A SYSTEMATIC REVIEW OF TREATMENTS FOR ATOPIC DERMATITIS

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A systematic review of treatments for atopic dermatitis

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Summary

Atopic dermatitis is a very common inflammatory skin disease, particularly in children. A systematic review of randomised controlled trials of treatments for atopic dermatitis (AD) was carried out to assess how many trials exist, what they cover, what they do not cover, the research gaps, provide a 'blue print' for future Cochrane Reviews and assist those making treatment recommendations by summarising the available RCT evidence, using descriptive statistics.

The Cochrane Collaboration systematic review process formed the basis of the methodology, from which over 4000 studies were located via electronic database searches and hand searching of journals. A total of 292 trials were finally included covering 9 treatment groups and over 48 individual treatments.

There are lots of trials covering lots of interventions but gaps are evident. However, there is evidence of a benefit in the treatment of atopic dermatitis with topical corticosteroids, psychological approaches, UV light, ascomycin derivatives, topical tacrolimus and oral cyclosporin.

Treatments that show limited evidence of a benefit include non-sedatory antihistamines, topical doxepin, the oral antibiotic Cefadroxil on clinically infected AD, the topical antibacterial Mupirocin on clinically uninfected AD, Chinese herbs, hypnotherapy and biofeedback, massage therapy, dietary manipulation, house dust mite reduction, patient education, emollients, allergen antibody complexes of house dust mite and thymic extracts.

Treatments that show no evidence of benefit include sedatory antihistamines, oral sodium cromoglycate, oral antibiotics on clinically uninfected AD, topical antibacterials, topical antifungals, aromatherapy essential oils, borage oil, fish oil, evening primrose oil, enzyme-free clothes detergent, cotton clothing, house dust mite hyposensitisation, salt baths, topical coal tar, topical cyclosporin and platelet-activating-factor antagonist.

When interpreting the conclusions of this thesis it is important to understand that lack of evidence does not equal lack of efficacy, particularly considering the interventions that are commonly in use today to treat atopic dermatitis that have not been subjected to RCTs, such as occlusive dressings, water softening devices and stress management among many others.

It appears this is the first review of its kind assessing all treatments of atopic dermatitis and is the first step in the chain of events that could lead to evidence based treatment recommendations for AD. If this research is to be put to good use it needs to be kept up-to-date and broken down into individual questions and subjected to the Cochrane review process, of which several are already under way.

Key words: eczema; dermatitis; atopic; systematic review; randomised controlled trial; evidence based medicine

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CONTENTS

CHAPTER 1

BACKGROUND

1.1 What is atopic dermatitis

1.1.1 Definition of atopic dermatitis

Atopic dermatitis stems from the ancient Greek word *atopy* which was further developed in the 1920's by Coca and Cooke, two American allergists, and Perry, a Colombian philologist [1]. In order to differentiate this skin disease form other 'similar' diseases they defined atopy as 'not in the right place or *strange*' [2].

Asthma, eczema/dermatitis and allergic rhinitis are generally regarded as the three most important atopic diseases. *Atopic* can be defined as "...the development of IgE antibody in response to antigen exposure" [3]. However, this is not always the case because people presenting with clinical atopic dermatitis may not be atopic, and those who are atopic may not present a clinical disease[4]; and only around 50% of atopic dermatitis patients have a history of other atopic diseases [5]. Hence, one can certainly identify with Coca and Cookes definition of not in the right place or strange.

There are a large number of synonyms in circulation for this condition including atopic eczema, atopic dermatitis, Besnier's prurigo, neurodermatitis, flexural eczema, childhood eczema and infantile eczema. Today in the UK atopic eczema and atopic dermatitis are the most commonly used terms. Disease definitions have tended to adapt to changes in our understanding of the disease, nevertheless, atopic dermatitis still lacks a definition of known validity and repeatability [3]. This is probably because it is a disease that varies from one person to the next in terms of distribution, morphology and time course, and hence difficult to pin down and pigeonhole. That said, in order to have a faint idea of what atopic eczema is, I have chosen the following from a plethora of definitions, because I would argue it encapsulates the diversity of the disease, the key elements of the disease and is easy to understand:

> "Atopic dermatitis (which is synonymous with atopic eczema) is an itchy, chronic, or chronically relapsing, inflammatory skin condition. The rash is characterised by itchy papules (occasionally vesicles in infants), which become excoriated and lichenified, and

typically has a flexural distribution. The eruption is frequently associated with other atopic conditions in the individual or other family members." [6].

The terms atopic eczema and atopic dermatitis will be used interchangeably throughout this thesis, as well as the abbreviation AD.

1.1.2 Diagnosis of atopic dermatitis

In the 1970's Hanifin and Rajka introduced their diagnostic guidelines [7], which revolutionised the precision of diagnosing this skin disease. The guidelines comprised 24 major and minor clinical symptoms and signs. To be diagnosed with atopic eczema patients are required to have at least 3 out of 4 basic features outlined in Table 1.

Table 1 Guidelines for the diagnosis of atopic dermatitis[7]

Must have 3 or more basic features:
Pruritis
Typical morphology and distribution
Flexural lichenification or linearity in adults
Facial and extensor involvement in infants and children
Chronic or chronically relapsing dermatitis
Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)
Plus 3 or more minor features:
Xerosis
Ichthyosis/palmar hyperlinearity/keratosis pilaris
Immediate (type I) skin test reactivity
Elevated serum IgE
Early age of onset
Tendency toward cutaneous infections (esp. *Staph. Aureus* and *Herpes simplex*)/ impaired cell-mediated immunity
Tendency toward non-specific hand or foot dermatitis
Nipple eczema
Chelitis
Recurrent conjunctivitis
Dennie-Morgan infraorbital fold
Keratoconus
Anterior subscapular cataracts
Orbital darkening
Facial pallor/facial erythema
Pityriasis alba
Anterior neck folds
Itch when sweating
Intolerance to wool and lipid solvents
Perifollicular accentuation
Food intolerance
Course influenced by environmental/emotional factors
White dermographism/delayed blanch

These guidelines however were never validated or tested for repeatability. Clinically they were not specific enough. In recent years the UK Working Party's Diagnostic Criteria has been introduced, as a modification of the Hanifin and Rajka guidelines, to counteract the problems associated with them. They have been validated, tested for repeatability, are simple to use, clinically useful and adapt to different ages and cultures:

Table 2 UK Working Party's Diagnostic Criteria for the diagnosis of atopic dermatitis[8]

Must have:
An *itchy* skin condition (or parental report of scratching or rubbing in a child)
Plus 3 or more of the following:
1 History of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles or around the neck (including cheeks in children under 10)
2 A personal history of asthma or hay fever (or history of atopic disease in a first-degree relative in children under 4)
3 A history of a general dry skin in the last year
4 Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4)
5 Onset under the age of 2 (not used if child is under 4)

1.1.3 Clinical features of atopic dermatitis

Although itch is a primary clinical feature of atopic eczema, most types of eczema are itchy. Distinguishing features of *atopic* eczema include vesicles and exudation on the face and hands of babies (Figure 1), which is often prone to secondary infection (Figure 2). Children over the age of 18 months develop atopic eczema in the flexures with signs of erythema and infraorbital fold involvement (Figure 3). Lichenification, excoriations and dry skin are other common signs. Most of the clinical signs are caused by the itch-scratch cycle, normally associated with this skin disease, which can lead to considerable sleep loss from sufferers and families of sufferers (Figure 4). Adults tend to be more chronic and severe with generalised, lichenified atopic dermatitis that can interfere with many aspects of life including work and social activities (Figure 5).

