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PC Potter MD, FCP(SA), DCH(SA)

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A therapeutic approach to atopic eczema

Potter PC, MD, FCP(SA), DCH(SA)

Allergy Diagnostic and Clinical Research Unit, Department of Medicine,
University of Cape Town Lung Institute and Groote Schuur Hospital, Cape Town, South Africa

Correspondence to: Dr Paul Potter, e-mail: Paul.Potter@uct.ac.za

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Abstract

Atopic eczema is a common problem in general practice. The underlying disorder is a barrier dysfunction of the skin, but exacerbations of eczema can be triggered by a range of external and internal factors. In young children, dietary factors are important triggers of exacerbations and specific IgE sensitivity to common allergens may be confirmed by skin prick testing or ImmunoCap® RAST tests.

True sensitivity to foods is best confirmed by a controlled food challenge, and cut off values have been published which indicate the predictive values of blood or skin tests for true food sensitivity to guide the clinician.

Elimination of identifiable triggers, the use of emollients and topical corticosteroids remain the mainstay of treatments.

Calcineurin inhibitors have a place for treatment of selected cases. The use of systemic corticosteroids is discouraged and patients who do not respond to emollients, specific food avoidance and corticosteroids topically should be referred to a dermatologist. The role of maternal diet in preventing the development of eczema in the offspring remains controversial.

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Introduction

Atopic eczema is an inflammatory disorder of the skin characterised by pruritis, a typical distribution of eczematous skin lesions, a chronic relapsing course and a personal or family history of atopic disease.¹

The disease often begins early in infancy. Although there is a paucity of data on the prevalence of atopic eczema in South Africa, the International Study of Asthma and Allergies in Children (ISAAC) Phase I study reported a prevalence of 5–10% in Cape Town school children.² Eczema is the most common cause for consultation with a dermatologist. The condition may be triggered by a range of external and internal factors, acting singly, or in combination. Not all eczematous skin diseases are atopic. Table I provides a list of the different forms of eczematous skin diseases.¹

In Figure 1, the World Allergy Organization (WAO) classification of eczema/dermatitis illustrates how atopic eczema fits into the general spectrum of dermatitis.³ This article will deal specifically with elements in the management of the allergic aspects of atopic eczema, although the principles of overall management are the same for both atopic and non-atopic eczema.

Table I: Eczematous skin diseases¹

Classification of eczematous skin diseases	
Disease	Feature
Allergic contact dermatitis	Provoked by local contact with allergen Haematogenous/drug induction possibly with allergen
Photoallergic dermatitis	Provoked by local contact plus UV radiation Haematogenous/drug induction possibly
Atopic dermatitis/ neurodermatitis	Extrinsic type (i.e. atopic dermatitis) Intrinsic type (i.e. neurodermatitis)
Irritant contact dermatitis	Provoked by local contact
Phototoxic dermatitis	Provoked by local contact plus UV radiation
Seborrhoeic dermatitis	Provoked by <i>Malassezia sympodialis</i> plus endocrine factors
Nummular dermatitis/ discoïd eczema	Provoked by inflammatory focus
Varicosis dermatitis/stasis eczema	Provoked by a state of chronic venous insufficiency

The term “eczema” describes an aggregation of several skin diseases with clinical characteristics which involve a genetically determined skin barrier defect. Addressing the barrier defect dysfunction is thus the foundation of management for all forms of eczema.⁴

