

Clinical review article: Atopic and non-atopic eczema and its management

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Methods

The following sources of information were used to write this review:

- PubMed search using the key words 'atopic eczema', 'atopic dermatitis', 'incidence', 'genetics', 'pathogenesis', 'treatment' and 'management'. Preference was given to original articles published in the last 3 years and recent review articles published in high-impact journals.
 - Search of the following Cochrane Library Databases: Cochrane Database of Systemic Reviews; Database of Abstracts and Reviews of Effectiveness; Cochrane Central Register of Controlled Trials.
- Personal archive of references

Introduction

Atopic eczema is a chronic, relapsing, inflammatory skin condition, associated with epidermal barrier dysfunction.

This article aims to provide an up to date summary of current knowledge regarding eczema and its management. A comprehensive review of this complex and rapidly-advancing field is out-with the scope of this article and interested readers are referred to bmj.com web extra as well as the specialist reviews in Box 1.

How do we define atopic eczema?

A definition based on clinical features¹ is shown in Box 2.

Atopic eczema and atopic dermatitis are terms that have been used synonymously, but a review committee of the World Allergy Organisation² has recommended the terminology illustrated in Box 3.

Eczema is subdivided into atopic and non-atopic eczema because a significant proportion of patients exhibit eczema without atopic features². Children with atopic eczema are at greater risk than those with non-atopic eczema of developing asthma later in life⁴ and their eczema more commonly persists into adulthood.^{2 7} However, there is no evidence that atopic and non-atopic eczema respond differently to treatment and patients with non-atopic eczema may subsequently develop atopic features.

The results of future studies relating clinical features, pathogenesis and molecular genetics are eagerly awaited with the hope that a clearer understanding will lead to more accurate sub-classification of eczema.

Why is eczema important?

Itch as a symptom is often underestimated in terms of the problems that it can cause.^{8 9} Sleep disturbance and worries about appearance are frequently reported⁸ as well as feelings of guilt and frustration as a consequence of a child's eczema.¹⁰

Whilst the effects of total sleep deprivation on human health are well recognised, recent studies have highlighted that recurrent, partial sleep disturbance, as often occurs in patients with atopic eczema¹¹, also results in significant neurocognitive impairment¹².

When taken together, the social/emotional and financial effects on a family looking after a child with moderate to severe eczema appear greater than caring for a child with type I diabetes¹³.

Box 1. Recommended key review articles for further reading.

- Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. **New insights into atopic dermatitis.** *J Clin Invest* 2004; **113**(5): 651-7.
This gives a detailed review on the pathophysiology of eczema and implications for new management strategies.
- Williams HC. **Atopic Dermatitis.** *N Engl J Med* 2005; **352**(22): 2314-24.
This review is written from the perspective of a clinical scenario.
- Hoffamn S, Epplen JT. **The genetics of atopic dermatitis: recent findings and future options.** *J Mol Med* 2005; **83**: 682-92.
This is a comprehensive review of the current knowledge regarding the genetic basis of atopic eczema.
- Cookson W. **The immunogenetics of asthma and eczema: a new focus on the epithelium.** *Nat Rev Immunol* 2004; **4**(12): 978-88.

This review discusses the immunological mechanisms of eczema, with helpful diagrammatic illustrations.

- Hoare C, Li Wan Po A, Williams H. **Systematic review of treatments for atopic eczema.** *Health Technol Assess* 2000; **4**(37).
This document summarises the evidence available from randomised controlled trials of treatments for atopic eczema published up to 2000.

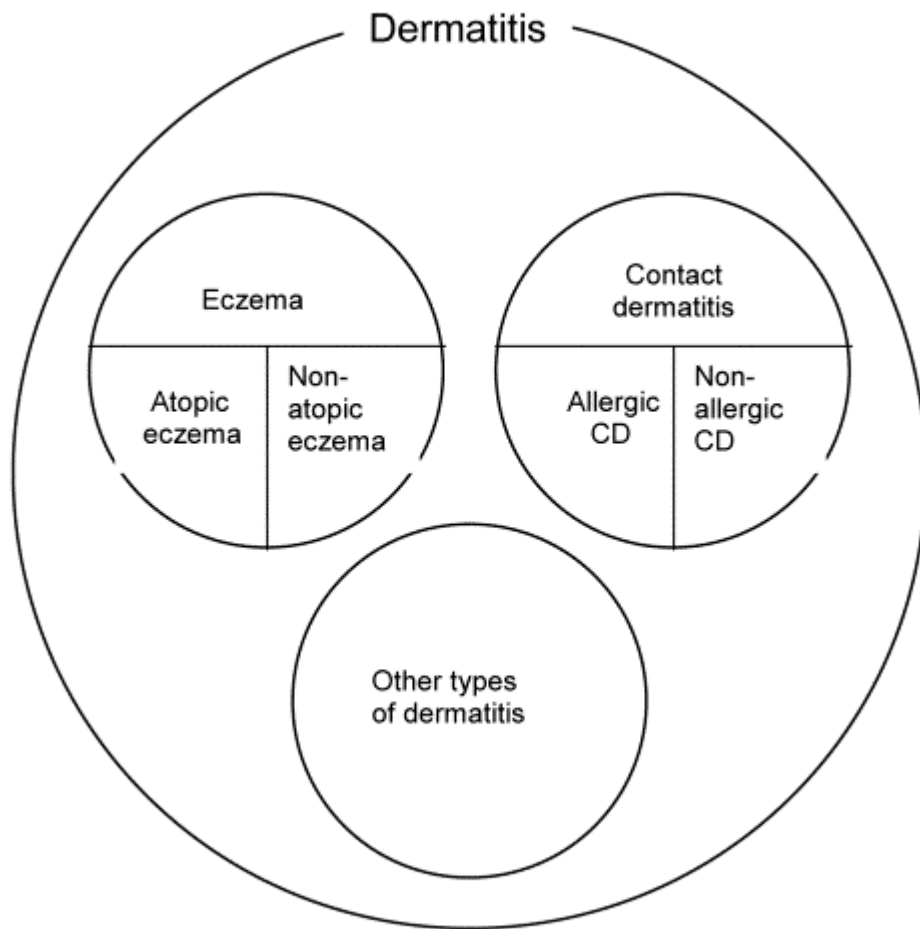
Box 2. Definition of atopic dermatitis – the UK refinement of the Hanifin and Rajka Diagnostic Criteria¹.