Figure 1: Infant with facial and hand atopic eczema

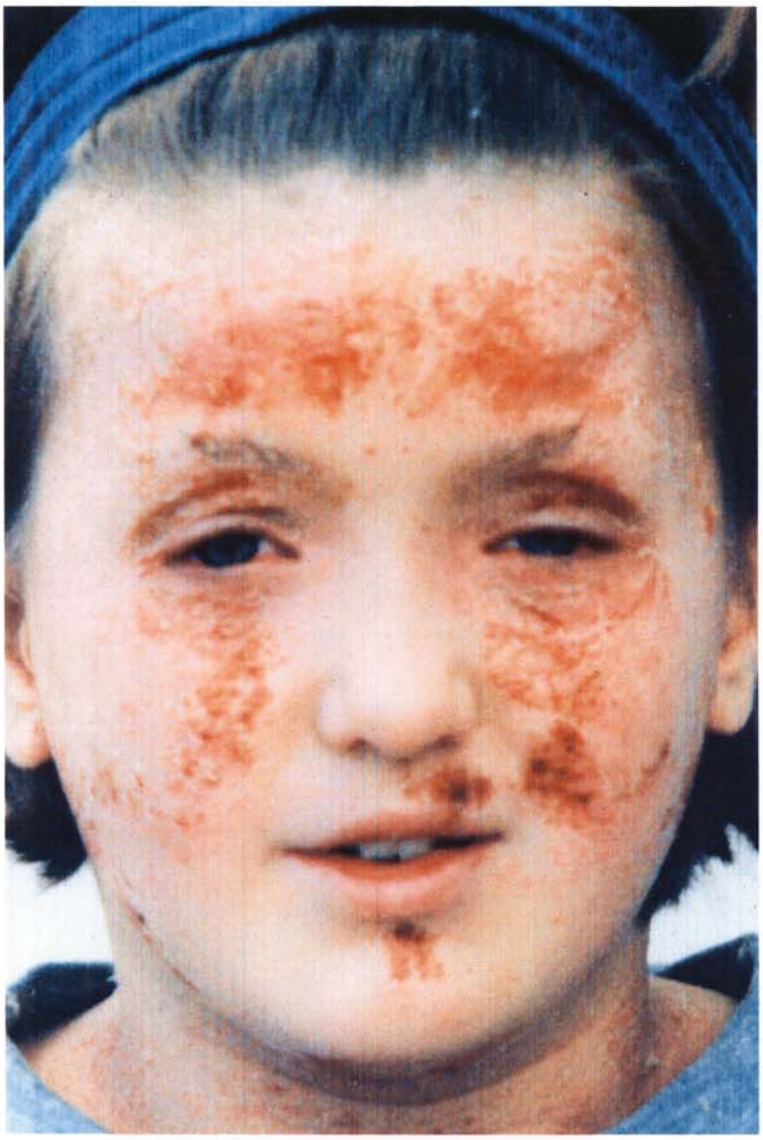


Figure 2: childhood atopic eczema with secondary infection

Figure 3: Flexural involvement of atopic dermatitis

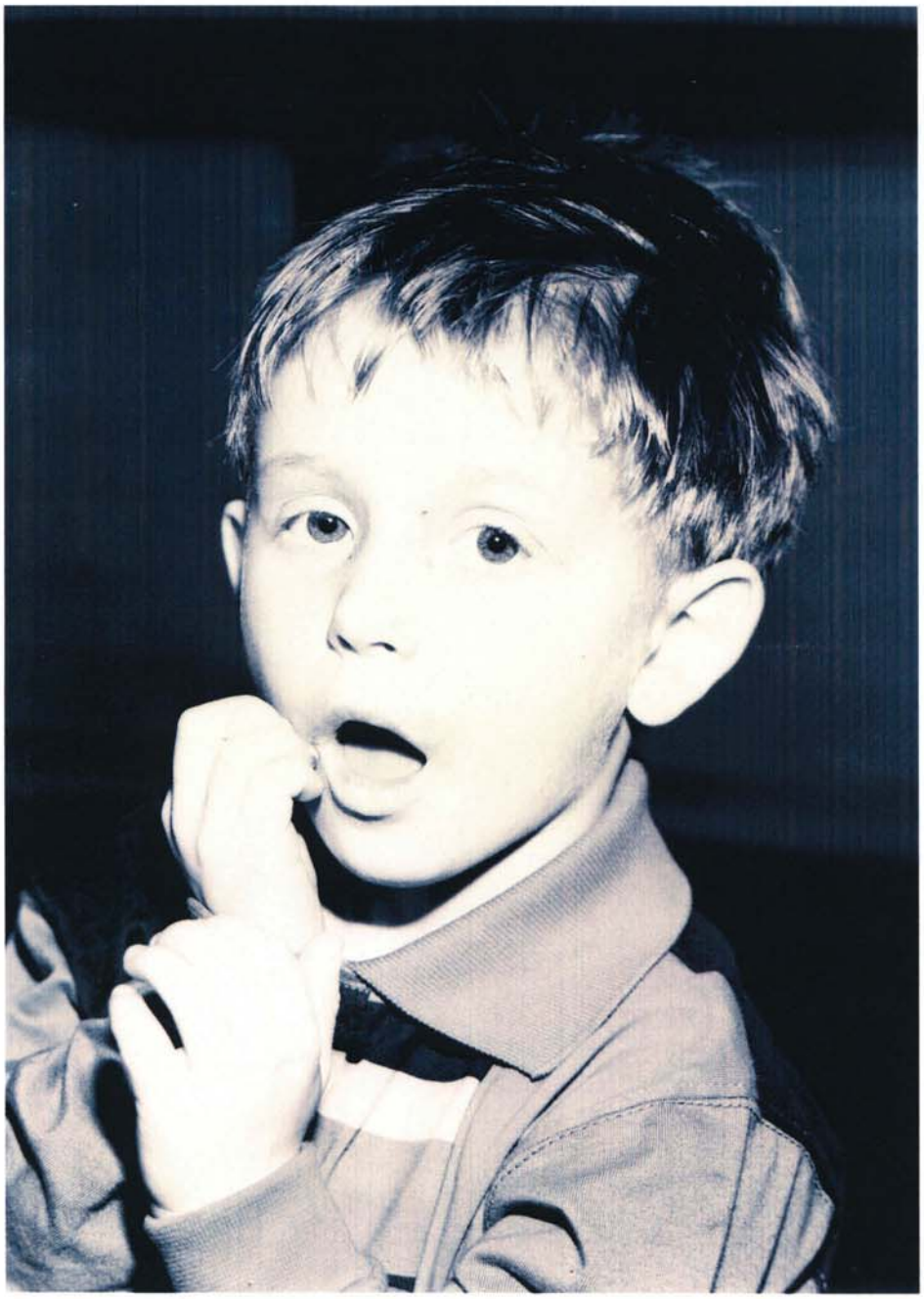


Figure 4: Itch-scratch cycle of atopic eczema

Figure 5: Adult atopic eczema

1.2 Epidemiology of atopic dermatitis

1.2.1 Incidence and prevalence of atopic dermatitis

Atopic eczema is the most common inflammatory skin disease of children in the UK[9]. A 1994 study [10] estimated the prevalence of childhood atopic eczema in a general population in the UK at 20% in children aged 3 to 11 years. Other studies, reviewed elsewhere [3], suggest a prevalence of 5-20% by age 7. Available data for adults puts prevalence somewhere between 1-2% [3], which tends to be more chronic and severe{Williams HC. 1999 #38820}. There is strong evidence to suggest AD is increasing in prevalence and has done so at an alarming rate over the last 30 years for reasons which are unclear[11]. Incidence data is scant but one study suggests around 50 cases per 1000 in the first year of life falling to around 5 new cases per year for the remainder of childhood [3].

Several factors have to be taken into account when interpreting this data. Firstly, the nature of AD is to relapse and remit making it difficult to develop an accurate picture of the total number of diseased subjects in a specific population at one point in time. Secondly, eczema types have been grouped together, that is, atopic eczema has not been recorded separately to contact eczema for example. Add this to other factors, such as the different measures used to calculate data, confusion between prevalence (a cross-sectional snap shot of the total number of cases (new and old) within a defined population at a point in time) and incidence (number of new cases in a defined period), disease definition inconsistencies, and the picture gets very cloudy indeed.

A research team identified the above shortcomings of prevalence data and collaborated on a worldwide project to estimate the prevalence of atopic eczema in children. The authors state that it is

> "...the first global comparison of the prevalence of atopic eczema symptoms by using standardized methods among 715,033 children in 56 countries." [12]

The results of the study suggest that atopic eczema affects 5-20% of children worldwide at ages 6 to 7 and 13 to 14.

1.2.2 Aetiology of atopic dermatitis

1.2.2.1 Genetic aspects of atopic dermatitis aetiology

Genetics play an important role in atopic eczema with twin studies demonstrating how monozygotic twins have an 86% chance of developing atopic eczema compared to that of dizygotic twins which is only 21% [13]. An important breakthrough found that chromosome 11q4 was mapped as the gene of AD, however, this only accounted for 60% of those with the disease and it was concluded that 11q4 mapped only the maternal line of inheritance [14]. Atopy can be inherited paternally, albeit less frequently than maternally[15], and research continues in this area.

1.2.2.2 Immunological aspects of atopic dermatitis aetiology

Immunoglobulin E (IgE) plays an important role in atopic dermatitis aetiology. Raised IgE levels in atopics, thought to be a response to common environmental allergens[16] were, up until fairly recently, seen to be a primary diagnostic feature. It is unclear why but evidence now shows up to one third of people with AD have normal IgE levels [14], thus raised IgE is not an explanation of the entire picture of AD. Another anomaly, yet to be explained, is the type of atopic disease that runs in a family, which is true to type. For example, parents with atopic eczema, tend to find their offspring primarily develop atopic eczema as opposed to the other atopic diseases that may or may not occur throughout an individual's life. [17 18].