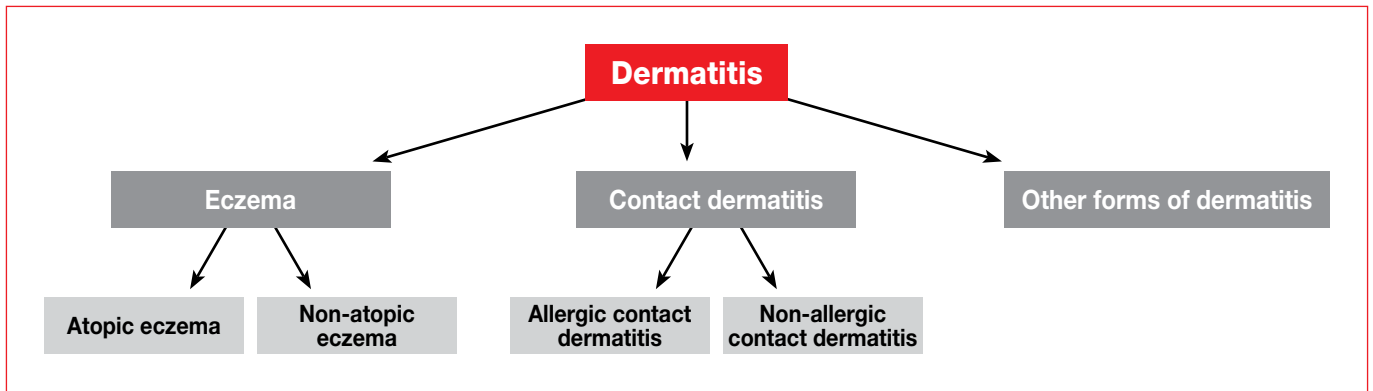


Figure 1: The new World Allergy Organization (WAO) classification of eczema/dermatitis (2004)³

Although atopic eczema is more frequently seen in affluent communities, a South African study conducted by Todd et al⁵ among Xhosa children found a point prevalence of dermatologist-diagnosed eczema of 0.7%, 1.1% and 3.7% in rural, peri-urban and urban settings, respectively.

Pathophysiology

There is increasing evidence that T cell responses to environmental or food allergens are important in the pathogenesis of atopic eczema.¹ The extrinsic variant, with sensitivity to food and inhalants is found in about 25–30% of eczema patients overall, but more commonly identified in younger children and in infants with atopic eczema (about 60%).⁴ The intrinsic variant has all the typical features of atopic dermatitis in the absence of elevated IgE levels. T cells may play a more dominant role in the intrinsic group, but both groups have a significant barrier defect.

In the extrinsic type the total IgE may be markedly elevated (more than 1 000 kU/L). Neural factors such as acetylcholine and substance P also play a role and some patients experience exacerbations when exposed to nonspecific (e.g. temperature, sunlight) as well as specific triggers, such as food and inhalants.¹

Patterns of reactions to foods

At least three cutaneous patterns are recognised following an oral challenge with a food in patients with eczema.⁶

Type I is an immediate reaction, such as urticaria, angioedema and erythema, occurring within minutes of ingestion. In addition, gastrointestinal, respiratory and cardiovascular symptoms may evolve. This is a typical Type I Gell and Coombs reaction, usually IgE mediated.

Type II is a pruritis reaction which occurs soon after ingestion (within an hour) and is followed by scratching and an exacerbation of the eczema, often IgE mediated.

Type III is a late reaction occurring 6–18 hours after ingestion, manifesting as an exacerbation of atopic dermatitis usually not dominantly IgE mediated, but may involve T cells, IgE epsilon bearing Langerhans cells and mast cells.

Diagnostic considerations

Factors which assist the clinician to make a clinical diagnosis include a family history, the presence of pruritis affecting the flexural area of the arms, knees, behind the neck or on the face, onset before the age of two years, other atopic disease (e.g. asthma, rhinitis, food allergy) and usually a good response to topical steroids (within a few days) and a poor relief of itching following non-sedating antihistamines.⁴

Prevalence of allergy in atopic dermatitis

Sicherer et al⁷ confirmed food allergy in 60% of a selected population of children with atopic dermatitis. The clinical profile of an exacerbation by food depends on whether the eczema is in an active phase or in remission.

A double-blind placebo-controlled food challenge (DBPCFC) in children in remission resulted in pruritis and urticaria, whereas a DBPCFC conducted in children with active disease resulted in eczematous eruptions.⁸

Food allergy is more likely to be present in more severe disease, particularly in children.⁹

Identifying food as a relevant trigger in the presence of a positive specific IgE test is relatively easy when the reaction follows soon after ingestion of the allergen.

It is however much more difficult to completely attribute delayed reactions to foods. For such reactions the clinician looks for an eczematous response occurring 4–6 hours after ingestion of the food. For challenge purposes the suspected food should be given over a period of two days after two challenge-free days. Guidelines for challenge procedures in children have been published by Bindslev-Jensen¹⁰ in a European Academy of Allergy and Clinical Immunology position statement.

In patients with atopic eczema who are sensitive to house dust mites, intensive house dust mite avoidance measures, including hot washing of the bed at 60°C and the application of mite impermeable bed, mattress and duvet covers play an important role in reducing the severity of symptoms.

Confirmation of the diagnosis of food allergy

The diagnosis is suggested by a detailed history followed by careful skin prick tests or ImmunoCap® RAST tests. Confirmation of the diagnosis may be made by open or double-blind placebo-controlled food challenge.