In order to qualify as a case of atopic dermatitis, an individual must have:

- An itchy skin condition in the last 12 months
- Plus three or more of the following:
 1. Onset below the age of two years
(not applicable in child under 4 years)
 2. History of flexural involvement
 3. History of generally dry skin
 4. Personal history of other atopic disease
(or history in first-degree relative if child is under 4 years)
 5. Visible flexural dermatitis.

These diagnostic criteria have been validated in hospital¹ and community³ settings have used in many epidemiological research studies worldwide.^{5 6}

Box 3. Diagrammatic illustration of the different subgroups of 'dermatitis'.



Some patients may have a combination of different types of dermatitis; this review focuses on atopic and non-atopic eczema.

Allergic CD – allergic contact dermatitis

Non-allergic CD – non-allergic contact dermatitis (irritant dermatitis)

Other types of dermatitis include nummular (discoid) eczema, photosensitive dermatitis and seborrhoeic dermatitis.

This classification is based on the World Allergy Organisation Nomenclature.²

Clinical features of atopic eczema

- Acute and chronic or relapsing skin inflammation
- Pruritus (itch)
- Erythema (redness) and scaling in ill-defined patches
- Tiny fluid-filled vesicles - often seen in acute eczema; break-down produces weeping lesions which may dry to produce crusting
- Lichenification (thickening of the skin with an increase in skin markings) - can occur in chronic eczema because of repeated scratching

- Limb flexural involvement is characteristic but infants and adults may show predominantly facial involvement and any part of the skin surface may be affected
- Features frequently associated with atopic eczema include:
 - Xerosis (dry skin with fine scale)
 - White dermographism – scratching the skin produces a line of pallor
 - Raised serum IgE
 - Positive skin prick tests demonstrating type I (immediate) hypersensitivity
- Erythrodermic eczema is defined as greater than 90% of body surface area involvement.



Figure 1: Atopic eczema on the shoulders and back, showing ill-defined patches of erythema and multiple excoriations.



Figure 2: Atopic eczema on the arm flexures showing crusting associated with *Staph aureus* infection.



Figure 3: Atopic eczema on the posterior neck, showing erythema, scale and lichenification.

Epidemiology

Is the incidence of atopic eczema rising?

The prevalence of atopic eczema varies widely between populations with estimates of less than 2% in Chinese and Iranian children but up to 20% in northern and western Europe, Australia and the United States.¹⁴⁻¹⁸ Many studies have demonstrated an increasing prevalence,^{16 19-22} but some recent research has suggested stable prevalence²³ and incidence.²⁴

The importance of environmental factors

The recent increase in prevalence cannot be explained by genetic change and environmental influences must therefore play a role in phenotypic expression. Migrant studies suggest a strong link between atopic eczema and environmental factors.²⁵ A higher incidence of atopic eczema is associated with urban/industrial settings, smaller families, lower birth order and higher socioeconomic status.²⁶

These observations have contributed to the so-called 'hygiene hypothesis' *ie* that infections early in life give protection against the development of atopic disease. Some but not all research findings support this hypothesis.^{27 28}

Little is known about the role of dietary factors in the aetiology of eczema. A protective effect of breastfeeding has been postulated but the evidence is conflicting.^{6 29-31} A Cochrane review concluded that there is inadequate evidence to advise women to avoid specific foods during pregnancy or breastfeeding with the aim of protecting their children from atopic diseases.³²

Pathophysiology – what do we know?

The clinical phenotype of 'eczema' has a multifactorial aetiology and the pathophysiology is incompletely understood.

Immune dysfunction

Multiple inter-related components of the immune system have been investigated in the context of atopic eczema and shown to be dysfunctional.