1.2.2.3 Environmental aspects of atopic dermatitis aetiology

The environment is believed to play an important role in AD aetiology. Research has been carried out that makes this plausible, for example, migrant studies, whereby immigrants compared to counterparts in their country of origin show increased prevalence of AD and increased susceptibility to AD[19-21]. Whether this is due to allergies, diet, irritants, climate or other factors is unclear.

Social class has been linked with AD aetiology with classes I and II demonstrating a higher prevalence rate than the lower classes [22]. The authors of the study suggest several possible reasons for this including educational status and positive health related behaviour, use of carpets and central heating, overuse of showers and/or soaps, decreased exposure to UV light, increased contact with pets and prenatal exposures including maternal age and diet. However, they identify another variable of possible parental over-reporting of the disease.

Family size is another area of interest as an environmental factor associated with the cause of AD whereby larger families have less attributed AD[23]. The link here is thought to be a protective role of cross infection from siblings[24].

The house dust mite (HDM) has generated a lot of interest as an important environmental factor in the cause and/or exacerbation of AD. It is the faecal pellets of the mite that carry the allergen, Der p1, for the majority of people with atopic disease[25], (the minority are probably not affected at all). HDMs feed on dander (dead skin cells) from humans and animals as well as fish food flakes, fungi, cereals and crumbs. They live in carpets, soft furnishings and even soft toys with the bed as its primary habitat [26], [27]. One study found a concentration of 61mites/5g dust taken from the floor, with a 100-fold increase in a mattress[27]. There is some evidence that homes of people with AD have higher levels of HDM[28] but no relationship has been found between amount of dander and amount of mites[27]. A person with AD that is affected by HDM will tend to have a worsening of symptoms, which may by relieved by the reduction of the mite and its droppings.

1.3 Histology of atopic dermatitis

AD is a type of 'spongiotic dermatitis', which means it is characterised by intercellular oedema and a widening of intercellular spaces, giving the epidermal layer a sponge-like appearance. Intercellular oedema is first detected as a result of the incorporation of clear oedema fluid. As fluid accumulates, intercellular bridges stretch, cell-to-cell junctions break and fluid-filled vesicles enlarge. Interepithelial cell oedema is accompanied by the infiltration of leukocytes that mediate an immune response. Abnormal scale ensues, along with progressive hyperkeratosis (increased production of cells) and hyperplasia (enlargement from increased production of cells) [29].

The lesions of *acute* atopic dermatitis are characterised by marked intercellular oedema in the epidermis. In the dermis, the inflammatory cell infiltrate consists primarily of T cells and occasional macrophages. Eosinophils, basophils and neutrophils are rarely present[30].

In the lichenified lesions of *chronic* atopic dermatitis, the epidermis is hyperplastic (enlarged due to increased production of cells) with prominent hyperkeratosis and an increased number of Langerhan's cells (antigen presenting cells in the epidermis). Macrophages dominate the dermal mononuclear cell infiltrate; mast cells and eosinophils increase in numbers[30].