To avoid conducting unnecessary food challenges it is useful, in children with eczema, to apply the 100% cut off values for skin prick tests⁹ or Cap RAST tests⁸ which will predict a positive food challenge (see Tables II and III).

Table II: Positive predictive values for skin prick tests (for open food challenge)⁹

	Older children	Infants ≤ 2 years
Cow's milk	8 mm	6 mm
Eggs	7 mm	5 mm
Peanuts	8 mm	4 mm

Table III: Specific IgE predictive values (for positive food challenges)⁶

Allergen	kU/L	PPV
Eggs* (> 2 years)	7	98
Milk* (> 2 years)	15	95
Peanuts	14	100
Fish	20	100
Tree nuts	15	95
Soy bean	30	73
Wheat	26	74

* For children less than two years, cut off values for egg and milk are 2 kU/L and 5 kU/L with a 95% positive predictive value respectively⁶ PPV: positive predictive value

Although the cut off values for wheal size or IgE level are highly predictive for positive challenge results some patients with lower values may also react with a positive challenge. The positive predictive value for eczematous reactions is 33% and 77% for other immediate reactions to the food challenge¹¹. The diagnostic significance of specific IgE values appears to be greater in children under 2 years, after which many eczema children “outgrow” their clinical sensitivity to the allergen, and specific IgE values fall with time.

A proper understanding of the indications and limitations of the ImmunoCap® values and skin prick testing results is essential to plan appropriate diets for children with atopic eczema. A negative open challenge will confirm the absence of food allergy and a positive double-blind placebo-controlled food challenge will irrefutably confirm clinical allergy suggested by the results of testing. If one considers the result of every immunologically positive test result to be clinically significant, there is a real danger of restricting many important foods unnecessarily leading to poor nutrition, especially in young children.

Previous evidence⁷ suggested that in high risk families for allergies, exclusive breastfeeding would reduce the development of atopic eczema. However, local studies conducted in poor urban South Africans indicate that the

protective effects of breastfeeding are overridden by a strong maternal history of allergy, i.e. breastfeeding tends to protect the development of allergy in non-allergic but not in allergic families.¹²

If mothers are unable to breast feed, a completely hydrolysed formula feed (e.g. Alfare® Nutramigen®) is recommended to prevent sensitisation. A partially hydrolysed formula such as Nan-HA® may also be given. However the mother should also avoid ingestion of cow milk proteins.

There is no evidence¹³ that substitution of breast milk with soya milk will prevent allergic sensitisation. However, in children with established and confirmed cow milk allergy, soya may be used as a good substitute for cow milk.

The importance in identifying whether the child with eczema has atopic disease and is sensitised to food with elevated specific IgE, lies in the fact that 30% of these infants are likely to follow an “atopic march”, going on to develop allergic rhinitis and allergic asthma. Early avoidance of inhalant allergen (e.g. dust mite) exposure in such infants may be beneficial. In a recent study there was no evidence that treatment of eczema infants with cetirizine will prevent the development of asthma, but there was a preventive effect on the development of urticaria.¹⁴

Treatment of atopic eczema

General principles

These include avoidance of known trigger factors, prevention of drying of the skin and specific anti-inflammatory therapy.

The South African Childhood Consensus document⁴ reported consensus in applying the following measures:

- Avoid overheating and external irritants.
- Keep the skin covered with clothing to reduce irritants and trauma from scratching. Many exacerbations are induced by bacterial infection, particularly staphylococcus aureus and topical and systemic antibiotics may be required when exacerbations are severe.
- Avoid irritants such as astringents and soaps.
- Avoid wool clothing or clothing with high texture or occlusive properties, cotton being preferable.
- Avoid excessive hand washing.
- Regular bathing assists in the hydration of the skin.
- Use a moisturising cleanser such as HEB rather than antibacterial cleansers. Aqueous creams may cause cooling through evaporation and may be more soothing in acute flare ups. Ointments stick longer.
- Apply emollients immediately after bathing.
- Avoid foods to which the child has clinically relevant sensitivity.
- Apply house dust mite measures on the bedding and floors for those sensitised to house dust mites.