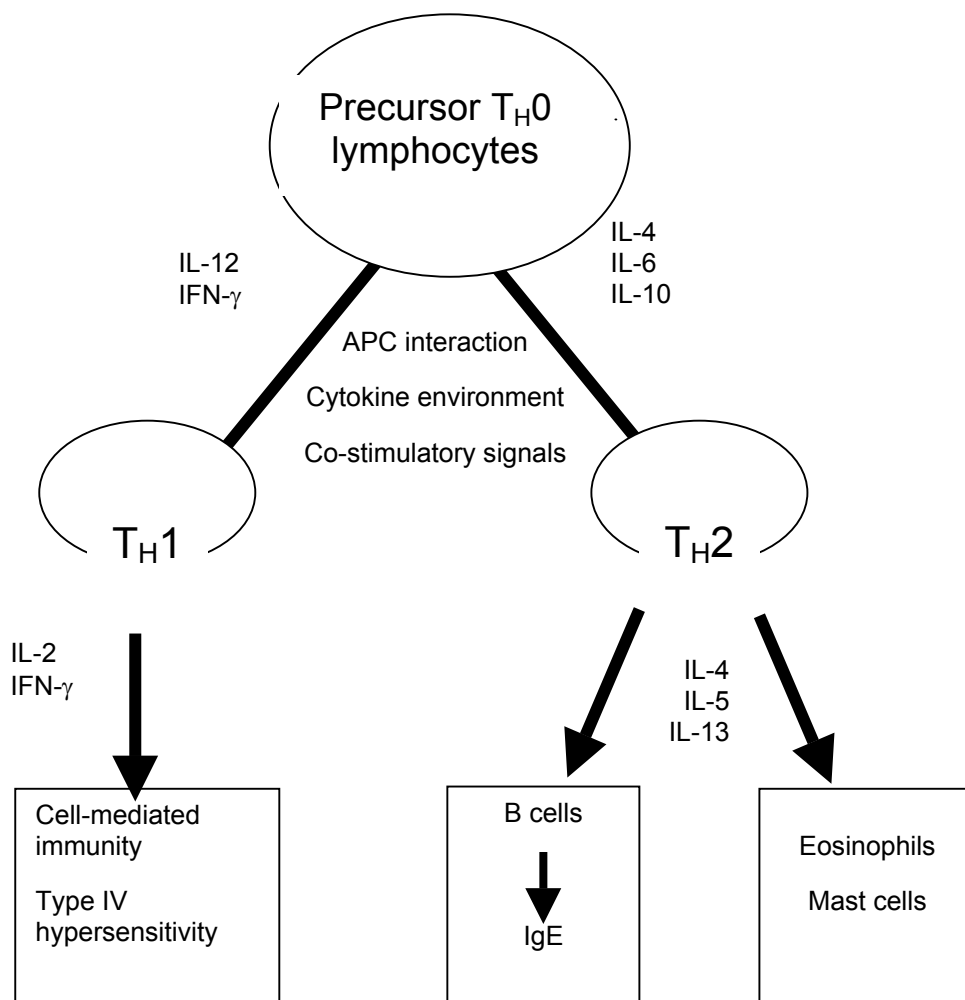
- **T-lymphocytes.**

The predominance of T_H2 over T_H1 subtypes in the systemic immune response is thought to be responsible for the first step in the 'atopic march' of eczema leading to allergic rhinitis and asthma.³³ In skin there appears to be a biphasic response, with T_H2 predominance in acute lesions and T_H1 in the chronic phase;³⁴ the reasons for this are unclear.

The differentiation of T-helper lymphocytes from T_H0 precursors is controlled by the cytokine environment at the time of interaction with antigen presenting cells³⁵ (see diagram in box 4). Compared with normal skin, biopsies of both acute and chronic atopic eczema lesions show more cells expressing messenger RNA (mRNA) for interleukin 2 (IL-2), IL-5 and IL-13.^{w2136 37} However, chronic lesions compared to acute lesions show significantly more IL-5 and IL-12 mRNA-expressing cells and fewer IL-4 and IL-13 mRNA expressing cells.³⁸ IL-12 may be pivotal in the switch from T_H2 in the acute phase to T_H1 in the maintenance/chronic phase.³⁹ Preferential apoptosis of circulating memory/effector T_H1 cells may contribute to the predominance of T_H2 over T_H1 subtypes. (Akdis, 2003)

T-regulatory cells (CD4+ CD25+ Tregs) have recently been identified as key regulators in immune processes and the maintenance of tolerance^{40 41} and it may emerge that the focus on T_H1/T_H2 balance may be an over-simplification of the true situation.

Box 4. The differentiation of T-helper lymphocytes.



The differentiation of T-helper (T_H) lymphocytes.³⁵

This simplified schematic diagram illustrates some important factors affecting the differentiation of T-cell subtypes:

Precursor T_{H0} lymphocytes are able to differentiate into T_{H1} or T_{H2} cells. This differentiation is controlled by the presence of cytokines at the time of interaction with dendritic antigen presenting cells (APC) and their cell-surface co-stimulatory molecules.

Interleukin-12 (IL-12) is required for T_{H1} differentiation and IL-4 drives T_{H2} differentiation.

T_{H1} cells produce IL-2 and interferon gamma (IFN-γ) and are effector cells in cell-mediated immunity and type IV (delayed-type) hypersensitivity.

T_{H2} cells produce IL-4, IL-5 and IL-13. These cytokines stimulate B-cells to produce IgE and also result in the activation of eosinophils and mast cells.

- **Keratinocytes.**

Barrier function is disturbed in the clinically uninvolved skin of patients with atopic eczema as well as in the eczematous lesions. Keratinocytes are not simply inert structural components of skin; they are primary inducers of cutaneous immunological reactions⁴² via the production of chemokines and cytokines including interferon-gamma.^{43 44} IL-1, IL-4 and TNF-alpha induce adhesion molecules which direct lymphocytes, macrophages and eosinophils to the cutaneous site of inflammation.^{38 43 45} There is also evidence that keratinocytes may act as 'non-professional' antigen presenting cells.⁴² Furthermore, induction of keratinocyte apoptosis by activated T-cells through interferon-gamma and Fas appears to be an important event in the development of eczematous lesions.⁴⁶

Keratinocytes produce ceramides which are important in the maintenance of the skin barrier; ceramide deficiency leads to barrier dysfunction in atopic eczema.⁴⁷ Keratinocytes in atopic dermatitis are also deficient in their ability to synthesize antimicrobial peptides (eg human beta-defensin and LL-37) needed for the innate immune response to microbes.^{43 48} This may contribute to the increased susceptibility to both bacterial and viral infection.

Finally, two recently published studies showed that over-expression of the cytokine thymic stromal lymphopoietin within epidermal keratinocytes results in an eczematous skin phenotype with raised serum IgE and increased T_H2 CD4⁺ T-cells^{49 50}. Although correlation with clinical features of atopic eczema in humans is not entirely straight forward these models illustrate that dysregulation of epidermal cytokine production can drive both cutaneous and systemic inflammation.