1.4 Pathophysiology of atopic dermatitis

Current theory suggests AD results from a combination of immunologic and non-immunologic mechanisms that trigger and maintain skin inflammation. Both the humoral and T cell-mediated immune responses are antigen-induced reactions that promote the migration of inflammatory cells to the skin. Non-immunologic mechanisms like the itch-scratch cycle also induce the migration of inflammatory cells, though not in direct response to an antigen[31].

1.4.1 Immunologic abnormalities of atopic dermatitis

Pathogenesis of AD remains to be clarified but there is evidence of defects in humoral immunity found in people with AD[32]. As previously stated many, but not all, people with AD have high levels of immunoglobulin E (IgE), suggesting that AD can be an antigen-induced disorder[6]. AD has been attributed to increased IgE production and binding to epidermal Langerhans' cells[32].

Antigen-induced activation of IgE-bearing mast cells and macrophages contributes to skin inflammation by releasing cytokines that induce the migration of inflammatory cells to the site of the allergic reaction[31]. High activity of cyclic AMP phosphodiesterase in mast cells and Langerhans' cells leads to a decrease in levels of cyclic AMP, a modulator of normal cell function. Inadequate modulation of cell function triggers an exaggerated release of histamines from mast cells as well as increased antigen presentation by Langerhan's cells[33].

1.4.2 Activation of IgE-bearing Langerhan's cells

The antigen-induced activation of IgE-bearing Langerhans' cells facilitates antigen presentation to T helper (Th) cells. Antigen presentation triggers Th cells to preferentially differentiate into T-helper type 2 (Th2) cells. Th2 cells secrete cytokines (e.g., IL-4 and IL-5) that promote the migration of

eosinophils to the site of inflammation[31]. Both Interleukin- (IL)-4 and IL-5 induce the synthesis of antigen-specific IgE antibodies by B cells[6].

1.4.3 Activation of IgE-bearing mast cells

The binding of an antigen to the cell's membrane-bound IgE molecules can trigger mast cell degranulation. Degranulation releases various mediators: histamines elicit immediate inflammatory effects, though they do not play a major role in the pruritis of atopic dermatitis. Prostaglandins may induce the production of a cellular infiltrate composed of neutrophils, eosinophils, and basophils. Leukotrienes are also released during degranulation[34].

1.4.4 Activation of IgE-bearing macrophages

Antigens can also activate IgE-bearing macrophages, causing them to secrete mediators such as leukotrienes, platelet activating factor, IL-1, and tumour necrosis factor that can contribute to skin inflammation[30].

1.4.5 Defects in the cell-mediated immune response

AD may be the result of an imbalance in T-cell populations. Antigen presentation triggers Th cells to differentiate into Th2 cells. A decrease in cyclic AMP stimulates the release of factors that enhance Th2 response. The development of Th1 cells is suppressed by IL-4[30].

Although the pathogenesis of AD is not completely understood it involves immunologic abnormalities such as humoral immune response and T cell-mediated immune response as well as non-immunologic mechanisms such as the itch-scratch-itch cycle, infection with *Staphylococcus aureus*, and environmental factors.

1.5 Treatment of atopic dermatitis

There is currently no cure for AD probably because it is an arbitrary and heterogeneous disease[11]. Treatments have been developed over the years that aim to cure AD but at best manage to suppress and relieve signs and symptoms. The mainstay of treatment for atopic eczema consists of explanation and discussion, emollients and topical corticosteroids[35], [36]. Emollients have been used in the treatment

of dry scaly skin conditions for over 2000 years[37], and topical steroids for over 50 years[36], but it is probably their ability to clinically reduce signs and symptoms of AD that has made topical steroids such an important element of the mainstay of treatment. To date nothing has been developed that could replace them, even though many developments have taken place in treatment and management. There are those, however, that are unresponsive to topical steroids, in which case there is a plethora of treatments that can be used including wet wrap bandages, oral steroids, UV light and immune suppression/modulation via drugs such as cyclosporin and more recently topical tacrolimus and pimecrolimus.

Atopic eczema is prone to complications such as secondary infection by *staphylococcus aureus,* in which case antibiotics, topical and/or oral, would be required.

Some people either turn their back on conventional medicine in search of 'safer' (*sic*) alternatives or seek complementary medicine to aid treatment of AD alongside conventional methods. This has led to developments in complementary medicine for eczema such as homeopathy, hypnotherapy, massage and Chinese herbal medicine. It is unclear what the benefits of complementary medicine are at present and indeed how they compare to conventional treatment.

The house dust mite (HDM) has been implicated as a major culprit in terms of environmental exacerbation or even cause of AD[25] as mentioned in section 1.2.2.3. Therefore, reduction of HDM seems a viable option in the treatment of AD, and there are those that argue the measures aimed at eliminating HDM can result in great clinical improvement of AD, but also identify it is difficult to predict which patients will benefit[25]. Chemical aracicides, special mattress covers, regular vacuum cleaning and damp dusting are examples of the methods used to reduce the mite and its droppings.

1.6 Prevention of atopic dermatitis

Prevention of atopic dermatitis has been reviewed elsewhere[38], [39], the conclusions of which show limited observational evidence to suggest that exclusive breast feeding for at least five months reduces the risk of eczema in infants with a family history of atopy. Limited evidence was found from one

systematic review of poor quality trials for maternal dietary restriction during lactation as protection against the development of eczema in infants with a family history of atopy.

1.7 Cost of atopic dermatitis

Atopic dermatitis is a disease that can be costly, not just financially but also in terms of its psychological and emotional impact. Partners, siblings, parents, grandparents and informal carers can all be affected. It can lead to time off work, bullying at school; it can affect leisure time, relationships, social activities and quality of life in general.

From an economics perspective a cohort study reported in 1996 produced some staggering results for the health service, the individual sufferer and the families and carers of those with the disease:

> "...each patient spent, on average, £325 in 2 months [which] lead to a mean health service expenditure per patient of £415, in 2 months. If results were extrapolated to the UK population, the annual personal cost to patients with atopic eczema would be £297m, the cost to the health service would be £125m, and the annual cost to society of lost working days would be £43m, making the total expenditure on atopic eczema £465m." [40]

The above figures include treatments, extra laundry, cotton bedding, cotton clothing and loss of salary, all of which add to the total cost of this common, increasingly prevalent, skin disease. The cost is probably considerably more today as this study was published in 1995 and was carried out in Scotland. Nevertheless, it gives an idea of how costly this disease can be to both the NHS and those living with this condition.

A paper recently published reports a cross sectional survey of 1761 children aged 1-5 years in the Nottingham area around a similar time, i.e., 1995-6[41]. According to this study, total 'mean' disease cost per child over 12 months is £79.59, which can be broken down as follows:

- NHS mean annual costs for consultations £28.62 (mainly primary care)

- NHS mean annual costs for prescriptions £22.03, mainly due to emollients and bath preparations
- Family care costs £28.94 per year

It was calculated that the 12 month period prevalence of AD was 16.5% (95% CI 14.7 – 18.2%), therefore, the annual UK cost of AD in children aged 1-5 years in 1995-96, according to this report, was £47million, that is, £30 million spent by the NHS and £17 million by the families of affected children.