Emollients

Although the literature lacks evidenced-based publications on the use of emollients, opinion base is strong on their value as first line agents for the topical management of children and adults with eczema, to address the barrier defect present in all eczema children and to prevent dryness of the skin.^{4,15}

Ointments and creams are preferred over lotions and should be applied frequently, at least four times in a 24-hour period. Sufficient quantities need to be supplied, e.g. 250 g/week for children and 500 g/week for adults to cover the whole body.

Slight burning may occur, however, with the urea containing products. Some with severe disease will benefit from wet wraps especially at night, where emollients are combined with topical steroids.

Topical steroids

Topical steroids confer significant benefit to patients with atopic eczema. There are many different topical steroid products with different strengths, making it difficult to compare different steroids. Table IV compares the potency of common different topical steroids⁴ available in South Africa.

Table IV: Degree of potency of topical cortisone preparations⁴

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

It is important to bear in mind that the vehicle used for a topical steroid may enhance its efficacy (e.g. fatty base) and that topical steroids are all effective if used once daily. There is no evidence to confirm that skin thinning is a problem with the correct use of topical corticosteroids. Creams are generally preferred for treatment of the face.

It is recommended that mild to mid-potency topical steroids should be used in conjunction with emollients as standardised disease management and that more potent steroids should be used for relief of acute flares for shorter periods.³

For young children, a 1% hydrocortisone cream is advised for mild to moderate eczema, especially for the face. To maintain control, once a remission has been induced, topical steroids can be used twice weekly. High potency steroids are also indicated for areas of lichenification of the skin. As inflammation subsides, use less topical steroids and more moisturiser. It is preferable to apply corticosteroids immediately after bathing. Steroids supplied in a fatty base are particularly useful for the treatment of very dry areas, especially on the knees and lower legs and in chronic cases with very dry skin.

Adverse events to corticosteroids include cutaneous skin atrophy, telangiectasia, hypopigmentation, steroid acne, increased hair growth and rosacea-like reactions.^{4,16} Systemic side effects such as suppression of the hypothalamic pituitary adrenal axis, growth retardation, glaucoma, cataract and Cushing's syndrome are rare.

Antihistamines

The value of antihistamines in atopic dermatitis is debated. Patients usually obtain minimal or no relief of pruritis from the use of non-sedating antihistamines. Some patients derive relief from the use of sedating antihistamines, such as Aterax® (Hydroxyzine 25 mg) (or 1 mg/kg/24 hrs) used at night, to ensure a good night's rest and relief of itch. In larger patients, higher doses may be required. Topical antihistamines may cause sensitisation and should thus be avoided.

Calcineurin inhibitors

Pimecrolimus has been approved in South Africa for short-term treatment of "flare ups for atopic eczema in children over the age of 2 years".⁴ Short-term treatment followed concerns that resulted in a black box warning by the FDA, until further long-term surveillance studies have been completed. Five year surveillance studies on safety have been completed and publications of these studies are awaited. Patients on pimecrolimus require adequate sun protection creams as well.

Tacrolimus is registered for the treatment of eczema in South Africa, and experience with this non-steroidal topical eczema treatment is promising. Steroid phobia is a recognised problem in patients with eczema and calcineurin inhibitors do provide an alternative for selected patients.

Other specialised treatments for eczema

Although there are few studies focussing on the clinical efficacy of tar preparations in the treatment of eczema, they may be effective if administered topically or in a bath tub,¹¹ however cosmetic side effects may affect compliance with such preparations.

Phototherapy may also be used under the supervision of a specialist dermatologist for the management of severe cases of eczema and is available as conventional UVA/UVB combination therapy, UVA therapy, photo chemotherapy with methoxsalen plus UVA (PUVA) and narrowband UVB (312 nm). PUVA therapy may be associated with severe side effects including the development of cutaneous neoplasms.³

Cyclosporin is also effective for the treatment of severe atopic eczema and may induce prompt relief of symptoms, but relapses are common, after stopping therapy. It may be given in 12 week cycles with at least seven days between each course to achieve a lower cumulative dose. It is important that renal function is carefully monitored.¹⁷

Systemic corticosteroids are known to be effective in the short term for atopic eczema, but their use is invariably followed by

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References:

1 Package Insert

2 Zaumseil R-P, et al. Methylprednisolone aceponate (Advantan) - an effective topical corticoid therapy with few side effects. *Jahrbuch der Dermatologie* 247-263 (1992/93)

For full prescribing information refer to the package insert approved by the medicines regulatory authority (MCC).