- **Antigen presenting cells.**

Eczematous skin shows increased levels of CD1a-positive Langerhans cells which express the high-affinity IgE receptor (FcεRI) on their surface.⁵¹ This plays a role in allergen presentation to T_H1 and T_H2 lymphocytes.

Atopic eczema lesions also contain another population of CD1a-positive dendritic epidermal cells called inflammatory dendritic epidermal cells (IDECs) that are not found in normal skin.⁵² IDECs express FcεRI on their surface as well as large amounts of the co-stimulatory molecules CD80 and CD86 necessary for T cell activation and proliferation. They also release pro-inflammatory cytokines (eg. IL-12, IL-18 and interferon-gamma).⁴³

A third type of antigen presenting cells called plasmacytoid dendritic cells (pDCs) have recently been identified³⁸ which produce large amounts of IFN-α and IFN-β.⁵³ pDCs are absent from atopic eczema lesions and this may explain in part the susceptibility to viral infection (eg eczema herpeticum).

- **Eosinophils and immunoglobulin E.**

The pathological roles of allergen-specific IgE and cross-linkage in immediate hypersensitivity as well as IgE-dependent late phase reactions and IgE autoreactivity⁴⁴ remain controversial; some authors believe these to be important mechanisms^{2 38 54} whilst others argue that they are simply epiphenomena.⁵⁵

Are 'allergies' important?

It is well established that immune sensitization in patients with atopic eczema occurs to common food and environmental allergens.⁵⁶⁻⁵⁸ This can be demonstrated by prick testing, atopy patch testing⁵⁹ and the measurement of specific IgE levels. However, whether these immune reactions are of pathogenic importance in precipitating or maintaining atopic dermatitis remains controversial. For example, a placebo-controlled double-blind trial showed that various house dust mite reduction measures could improve severe atopic eczema⁶⁰ but this finding was not reproduced in a more recent study with similar design.⁶¹

Clinical experience suggests that food allergy is not commonly an important factor in the relapse of atopic dermatitis; in the small number of patients where food allergy is significant, this is usually obvious to the patient or their carers.⁵⁶

Non-allergic factors

- **Irritants** eg detergents disrupt the barrier function of skin and may precipitate flare-ups of pre-existing dermatitis.
- **Pruritus and scratching.** Pruritus results in scratching behaviour that causes additional damage to the skin barrier, predisposing to secondary infection. This perpetuates the so-called 'itch-scratch cycle'.
- ***Staphylococcus aureus*** is commonly isolated from eczematous lesions as well as uninvolved skin and overgrowth is associated with relapse of atopic dermatitis.^{62 63} *S. aureus*

superantigens directly stimulate T-cell and macrophage activation;⁴³ Staph exotoxin B also induces IL-5 and IL-13 in atopic eczema.⁶⁴ Increased binding of *S. aureus* to skin is facilitated by T_H2-mediated inflammation as well as deficiencies in antimicrobial peptides in atopic skin.⁴³
48 65

- **Psychological stress** may be an additional environmental stimulus perhaps through neuroimmunoregulation.⁶⁶ Objective investigation is clearly difficult but a recent questionnaire-based study demonstrated that patients with atopic eczema had higher anxiety levels than controls, and trait anxiety was higher than state anxiety suggesting a causal rather than resultant effect.⁶⁷

The genetic basis of atopic eczema

The importance of genetic factors in the aetiology of atopic disease

There is strong evidence to suggest that genetic factors are important in the predisposition to atopic eczema. Twin studies show concordance rates of 0.72-0.86 in monozygotic compared with 0.21-0.23 in dizygotic twin pairs.^{68 69} Eczema and other the atopic disorders show clustering within families.^{70 71} Children whose parents have atopic eczema have a higher risk of developing eczema than children of parents with asthma or hay fever,^{72 73} suggesting additional skin genes may influence the eczema phenotype.

Eczema as a complex trait

Multiple genes interact with environmental factors and there is likely to be considerable genetic heterogeneity within the clinical phenotype of 'eczema'. The search for which genes are important in atopic eczema is ongoing.⁷⁴

To date, three main approaches have been used in the search for genes responsible for atopic eczema: candidate gene association, genome-wide linkage screens and DNA microarray analysis.

• Candidate genes

Many different genes have been studied because of their theoretical roles in the aetiology of atopic eczema; a selection is presented in table 1.

Early research focussed on the β -subunit of the **high-affinity IgE receptor** (FC ϵ RI- β).⁷⁵⁻⁷⁷ Promoter polymorphisms in the **mast cell chymase gene** (CMA1) have shown associations with atopic eczema in some studies but not others⁷⁸⁻⁸⁰. Multiple candidate genes in the cytokine gene cluster on chromosome 5q31-33 have been investigated in small studies with varying methodology and few positive findings have been replicated^{78 81}

Several genes known to be associated with asthma/atopy have been investigated for linkage with atopic eczema but surprisingly they do not appear to share the same genetic loci.^{78 82 83}

Identification of mutations in the **SPINK5** gene (serine protease inhibitor Kazal-type 5) as the cause of Netherton's syndrome⁸⁴ led to the screening of this gene for polymorphisms in patients with atopic eczema, since Netherton's is characterised by an eczematous rash and elevated IgE. SPINK5 polymorphisms have been associated with atopic eczema in cohort studies from Britain,⁸⁵ Japan^{86 87} and Germany⁸⁸ although this finding was not replicated in a recent study in Northern Germany.⁸⁹ SPINK5 encodes a serine protease inhibitor which is expressed in epithelial surfaces.^{82 90} Its mechanism of action in the aetiology of eczema is as yet unknown but it may provide protection against other serine proteases which are allergenic.⁸⁵