The first set of figures[40] covered a wide age range (-2 to +65 years) in the community. In contrast, the second set of figures, [41], was calculated from children aged 1-5 years only and purports to include more severe cases of AD.

From a quality of life perspective, AD can be very costly. Apart from the impact on the person suffering from AD, those who are involved in the life of that person may also suffer. A survey was carried out in the mid 1990's [42]in the form of a postal questionnaire which was sent to all the members of the National Eczema Society, a voluntary organisation dedicated to improving the lives of those affected by eczema/dermatitis. The aim was to establish the effect of eczema upon the lives of sufferers. Although it didn't just address those with atopic eczema, it gave some useful feedback. Difficulties such as extra laundry and the burden this can have on a family, impaired sex lives of couples, disturbed sleep in children and the impact this can have on the entire family, school activities, sports, holidays and interactions with others were among the specifics mentioned. The shortcomings of the study must be taken into account, i.e., members of a charity and those responding to the questionnaire are arguably a highly motivated subset of people. Nevertheless, the information was very helpful to those that work in the field of dermatology to understand the costs of this skin disease, other than economic, and to provide the National Eczema Society with valuable feedback about what people with eczema require in terms of information and support.

1.8 The need for a systematic review of treatments for atopic dermatitis

We live in a fast developing society in terms of scientific information and technology. Research into treatment of disease, such as atopic eczema, is carried out worldwide and specialist journals are produced informing those that read them of these new developments. However, with over 200 journals worldwide in dermatology alone [43], it is impossible for anyone to keep on top of this vast quantity of research.

Reviews aim to address this problem by summarising studies that have asked the same or similar questions. However, there is no standardised scientific method implemented to capture all published or unpublished studies world-wide on a specific topic; researchers and scientists often review what they already know about or have access to in their archives [43]. Hence, standard reviews, by their very nature, are biased.

In the early 1990's The Cochrane Collaboration introduced a system that addressed the biases of standard reviews by developing a systematic, standardised procedure - called a 'Systematic Review'. A systematic review is different to a standard review because it contains an explicit statement of objectives, materials, and methods and has been conducted according to explicit and reproducible methodology[44]:

1. State objectives of the review of randomised controlled trials and outline eligible criteria
2. Search for trials that seem to meet eligibility criteria
3. Tabulate characteristics of each trial identified and access its methodological quality
4. Apply eligibility criteria and justify any exclusions
5. Assemble the most complete data-set feasible, with assistance from investigators, if possible
6. Analyse results of eligible randomised controlled trials by using statistical synthesis of data (meta-analysis) if appropriate and possible
7. Compare alternative analyses, if appropriate and possible
8. Prepare a critical summary of the review, stating aims, describing materials and methods, and reporting results [45]

1.9 Aims and objectives

The aims and objectives of this thesis are to systematically review randomised controlled trials (RCTs) that have investigated treatments of atopic dermatitis to provide a ' map' of what trials have been carried out, what they cover, and what they do not cover, identify major research gaps, provide a 'blue print' for future Cochrane Reviews and assist those making treatment recommendations by summarising the available RCT evidence using descriptive statistics.

CHAPTER 2

METHODS

2.1 General introduction to methods

The Cochrane Collaboration Handbook[44]will be used where possible as a reference tool for the methodological structure of this systematic review. This is because the handbook was developed to guide those wishing to carry out systematic reviews of randomised trials by using a standard format, thus encouraging a systematic approach throughout. In addition, the guidelines produced by the NHS Centre for Reviews and Dissemination[46] will be used as a template and guide where appropriate.

The simplified steps of preparing and maintaining systematic reviews are:

- Formulating the problem
- Locating and selecting studies
- Quality assessment of studies
- Collecting data
- Analysing and presenting results
- Interpreting results
- Improving and updating reviews[44]

Most Cochrane Reviews are question driven and place a lot of emphasis on the development of a well-formulated question to guide the review process. However, this review has different objectives than that of a Cochrane review, as it is data driven as opposed to question driven. (See aims and objectives in section 1.8 'The need for a systematic review of treatments for AD' for more details).

2.2 Types of studies included in this review

Randomised Controlled Trials (RCTs) lend themselves well to questions about interventions of treatment or prevention, and depending upon the question being asked, randomised controlled trials are seen as the 'gold standard' of research methodology. They are given this title because it is believed that well designed RCTs give more reliable estimates of effect than any other study design[46]. Note 'well-designed' as it could be argued that a well-designed and reported case study is more reliable and

informative than a poorly designed RCT. The quality, design and reporting of RCTs will be discussed in more depth later in this report.

In order to qualify as a randomised controlled trial several criteria have to be met[43]:

1. A trial must involve a single original population of living human beings (no studies involving cadavers, extracted teeth, or cell lines) or groups of human beings or parts of their bodies (e.g., arms or eyes).
2. A trial must be prospective (i.e., planned in advance), so historical controls cannot be used, and it must be a comparison of 2 or more interventions.
3. The allocation of the interventions (one may be experimental and the other controlled) to the single population should be randomized, and the report should explicitly state that the allocation was random.

To be included in this review the RCTs have to address the treatment of atopic dermatitis.

2.3 Study participants

RCTs that include anyone who has been diagnosed with atopic eczema by a physician will be included. Diagnostic criteria such as the Hanifin and Rajka definition [7] or the UK modification [8] will be acceptable, using the terms 'atopic eczema' or 'atopic dermatitis'.

The term 'eczema' will be acceptable only when referring to children as it will be presumed eczema in children is childhood eczema, which is a synonym for atopic eczema (see Table 3). All other terms such as 'Besnier's Prurigo' or 'Neurodermatitis' will need additional evidence of atopic eczema in the flexures, i.e. crooks of arms and backs of knees, before inclusion.

To decide what is definitely atopic eczema, possibly atopic eczema and not atopic eczema, I consulted 5 Dermatologists (3 Specialist Registrars, 1 Consultant and 1 Professor) from the Dermatology Department, Queen's Medical Centre, Nottingham, UK. I provided a list of terms that I had come across during my background reading and asked the dermatologists whether or not the term could be atopic eczema. Table 3 shows the results of the consultation.

