apply:**

- The diagnosis is or has become uncertain.
- AE on the face has not responded to appropriate treatment.
- The AE is associated with severe and recurrent infections.
- Contact allergic dermatitis is suspected.
- The AE is giving rise to serious social or psychological problems for the child, parent, or carer.
- The child, parent, or carer might benefit from specialist advice on treatment application.
- Management has not controlled the AE satisfactorily according to a subjective assessment by the child, parent, or carer.

\*KVE=Kaposi's varicelliform eruption. KVE refers to viral (HSV/eczema herpeticum, vaccinia virus / eczema vaccinatum, and Coxsacki virus/eczema coxsackium) infection superimposed on AE. Eczema herpeticum is the commonest by far.

Patients, parents(s) or caregivers with corticosteroid phobia (CSP) should be referred. CSP is frequent and is not an irrational fear. CSP is the term to describe all types of fear about steroid use. In routine clinical practice, it is not unusual for patients to express fear or anxiety about using topical CS. Topical CSP, a complex phenomenon, may lead to poor adherence and lack of response.

All patients presenting with erythroderma (dermatitis involving more than 90% of BSA), any acute flare, spontaneous or precipitated by irritation of the skin, infection, stress and inadequate itch control need referral.

## **Complementary / alternative therapies for atopic dermatitis**

These treatments can be defined as forms of therapy or examination that have no scientific basis and for which no effective or diagnostic reliability has been demonstrated by scientific methods.<sup>1</sup> These modalities are becoming more and more popular,<sup>2</sup> which is understandable when people are faced with an intractable, incurable, highly symptomatic condition for which conventional medicine seem to be only partially beneficial. Approximately 30%<sup>3</sup> to 42.5%<sup>1</sup> of patients with allergies report the use of complementary treatments in Europe; these tend to be younger women with a higher educational background.<sup>3</sup> No reliable figures or records of treatment methods exist for the treatment of atopic dermatitis by African traditional healers.

## **A. Phytotherapy**

### Chinese herbal medicine (CHM) [1-; C]

Conflicting evidence exists regarding the efficacy and toxicity of these medicines, probably because there is a big variation in the actual composition of the different products as used by different practitioners.<sup>4,5</sup> Some preparations were found to illegally contain potent topical corticosteroids.<sup>6</sup> Potent inhibition of mast cell histamine release by a pentaherb formula has been demonstrated.<sup>7</sup> Few randomised controlled clinical trials exist to demonstrate the efficacy (or lack of) for this type of therapy, but some articles show promising results and many case reports have been published that seem to indicate a beneficial effect in some patients.<sup>8</sup>

### Kampo (Japanese herbal medicine) [3 ; D]

These treatments include composite herbs like Zemaphyte, Shofu-san, Ji-zuso-ippo, Eppika-jutsu-to and Hochu-ekki-to.<sup>9,10</sup> The levels of efficacy claimed and the available evidence for that is very much the same as for CHM.

### Siddha/Ayurveda [3; D]

These are complicated ancient medical systems from India, comprising herbal treatments, lifestyle modifications and diet. Claims of excellent efficacy are made, but supportive evidence is lacking.<sup>11</sup>

### Tea tree oil [0]

No controlled trials to prove efficacy in atopic dermatitis have been done. Allergic contact dermatitis is a frequent complication, mainly due to the sesquiterpine content.<sup>12</sup>

### Essential fatty acids [1++; 0]

There are no grounds for the use of these preparations, as no benefit could be demonstrated in a meta-analysis<sup>13</sup> of 34 publications.

### Other herbal medicine [0]

No evidence exists to support the use of arnica, calendulae flos and German chamomile.

## **B. Homeopathy [0]**

An open study on homeopathy for atopic dermatitis showed some benefit in 225 children,<sup>14</sup> but a comparative trial with conventional treatments showed inferior results for homeopathy.<sup>15</sup> A meta-analysis of controlled trials failed to show any benefit with homeopathic therapy. Most studies are methodologically severely flawed.<sup>16</sup>

## **C. Complementary psychotherapy: hypnosis, biofeedback and stress management [2-; D]**

Evidence supporting its use is weak, but some studies show promising results.<sup>17,18</sup> Hypnotherapy employs ego strengthening, direct suggestion, symptom substitution and hypnoanalysis. Evidence consists of case reports and open trials in adults, which suggest that it may be a useful complementary therapy to reduce pruritus, compulsive scratching, sleep disturbance and tension.<sup>19</sup> Biofeedback employs instrumentation that measures autonomic nervous system activity in the skin, providing feedback through visual, audible or kinetic sensory stimuli to the patient. Evidence pertaining to its efficacy in atopic dermatitis is lacking.<sup>16</sup> Cognitive-behavioural methods can reduce the conditioned scratching impulse in atopic dermatitis.<sup>20</sup>



#### **D. Other complementary therapies without proven efficacy**

Acupuncture,<sup>21</sup> bioresonance treatment,<sup>22</sup> balneotherapy, cleansing of the colon with enemas, massage therapy,<sup>23</sup> autologous blood therapy,<sup>24</sup> Reiki<sup>25</sup> and topical Streptococcal application<sup>26</sup> fall in this group. Sublingual immunotherapy has shown some promising provisional results in respiratory allergies, but no evidence exists for efficacy in dermatitis.<sup>27</sup>

#### **Interactions between herbs and conventional medicine**

Herbs and other complimentary medications can interact with conventional medication:

- Evening primrose oil (gamma-linolenic acid) can reduce efficacy of anticonvulsant drugs in epilepsy
- CHM can induce hepatitis<sup>28</sup>
- CHM can potentiate the hepatotoxicity of methotrexate<sup>28</sup>

#### **Complementary and alternative allergy tests**

The following tests have no scientific foundation or proof of validity.<sup>39</sup> These include:

- The leucocytotoxic test
- The IgG ELISA allergy test
- Applied kinesiology
- Electrodermal testing
- Hair analysis
- Auriculocardiac reflex
- Nampudripad's allergy elimination technique
- Live blood analysis
- Stool analysis and microscopy for yeasts and parasites

#### **Table 9: Advice to patients regarding complementary medicines as treatment for atopic dermatitis**

- The safety and efficacy of therapies such as herbal medicine, homeopathy, massage and food supplements for atopic dermatitis have not been adequately investigated in clinical trials.
- They should be cautious with the use of herbal medicines in children.
- Topical corticosteroids are sometimes illegally added to some herbal medications intended for use in atopic dermatitis.
- Liver toxicity can occur with the use of some Chinese herbal medicines.
- Emollient treatment should continue, even when complementary therapies are being used.
- Regular massage with emollients may improve the dermatitis.
- Healthcare professionals should be informed if they are using complementary therapies.

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