Candidate gene	Locus	Rationale	Evidence	References
FCεR1-β (high-affinity IgE receptor)	11q13	Known linkage to atopy.	Linkage of atopic eczema to 11q13 has not been consistently found.	75-77
CMA1 (mast cell chymase)	14q11	Known role of mast cell degranulation in atopy.	Promotor polymorphisms are associated with eczema in some studies but not all.	78-80
IL-13	5q 31	Produced by T _H 2 cells and up-regulated in eczematous skin.	Two functional SNPs identified with associations to eczema and atopy.	78 81
IL-4RA (α-chain of IL-4 receptor)	16p11.2-12.1	IL-4 plays a key role in the T _H 2 response. The α-chain of IL-4 receptor is shared with the IL-13 receptor.	Several haplotypes studied but no consistent association with atopic eczema.	Reviewed in ⁷⁸
IL-12RB1 (IL-12 receptor β1)	5q33-34	IL-12 promotes differentiation of the T _H 1 subset, hence reduced gene transcription may favour the T _H 2 response.	Promotor polymorphisms in IL-12RB1 are associated with increased risk of atopic eczema, possibly via a reduction in gene transcription.	91
IL-18	11q22.2–q23.3	IL-18 enhances IL-4 and IL-13 production and hence increased IgE. Serum IL-18 increases in eczema patients when their disease is active.	SNPs in IL-18 gene promoter regions showed association with atopic eczema in a German case-control study.	92
RANTES (regulated upon activation, normally T-cell expressed)	17q11.2-q12	Known role of T-cells in atopic eczema.	Gene associated with atopic eczema but not asthma in a German study; finding not replicated in a Hungarian population.	93 94
SPINK5 (serine protease inhibitor Kazal-type 5)	5q31	Mutations in this gene which is near the IL-4 cytokine cluster cause Netherton's syndrome.	Polymorphisms associated with atopic eczema in several cohort studies.	85-88
NOD1 (nucleotide-binding oligomerisation domain protein 1)	7p14-p15	NOD1 is a cytosolic receptor for a peptide found in Gram-negative bacterial cell walls.	Several polymorphisms are associated with atopic eczema and other atopic disorders.	95
SCCE (stratum corneum chymotryptic enzyme)	19q13	Role in epidermal desquamation, SCCE cleaves proteins within the stratum corneum.	Screening for variations in a British case-control study has identified a 4 base-pair insertion associated with atopic eczema.	96
ST2 (important receptor for T _H 2 cells)	2q12	ST2 expression induces preferential activation of the T _H 2 response	Functional SNPs in the distal promoter region of the ST2 gene are associated with atopic dermatitis in a Japanese case control study; keratinocytes stain for ST2 expression in acute eczema.	97

Table 2. Candidate genes for atopic eczema, their rationale and experimental evidence. This list is not exhaustive and interested readers are referred to recent specialist reviews for greater detail.⁷⁸

- **Genome-wide screens** have so far been completed in families with atopic eczema from four different populations.⁹⁸⁻¹⁰¹ Regions on chromosomes **3q, 3p, 17q25 and 18q** showed evidence of linkage in two or more studies, suggesting candidate regions for atopic eczema.⁷⁸ Interestingly, only two of these four regions have shown linkage to asthma or other atopic disorders in more than one study⁷⁸ indicating that separate genes may be responsible for eczema. Furthermore, the regions on **1q21, 3q21, 17q25, and 20p** linked to atopic eczema overlap with known psoriasis susceptibility loci⁸² although a recent investigation of the 17q25 locus failed to demonstrate variants in the known PSORS2 psoriasis locus in children with atopic eczema.¹⁰² The co-localisation of eczema and psoriasis genes supports the concept that specific skin genes may influence the eczema phenotype via control of epidermal function, immunity and inflammation.⁸²

- **DNA microarray analysis**

A recent large-scale DNA microarray analysis has shown that four genes encoded on **1q21** show different levels of expression in eczema lesional skin compared with controls.¹⁰³ These findings suggest that epidermal differentiation complex genes may be responsible at least in part for the epidermal barrier dysfunction that is characteristic of atopic eczema. Another, independent microarray analysis¹⁰⁴ has shown an increase in the expression of genes encoding **CC chemokines** in eczematous skin, known to attract T_H2 cells and eosinophils. The functional significance of other new genes and partial DNA sequences identified by DNA microarray analysis remain to be elucidated.¹⁰⁵

Future research strategies

Candidate gene studies and genome-wide screens each have their disadvantages (genome-wide screens require the collection of family material and candidate gene studies rely on the appropriate genes being chosen) and results are notoriously difficult to replicate. The discovery that eczema and other atopic disorders do not appear to share as much common genetic aetiology as was expected has paved the way for further candidate gene studies. These may focus on genes expressed locally in the skin and more specifically involved with epidermal and keratinocyte function.

In the future, **genome-wide association studies** to assess hundreds of thousands of single nucleotide polymorphisms (SNPs) across the genome should be possible. Complex statistical analytical methods will be required to interpret the vast amount of data generated by such an approach¹⁰⁶ but this strategy holds the promise of detecting unexpected links between genes and biological pathways which may lead to novel therapeutic interventions.¹⁰⁷

How to treat atopic eczema

The fluctuating course of atopic eczema and a significant placebo response highlight the need for randomised controlled trials for the evaluation of treatments or interventions. Clinical practice indicates that the management of acute weeping eczema is rather different from chronic lichenified eczema but these factors are not always discussed or included within the entry criteria of clinical trials.