Table 3 Terms used to identify trial participants with definite, possible and definitely not atopic eczema

Definite atopic eczema (include if study was a randomised controlled trial)	**Possible atopic eczema** (implies original paper must be obtained and read before a judgement is made to include or exclude by one of the authors based on additional features such as a good clinical description of atopic eczema with atopy)	**Not atopic eczema** (implies that the author did not accept this term as representing atopic eczema)
Atopic eczema Atopic dermatitis Besnier's prurigo Neurodermatitis atopica (German) Flexural eczema/dermatitis	Periorbital eczema Childhood eczema Infantile eczema "Eczema" unspecified Constitutional eczema Endogenous eczema Chronic eczema Neurodermatitis Neurodermatis (German)	Seborrheic eczema Contact eczema Allergic contact eczema Irritant contact eczema Discoid/Nummular eczema Asteatotic eczema Varicose/stasis eczema Photo/light sensitive eczema Chronic actinic dermatitis Dishydrotic eczema Pompholyx eczema Hand eczema Frictional lichenoid dermatitis Lichen simplex Occupational dermatitis Prurigo

2.4 Outcome measures

Primary outcome measures

1. Patient-rated clinical response

a) Proportion of patients with clinically significant changes in patient-rated symptoms (e.g. itch and sleep loss) - as defined by each of the studies and/or average score/change in patient-rated symptoms

b) Proportion of patients with clinically significant response in patient-rated global (overall) changes- as defined by each of the studies and/or average score/change in patient-rated global state

c) Proportion of patients with clinically significant changes in patient-rated signs (e.g. dryness and cracking) - as defined by each of the studies and/or average score/change in patient-rated signs

2. Doctor-rated clinical response

a) Proportion of patients with clinically significant response in doctor-rated global changes - as defined by each of the studies and/or average score/change in doctor-rated global state

b) Proportion of patients with clinically significant changes in doctor-rated signs - as defined by each of the studies and/or average score/change in doctor rated signs

c) Proportion of patients with clinically significant changes in doctor-rated symptoms - as defined by each of the studies and/or average score/change in doctor rated symptoms

In the absence of any indication by the studies on what is deemed clinically significant, the default procedure will be to use the proportion of patients with good to excellent improvement as the main outcome.

3. Adverse effects

a) General

b) Specific

Secondary outcome measures

Changes in individual signs of atopic eczema as assessed by a doctor:

- Erythema (redness)
- Purulence (pus formation)
- Excoriation (scratch marks)
- Xerosis (skin dryness)
- Scaling
- Lichenification (thickening of the skin)
- Fissuring (cracks)
- Exudation (weeping serum from the skin surface)
- Pustules (pus spots)
- Papules (spots that protrude from the skin surface)
- Vesicles (clear fluid or 'water blisters' in the skin)
- Crusts (dried serum on skin surface)
- Infiltration/oedema (swelling of the skin)
- Induration (a thickened feel to the skin)

2.5 Trial identification - the searching process

In order to identify randomised, controlled trials of atopic dermatitis, electronic databases Medline[47], Embase[48 49], CCTR (Cochrane Controlled Trials Register) and The Cochrane Skin Group Specialised Register[43] were searched:

- Medline from 1966 to 2000 - Produced by the U.S. National Library of Medicine, the Medline database is widely recognized as the premier source for bibliographic and abstract coverage of biomedical literature. Medline encompasses information from Index Medicus, Index to Dental Literature, and International Nursing, as well as other sources of coverage in the areas of allied health, biological and physical sciences, humanities and information science as they relate to medicine and health care, communication disorders, population biology, and reproductive biology. More than 9.5 million records from more than 3,900 journals are indexed, plus selected monographs of congresses and symposia (1976-1981). Abstracts are included for about 67% of the records.
- Embase from 1980 to 2000 - the Excerpta Medica database, produced by Elsevier Science, is a major biomedical and pharmaceutical database indexing over 3,500 international journals in the following fields: drug research, pharmacology, pharmaceutics, toxicology, clinical and experimental human medicine, health policy and management, public health, occupational health, environmental health, drug dependence and abuse, psychiatry, forensic medicine, and biomedical engineering/instrumentation. There is selective coverage for nursing, dentistry, veterinary medicine, psychology, and alternative medicine. Embase is one of the most widely used biomedical and pharmaceutical databases because of its currency and in-depth indexing. Frequent updates allow access to the latest medical and pharmacological trends. Approximately 375,000 records are added yearly.
- CCTR Issue 1 2000 - since 1996 the Cochrane Collaboration has been developing its own register of trials that may be relevant for inclusion in systematic reviews.
- Cochrane Skin Group Specialised Register 2000[43], [50].
- Sections on topical corticosteroids, topical tacrolimus and ascomycin derivatives will be updated to August 2002. This is because new treatments, such as topical tacrolimus, are reported to have the potential to change the face of atopic dermatitis treatment[51] and an unanswered question

regarding the use of steroids has now been answered via a recent RCT[52]. Ascomycin derivatives, namely, pimecrolimus, is due to be launched in the UK later this year for mild to moderate AD (in contrast to tacrolimus which is licensed in the UK for moderate to severe AD) as an alternative to the mildest topical steroid, hydrocortisone acetate. The update may also go someway to answering the primary research questions identified by 25 clinicians and six consumers identified in an earlier version of this review[39]

The tool used to identify RCTs is referred to as a 'highly sensitive electronic search string', developed by The Cochrane Collaboration to initiate a high-enough recall of references to avoid exclusion of anything that might be a trial (see numbers #1 to #29 of the search string below). By adding specific search terms relevant to the subject area, in this case atopic eczema (see numbers #30 to #40 of the search string below), an element of specificity is given to prevent an unmanageable volume of inappropriate references[53]:

#1 RANDOMIZED CONTROLLED TRIAL.pt.

#2 CONTROLLED CLINICAL TRIAL.pt.

#3 RANDOMIZED CONTROLLED TRIALS.sh.

#4 RANDOM ALLOCATION.sh.

#5 DOUBLE BLIND METHOD.sh.

#6 SINGLE BLIND METHOD.sh.

#7 or/1-6

#8 (ANIMAL not HUMAN).sh.

#9 7 not 8

#10 CLINICAL TRIAL.pt.

#11 exp CLINICAL TRIALS/

#12 (clin$ adj25 trial$).ti,ab.

#4 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.

#14 PLACEBOS.sh.

#15 placebo$.ti,ab.

#16 random$.ti,ab.

#17 RESEARCH DESIGN.sh.

#18 or/10-17

#19 18 not 8

#20 19 not 9

#21 COMPARATIVE STUDY.sh.

#22 exp evaluation studies/

#23 follow up studies.sh.

#24 prospective studies.sh.

#25 (control$ or prospectiv$ or volunteer$).ti,ab.

#26 or/21-25

#27 26 not 8

#28 26 not (9 or 20)

#29 9 or 20 or 28

#30 explode dermatitis, atopic/

#31 dermatitis, atopic.ti,ab,rw,sh.

#32 eczema, atopic.ti,ab,rw,sh.

#33 eczema.ti,ab,rw,sh.

#34 atopic eczema.ti,ab,rw,sh.

#35 atopic dermatitis.ti,ab,rw,sh.

#36 infantile eczema.ti,ab,rw,sh.

#37 childhood eczema.ti,ab,rw,sh.

#38 neurodermatitis.ti,ab,rw,sh.

#39 besniers prurigo.ti,ab,rw,sh.