S4 Advantan cream, Ointment, Fatty Ointment, Milk, Scalp Solution. Contains methylprednisolone aceponate 1 mg/g/ml. **PHARMACOLOGICAL CLASSIFICATION.** A. 13.4.1 Corticosteroids without anti-infective agents. **INDICATIONS.** Eczema. **DOSAGE AND DIRECTIONS FOR USE.** For external use only. Apply thinly once per day to the diseased areas of skin. Duration of use should not generally exceed 12 weeks in adults and four weeks in children. **CONTRA-INDICATIONS.** Tuberculous or syphilitic processes in the area to be treated; virus diseases. Advantan should not be used during pregnancy. **PRECAUTIONS.** If a secondary microbial or fungal skin infection is present a suitable concomitant anti-microbial or anti-mycotic therapy should be instituted. Use with particular caution in facial dermatoses, and only for short periods. A steroid rosacea-like facies may be produced. Do not apply to the face if rosacea or perioral dermatitis is present. Avoid contact with the eyes. Use with caution in nursing mothers. Review regularly the necessity for continuing therapy. Do not use in the nappy areas in infants for flexural eruptions. Ideally it should not be applied to infants and young children. The treatment of psoriasis with potent topical corticosteroids may provoke the pustular form of the disease. Do not apply to skin crease areas. **SIDE EFFECTS.** Local concomitant symptoms such as itching, burning, erythema or vesiculation may occur. The following side effects may occur: folliculitis, hypertrichosis, perioral dermatitis, allergic skin reactions to one of the ingredients of the formulations. Avoid long-term continuous treatment with topical corticosteroids as far as possible as this may cause allotropic changes in the skin, particularly on the face and when occlusive dressings are used. Acneiform skin conditions can occur under therapy with potent corticoids. Systemic absorption of topically applied corticosteroids may occur, particularly when large quantities are used, or when application is made to wide areas of the body, or to damaged skin, when potent topical corticosteroids are used, and when the occlusive dressing technique is applied. Depression of the hypothalamic-pituitary-adrenal axis with consequent suppression of the adrenal gland may occur. The effects are most likely to be severe in children. Growth may be retarded and a Cushingoid state may be produced. To date no clinical data are available for the use of Advantan Scalp Solution in children. **REGISTRATION NUMBER.** Advantan Cream: X/13.4.1/384, Advantan Ointment: X/13.4.1/385, Advantan Fatty Ointment: X/13.4.1/386, Advantan Milk: 32/13.4.1/0362, Advantan Scalp Solution: 32/13.4.1/0361

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rebound flare ups and there are significant dangers of systemic steroid side effects with long term use. Toxicity also limits the potential use of azathioprine, or interferon gamma and none of these three treatments should be prescribed by a general practitioner. Treatment with gamma interferon is still regarded as experimental.

Probiotics such as *Lactobacillus rhamnosus* (ATCC 53103) administered to at-risk infants in the first two years of life has been reported to reduce the risk of development of atopic eczema.¹⁸ More studies are needed and a firm general recommendation for the early use of probiotics to prevent eczema in high risk families cannot be made.⁴

Systemic antibiotic treatment is indicated for widespread secondary bacterial infection primarily *S. aureus*. First or second generation cephalosporins or semi synthetic penicillins for 7–10 days are usually effective. Erythromycin-resistant organisms are fairly common making macrolides less useful alternatives.¹⁹ In cases of penicillin or cephalosporin allergy, clindamycin or oral fusidic acid are possible alternatives.²⁰

Maternal diet and prevention of eczema

There is ongoing debate as to whether breastfeeding is protective for the development of atopic eczema in the offspring. In a recent study by Yan et al²¹ sensitisation to egg was higher in a breast fed group compared to a formula-fed group of infants. In another recent study by Saito et al²² it was found that higher maternal meat intake may increase the risk of infantile atopic eczema and that there was no evidence that maternal intake of fish and n-3 polyunsaturated fatty acids protected against infantile atopic eczema.

Treatments with no proven benefit

Although exposure to house dust mites may exacerbate eczema flares in patients sensitised to house dust mites, there is no evidence that allergen immunotherapy is beneficial either by the subcutaneous or sublingual route.³ However, new studies on this are in progress.

Likewise, Chinese herbal medicine, ingestion of unsaturated fatty acids (e.g. evening primrose oil), homoeopathy, acupuncture, climatotherapy, African traditional medicine and massage therapy have no evidence-based efficacy and are thus not recommended for the treatment of atopic eczema.⁴

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