Mild to moderate eczema: emollients and topical steroids

Mild–moderate eczema is very common and patients are usually managed in primary care. The mainstay of treatment remains the appropriate use of emollients and topical steroids. There is a good evidence base supporting the efficacy of topical steroids¹⁰⁸, which need only be applied once daily. Surprisingly however, there is limited evidence to support the beneficial effects of emollients¹⁰⁸ although emollients have been shown to reduce the requirements for topical steroids by up to 50%¹⁰⁹. Short term bursts of potent topical steroid are equivalent to prolonged use of mild steroids¹¹⁰ and prolonged use of intermittent potent steroids (2 days per week) reduced flares compared to emollient¹¹¹.

The importance of a **multi-disciplinary approach** is increasingly recognised especially with respect to patient/family education including information about irritant/allergy avoidance and demonstration of topical treatments. With raised awareness about the side effects from topical steroids, patients and families may otherwise under-treat.

It is important to **recognise complications** such as secondary bacterial infection, eczema herpeticum (herpes simplex virus infection) and skin atrophy induced by the overuse of topical steroids. Indications for referral to secondary care include concern over diagnosis, a poor response to first line therapy or the development of complications.

Moderate to severe eczema: second line treatments

Second line therapies for patients whose eczema has not responded to adequate topical steroids include topical calcineurin inhibitors, ultraviolet (UV) phototherapy and systemic agents. There is good evidence for the efficacy of these therapies but longer term studies to monitor safety are now required as well as comparisons between the different modalities.

• Topical calcineurin inhibitors

The discovery that systemic ciclosporin is an effective treatment for atopic eczema led to the development of topical calcineurin inhibitors, and **pimecrolimus** and **tacrolimus** have been introduced into clinical practice.

Experimental evidence: A recent systematic review¹¹² and meta-analysis¹¹³ found limited evidence that pimecrolimus is more effective than placebo in the treatment of mild to moderate atopic eczema and that tacrolimus is more effective than placebo and mild topical steroids in the treatment of moderate to severe atopic eczema. Since then, a randomised controlled trial (RCT) involving 487 adult patients with moderate to severe atopic eczema has been published which showed that 0.1% tacrolimus was more effective than moderately potent topical steroids at achieving at least a 60% improvement at 3 months (72.6% and 52.3% respectively)¹¹⁴. However formal evidence is lacking for the efficacy of these agents in patients who have failed to respond to topical steroids¹¹³.

Concern regarding side-effects: A sensation of skin burning may be troublesome during the first weeks of therapy; the long term safety profile of topical calcineurin inhibitors is currently unknown. Post-marketing tumour adverse events in patients using topical calcineurin inhibitors combined with reports of lymphoma in non-human primates treated with systemic pimecrolimus has raised concerns. It is therefore currently recommended that topical calcineurin inhibitors are used as second line agents. According to their licence they should be prescribed by doctors with a special interest and experience in skin diseases for short term or intermediate use in patients who have had atopic eczema for >2 years and are unresponsive to conventional therapy. (http://www.fda.gov/cder/drug/advisory/elidel_protopic.htm) (<http://www.nice.org.uk/page.aspx?o=219063>)¹¹⁵

• UV phototherapy: UVB is more effective than UVA

Patients with atopic eczema often report improvement following exposure to natural sunlight. A RCT involving 73 patients with moderate to severe atopic eczema showed that twice weekly narrow band (311nm) UVB for 12 weeks induced a 28% mean reduction in disease activity compared to a 1.3% mean reduction from exposure to visible light (placebo)¹¹⁶. Significant improvement was maintained at 3 months. The treatment was well tolerated but the potential increased risk of skin cancer needs to be explained to patients and monitored in the longer term.

In contrast, UV exposure from conventional sunbeds (predominantly UVA: 315-400 nm) appeared relatively ineffective. High dose UVA1 (340-400nm) improves acute severe eczema¹¹⁷ but specialist irradiation devices are required. A further comparison of narrow-band UVB versus medium dose UVA1 indicated that narrow-band UVB was more effective¹¹⁸.

- **Systemic immunosuppressants: ciclosporin and azathioprine**

Moderate to severe atopic eczema may only be partially responsive to topical agents and may relapse following phototherapy necessitating consideration of systemic agents. Moderate to severe disease occurs more frequently in adults than children and ethical issues mean that the RCTs of systemic agents have principally involved adults.

Oral ciclosporin

Experimental evidence: The efficacy of this systemic calcineurin inhibitor in the treatment of moderate to severe atopic eczema is well established.^{119 120} An open study in adults suggested that 6 week courses of ciclosporin resulted in long term remission of atopic eczema at 1 year¹²¹ but open trials in children suggest that continuous rather than intermittent usage achieved better control.¹²²

Concern regarding side-effects: Careful monitoring is required with prolonged ciclosporin use. Documented side-effects include nephrotoxicity, immunosuppression and predisposition to cancer, particularly cutaneous non-melanoma skin cancer and lymphoma. Direct evidence with respect to atopic eczema is currently confined to case reports^{123 124}.

Oral azathioprine

Experimental evidence: Several open studies suggested that this purine analogue may be effective in moderate to severe disease¹²⁵ and this has been confirmed by two recent RCTs^{126 127}. The results of a cross-over trial using 2.5mg/kg azathioprine showed a 25% improvement in disease activity but 35% of subjects withdrew due to side effects. Using a parallel-group design and dosing azathioprine according to thiopurinemethyltransferase (TPMT, a key enzyme in thiopurine metabolism status), Meggitt *et al* observed a larger mean improvement in disease activity (37%) and a lower drop-out rate of 15%. Sustained improvement for at least 3 months after stopping azathioprine may also occur¹²⁷. In a retrospective open study, Murphy *et al* found that azathioprine resulted in a good/excellent response in 41/48 (85%) children with atopic eczema¹²⁸.