#40 or/30-39

#42 29 and 40

(Key: $ = wild card)

The above search strategy is not directly transferable to other electronic databases due to the different formats, therefore, Embase was searched using a search strategy developed by the BMJ Publishing

Group for its *Clinical Evidence* series[54]. (Embase has a higher yield of non-English studies, which is important in a systematic review to avoid language bias[44]). Again the AD terms add specificity to the search:

#1 exp clinical trial/ or clinical trial.ti,ab,hw,tn,mf.

#2 exp controlled study/

#3 (clinical trial$ or controlled clinical trial$).ti,ab,hw,tn,mf.

#4 (random$ or placebo$).ti,ab,hw,tn,mf.

#5 double blind.ti,ab,hw,tn,mf.

#6 exp Randomized Controlled Trial/

#7 or/1-6

#8 limit 7 to human

#9 explode dermatitis, atopic/

#10 dermatitis, atopic

#11 eczema, atopic

#12 eczema

#4 atopic eczema

#14 atopic dermatitis

#15 infantile eczema

#16 childhood eczema

#17 neurodermatitis

#18 besniers prurigo

#19 8 and 18

CCTR was searched by using the 'explode' option for the disease-specific search terms separated by the Boolean 'AND' with the advanced search option.

The Cochrane Skin Group Trials Search Co-ordinator searched Cochrane Skin Group Specialised Register using disease-specific terms.

Handsearching is a process adopted by the Cochrane Collaboration to identify trials not identified by or available from electronic databases. It is literally manually searching hard copies of journals for randomized controlled trials[43]. The Cochrane Skin Group (CSG), which is part of the Cochrane Collaboration, initiated a handsearching program in 1998 to handsearch more than 200 dermatology journals published worldwide since 1948. At the time of this review's searches, the CSG was in its infancy in terms of handsearching. Being too great a task for this review, handsearching was not carried out. This is an important point because electronic databases such as Medline, have been shown to miss a large proportion of trial reports[53]. However, as the CSG progressed with the handsearching program, trials identified were checked and transferred onto the Specialised Skin Register. Therefore, after updates until mid 2000, of all databases mentioned, any handsearched journals were included in the searches of the Specialised Skin Register. This included the following journals:

- *Acta Dermato-Venereologica Supplementum* 1970-91
- *Archives of Dermatology* 1976-98
- *British Journal of Dermatology* 1991-97
- *Clinical & Experimental Dermatology* 1976-99
- *Cutis* 1967-99
- *International Journal of Dermatology* 1985-98
- *Journal of Investigative Dermatology* 1991-97
- *Journal of the American Academy of Dermatology* 1987-99

2.6 Filtering and paper-copy retrieval

A yield of over 4000 records was obtained from the electronic database searches, which were printed off and scanned manually for anything that could be a trial of treatments for eczema, i.e., anything that was definitely not a trial of treatments for eczema was crossed off and not retrieved in paper format. Many had abstracts while some were title only. All 'title only' references were retrieved in hard copy to avoid naïve judgement/be 'on the safe side', indeed many with abstracts were retrieved for this reason also - only when it was absolutely clear that a reference was not a trial was it given the tag 'reject'. The terms used in the electronic search string gave guidance for trials and the search terms for AD gave guidance for disease. Where uncertainty arose, a second person's opinion was sought

(Professor Hywel Williams). Paper copies were obtained via medical libraries and interlibrary loans from the British Library.

Once the paper was retrieved it was read thoroughly to ascertain if it was a trial of eczema and if uncertainty arose, a second opinion was sought, if it still wasn't clear the original author was contacted for clarification.

References were catalogued and maintained using specialist reference management software ProCite[55]. This sort of software is an essential aspect of a systematic review for various reasons including the identification of duplicate records and maintaining records. All records including those excluded were kept on the database for reference and checking purposes and appropriately labelled.

Several processes were used to identify randomised, controlled trials of treatments for atopic eczema, the details of which are shown in Figure 6.

2.7 Quality assessment of the studies

Over 25 checklists and scales exist to assess the quality of randomised controlled trials, which vary in complexity - up to 57 items taking up to 45 minutes to complete[56]. One problem, and there are many, that can arise from these scales is confusion between quality of reporting and study quality[44]. With no gold standard or validated scoring system, quality assessment using a scale is limited. Therefore, the following 3 potential sources of bias were evaluated as they are reported to be good predictors of possible bias in effect estimates[57]:

- Quality of the randomisation procedure;
- Extent to which the primary analysis included all participants initially randomised (i.e., an intention-to-treat analysis);
- Extent to which those assessing the outcomes were aware of the treatments of those being assessed (blinding).

2.8 Reporting of results

With such a vast quantity of data the results will be presented in 2 ways:

- 5 or less trials will be presented narratively:
    - Study details including outcome measures
    - Results
    - Adverse effects
    - Notes, which are my comments on anything important that stands out in the study and/or quality issues
- 6 or more will be presented in tabular form:
    - Author and date of study
    - Interventions
    - Population, sample size and study duration
    - Trial design
    - Outcome measures
    - Main reported results
    - Quality of reporting
    - Notes, which are my comments on anything important that stands out in the study and/or quality issues