Concern regarding side-effects: Dose-dependent nausea is the commonest side effect, followed by bone marrow and hepatic toxicity. Within the RCTs no participants developed serious laboratory abnormalities although azathioprine hypersensitivity occurred in two patients¹²⁷.

Measurement of TPMT is now recommended prior to initiation of azathioprine therapy. The aim is to exclude patients who have absent TPMT activity because they are at profound risk of developing myelotoxicity¹²⁹ and to facilitate lower dosing in patients who have low TPMT activity¹²⁷. Regular haematological monitoring is still required as polymorphisms in other enzymes may contribute up to 35% of episodes of neutropenia in patients receiving azathioprine¹³⁰.

The longer term risks of azathioprine in atopic eczema are unknown but data from patients with rheumatoid arthritis and inflammatory bowel disease suggests that any risk of malignancy is small^{131 132}.

- **Other systemic agents**

A variety of systemic immunosuppressives, immunomodulators and anti-metabolites have been reported in case series or uncontrolled trials to be of benefit in patients with moderate to severe atopic eczema.

Mycophenolate mofetil (MMF) is an immunosuppressive drug and its active metabolite mycophenolic acid selectively inhibits de novo purine synthesis in lymphocytes through an effect on inosine monophosphate dehydrogenase. Two open trials using 2.0g MMF per day reported improvement in disease activity of 68% median reduction and 55% mean reduction

respectively^{133 134} whereas a third study using 2.0-2.5g daily reported no clinically relevant effect in 5 patients.

Adverse effects of MMF relate principally to its inhibitory effects on the haematopoietic and immune system including leucopenia, lymphopenia and anaemia and require appropriate monitoring but symptomatic side effects include gastro-intestinal disturbance. An increased risk of herpetic infections was reported when mycophenolic acid was originally introduced for the treatment of psoriasis^{135 136} which may be of concern for patients with atopic eczema and indeed one patient developed herpes retinitis¹³⁴.

Probiotics: do they help to prevent atopic eczema?

Probiotics are live bacterial cultures of commensal gut microflora that through oral ingestion may modulate the immune system. They are readily available over the counter as bio-yoghurts, drinks and supplements. Many different bacterial strains have been used, the most common being the lactic acid bacteria lactobacilli and bifidobacteria. Their use as therapeutic agents in atopic disease is based upon the hygiene hypothesis and modulation of T_H1 and T_H2 responses and there is some evidence to support an effect of probiotics on TGF- β and IL-10.

Experimental evidence: A placebo-controlled RCT involving 159 participants demonstrated that *Lactobacillus* GG, administered daily pre-natally to mothers for 2-4 weeks and post-natally to their infants (or breast-feeding mothers) at risk of atopic disease for 6 months, reduced the frequency of eczema from 46% to 23% at 2 years (relative risk 0.51, 95% CI 0.32-0.84), although the severity of atopic eczema and IgE reactivity was similar in the placebo and *Lactobacillus* GG groups¹³⁷. A follow up study involving 107 children of 132 who completed the 2 year follow suggested a persistent beneficial effect of *Lactobacillus* GG at 4 years with respect to frequency of eczema (relative risk 0.57) but not eczema severity, allergic asthma or hay fever. Furthermore the prevalence of eczema in the placebo group was relatively high (46%).

In contrast, there is no evidence to indicate that probiotics improve established atopic eczema. Thus, for example, in a placebo-controlled RCT, two probiotic *Lactobacillus* strains did not significantly reduce the severity of eczema compared to placebo¹³⁸.

Conclusion

Eczema is a common and distressing condition. The aetiology and immunopathogenesis are incompletely understood and therapeutic options are at present relatively limited. It is hoped that developments in the rapidly-advancing fields of research in eczema epidemiology, pathogenesis and genetics will, in the foreseeable future, lead to the development of management strategies that are more specifically targeted to pathogenic mechanisms.

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Conflict of interest statement

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Summary points

- Atopic eczema is an itchy inflammatory skin condition with associated epidermal barrier dysfunction.
- The prevalence of atopic eczema appears to be rising but the factors responsible for this rise are incompletely understood.
- The pathophysiology of eczema involves systemic as well as cutaneous immune and epidermal dysfunction.
- Eczema is a complex trait with significant genetic and environmental influences.
- Emollients and topical steroids are the mainstay of treatment for mild-moderate eczema; moderate-severe eczema may require the addition of second-line agents such as topical or systemic calcineurin inhibitors, UV phototherapy, or systemic azathioprine.

It is expected that a clearer understanding of the genetic basis and hence pathophysiology of eczema will lead to novel therapeutic interventions in the future.

Abbreviations:

IgE	immunoglobulin E
T_H	T-helper lymphocyte
IL	interleukin
mRNA	messenger ribonucleic acid
Tregs	regulatory T-lymphocytes
IDEC	inflammatory dendritic epidermal cells
FcεRI	high-affinity IgE receptor
pDC	plasmacytoid dendritic cell
IFN	interferon
APC	antigen presenting cell
SNP	single nucleotide polymorphism
RANTES	regulated upon activation, normally T-cell expressed
SPINK5	serine protease inhibitor Kazal-type 5
NOD1	nucleotide-binding oligomerisation domain protein 1
SCCE	stratum corneum chymotryptic enzyme

Definitions:

- **Atopy** - a personal and/or familial tendency to become sensitised and produce IgE in response to exposure to common environmental allergens.
- **Atopic diseases** – asthma, eczema and allergic rhinitis (some authors also include food allergy).
- **Atopic march** – the observation that the development of eczema in an individual may precede the development of asthma and allergic rhinitis later in life.
- **Allergens** – antigens which cause allergy, eg proteins reacting with IgE and IgG and nickel reacting with T-cells.
- **Allergy** – a hypersensitivity reaction initiated by immunological mechanisms.
- **Hygiene hypothesis** – this postulates an inverse relationship between atopy and environmental exposure to pathogens. It is based on the theory that a cleaner microenvironment results in decreased stimulation of the immune system early in infancy thus facilitating the development of abnormal, allergic reactions.
- **Itch–scratch cycle** – the pruritus that is characteristic of eczema results in scratching behaviour which exacerbates epidermal barrier dysfunction. This increases *Staph aureus* infection which exacerbates eczema pruritus and results in more scratching and perpetuates a vicious cycle.
- **Genotype** – the genetic constitution of an organism which is modulated by the environment before being expressed as a phenotype.

- **Phenotype** – the expressed traits or characteristics of an organism as a result of the genotype and environmental influences, eg the presence/absence of a disease.
- **Polymorphism** – a segment of the genome, within or outside a gene, in which different forms (**alleles**) are present.
- **Locus** – a segment of the genome.
- **Single nucleotide polymorphism (SNP, pronounced ‘snip’)** - DNA sequence variations that occur when a single nucleotide in the genome sequence is altered. For a variation to be considered a SNP, it must occur in at least 1% of the population. SNPs make up about 90% of all human genetic variation.
- **Complex trait** – any phenotype which results from the effects of multiple genes at two or more loci, with the addition of possible environmental influences. This is in contrast to simple **Mendelian inheritance** where a single gene is responsible for defining a single phenotypic trait.
- **Candidate gene** – a known gene suspected to be associated with the disease of interest on the basis of the biological function of its protein product.
- **Genetic linkage** – the phenomenon whereby a phenotype and a gene are inherited together with a known **marker polymorphism** more often than is expected by chance alone. This indicates that the gene may be contributing partially or completely to the phenotype.
- **DNA microarray analysis** – in this technique thousands of messenger RNAs are simultaneously compared in order to investigate patterns of tissue inflammation eg within a skin biopsy sample.
- **Genetic association study** – comparison of the frequency of alleles in candidate genes between affected and unaffected individuals.
- **Whole genome scan** – linkage analysis in which markers placed at regular intervals covering the whole genome are typed.

A patient’s story – Rachel aged 15 years, in her own words.

“I have had eczema since I was born and had asthma as well. Having eczema is not really nice because some people stare and makes nasty remarks about my skin and it puts me down and it also upsets me.

When I’m at home I’m OK and happy because my family are there. When at school I’m mostly upset because people call me names like scabby and cornflake and more. My friends are really great help because they tell me to just let them people that call me names just let it blow over your head.

At home my Mam, Dad and sister helps with my treatment. And also the nurse at the hospital helps with my treatment when I have to come in. And also my antie helps with my treatment when I stay at her house.

Its nice when I have to put my cream on but when I have to put the bandages on its not nice because they are really cold and they sometimes get really tight and I just get all agravated and ichey.

I would love to go and live in a hot and sunny place so that my skin would always be nice.”

Management of eczema – basic principles

Eczema can be a very rewarding condition to treat.

Different modes of treatment should be used simultaneously for optimal management:

- 1) Avoid irritants such as soap and detergents – use a **soap substitute**.
- 2) Apply an **emollient** after washing – greasy ointments are more effective than water-based creams unless the eczema is exuding a lot of fluid.
- 3) **Topical corticosteroid creams or ointments** - mild, moderate, potent or very potent depending on the severity of the eczema and its site.
Facial and flexural skin is more at risk of local side-effects and special care is required in the treatment of young children.
Ointments are more potent than creams because their occlusive effect aids tissue penetration; creams are preferable where eczema is weeping.
- 4) **Topical antiseptics and/or oral antibiotics** – when the eczema is secondarily infected. *Staph aureus* infection is commonly associated with disease flares.
- 5) Sedating **oral antihistamine** medication may be useful at night.
- 6) Occlusive **bandaging** may be helpful but objective evidence is lacking. The aim is to prevent scratching and increase the absorption of topical steroids and emollients.
Medicated bandages containing anti-inflammatory preparations (eg zinc oxide) may also be used, but again this is based on experience rather than experimental evidence.
- 7) **Referral** to a dermatology specialist is indicated when the managements listed above do not produce adequate control or if steroid-induced dermal atrophy is a concern.
- 8) **Second-line treatments** include:
 - Topical immunosuppressants – calcineurin inhibitors
 - Ultraviolet light treatment – eg narrow band UVB
 - Systemic immunosuppressants – cyclosporin and azathioprine.

Patient information and support groups:

- National Eczema Society www.eczema.org This organisation also provides information leaflets.
- Talk Eczema www.talkeczema.com A free online support service for people with eczema and their families.
- British Association of Dermatologists <http://www.bad.org.uk/public/leaflets> Information on the diagnosis and treatment of eczema and other skin conditions.

American Academy of Dermatology patient information service
www.aad.org/public/publications/pamphlets/eczemaatopic_dermatitis.htm

Additional educational resources:

- The British Association of Dermatologists provides evidence-based and up-to-date information for healthcare professionals.
<http://www.bad.org.uk/healthcare/guidelines/>
- www.nottingham.ac.uk/dermatology/eczema/index.html Online manual of the UK Diagnostic Criteria for atopic dermatitis.
- The National Institute for Health and Clinical Excellence (NICE) provides national guidance in England and Wales on the treatment of eczema. <http://www.nice.org.uk/search.aspx?search-mode=simple&ss=eczema>
- The American Academy of Dermatology guidelines on the management of eczema have recently been published:
Hanifin JM, Cooper KD, Ho VC *et al.* Guidelines for care of atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association "Administrative Regulations for Evidence-Based Clinical Practice Guidelines." *J Am Acad Dermatol* 2004; **50**; 391-404.

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