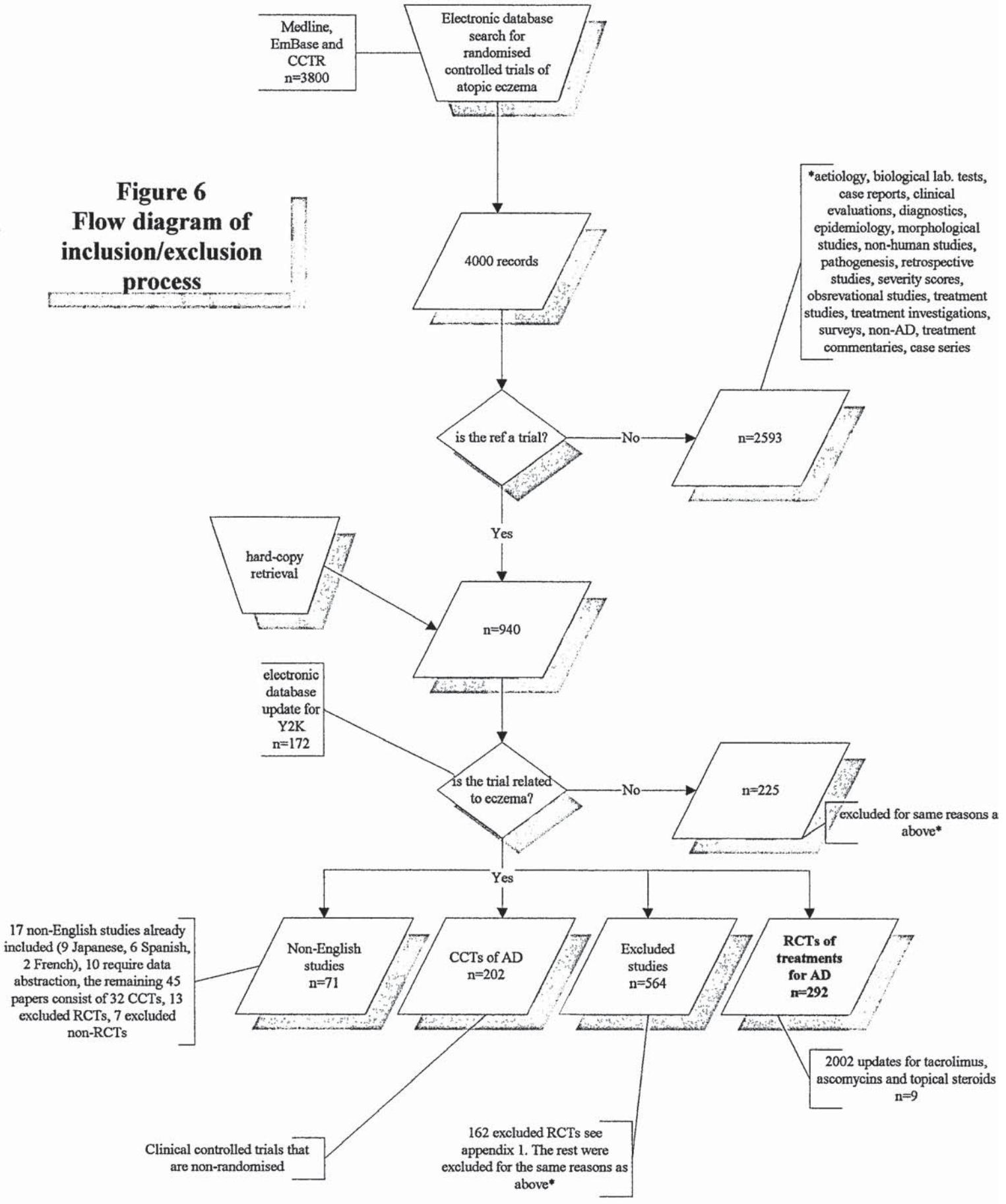
2.9 Non-English studies

If an English translation of a non-English study was not available, it was sent to a Cochrane Group in the relevant country or a dermatology colleague that spoke the language of the trial for translation and, if appropriate, data abstracted. The translator was asked two initial questions:

1. Is the paper a randomised controlled trial comparing two or more treatments or interventions in humans?
2. Is the disease atopic eczema?

If the answer was yes to both questions, the translator filled out a data abstraction form, which mirrored the table layout in the results section of this report. If the answer was no to one or both questions the paper was excluded, the reason why was recorded, and, if appropriate, added to the list of excluded studies in appendix 1.

Figure 6
Flow diagram of inclusion/exclusion process



CHAPTER 3

RESULTS

3.1 Included studies

Of the 4000 records that were captured via the electronic database searches, 292 studies met the inclusion criteria of 'randomised controlled trial of treatments for atopic eczema'. The included trials cover 48 different interventions. The following is an A-Z list of the 48 interventions:

1. Allergen-antibody complexes of house dust mite
2. Antihistamines
3. Antimicrobials
4. Antiseptics
5. Aromatherapy
6. Ascomycins
7. Biofeedback
8. Bioresonance
9. Chinese herbal medicine
10. Clothing
11. Coal tar (topical)
12. Corticosteroids (topical)
13. Cyclosporin
14. Detergents
15. Dietary restriction
16. Doxepin cream (topical)
17. Education (nurse)
18. Emollients
19. Essential fatty acid supplementation
20. Homeopathy
21. House dust mite hyposensitisation
22. House dust mite reduction
23. Hypnotherapy

24. Immunoglobulin
25. Interferon gamma
26. Ketotifen
27. Levamisole
28. Lithium Succinate ointment
29. Massage therapy
30. Nedocromil sodium
31. Nitrazepam
32. Papaverine
33. Platelet-activating factor antagonist
34. Psychological approaches
35. Pyridoxine
36. Ranitidine
37. Salbutamol
38. Salt baths
39. Sodium cromoglycate
40. Suplatast tosilate
41. Tacrolimus
42. Theophylline
43. Thymic extracts
44. Tiacrilast
45. Transfer factor
46. UV light
47. Vitamin E and multivitamins
48. Zinc supplementation

In order to analyse and make some sense of the data, the list of interventions was grouped into treatment types. This process was complicated by lack of clarity over which intervention was being researched. In addition, some papers had reported two or more different combinations of treatments that crossed groups or created sub-groups or questions. An example of this is the corticosteroid

section, which had to be broken down further into 9 subsections. The following groups incorporate all the trials included in this review however, it was impossible to avoid a miscellaneous group (they are in A-Z order):

1. Antihistamines and mast cell stabilisers
2. Antimicrobials and antiseptics
3. Complementary medicine
4. Dietary interventions
5. Miscellaneous
6. Non-pharmacological treatments
7. Other topical agents
8. Systemic immunomodulatory agents
9. Topical steroids

Interventions included in the treatment type groups:

Antihistamines and mast cell stabilisers

- Antihistamines
- Doxepin cream (topical)
- Ketotifen
- Nedocromil sodium
- Sodium cromoglycate
- Tiacrilast

Antimicrobials and antiseptics

- Antimicrobials and antiseptics

Complementary medicine

- Aromatherapy

- Biofeedback
- Bioresonance
- Chinese herbal medicine
- Homeopathy
- Hypnotherapy

Dietary interventions

- Dietary restriction in atopic eczema
- Pyridoxine
- Supplementation with essential fatty acids
- Vitamin e and multivitamins
- Zinc supplementation

Miscellaneous

- Nitrazepam
- Papaverine
- Ranitidine
- Salbutamol
- Suplatast tosilate
- Theophylline

Non-pharmacological treatments

- Avoidance of enzyme-enriched detergents
- Benefit from specialised clothing
- House dust mite hyposensitisation
- House dust mite reduction
- Education (nurse)
- Psychological approaches
- Salt baths

- UV light

Other topical agents

- Ascomycins
- Emollients
- Lithium succinate ointment
- Tacrolimus
- Topical coal tar

Systemic immunomodulatory agents

- Allergen-antibody complexes of house dust mite
- Cyclosporin
- Levamisole
- Platelet-activating factor antagonist
- Interferon-gamma
- Thymic extracts and their synthetic derivatives
- Immunoglobulin
- Transfer factor

Topical steroids

- Versus placebo
- Versus other topical corticosteroids
- Versus other topical preparations
- Plus additional agents
- Different formulations of the same topical corticosteroid
- Once-daily versus more frequent use of the same topical corticosteroids
- Prevention of relapse using topical corticosteroids
- Trails that have specifically examined adverse effects of topical corticosteroids
- Trials that evaluated oral steroids

3.2 Excluded studies

There are several groups of excluded studies; firstly, those that were excluded early on at abstract level that were clearly not trials of eczema (the majority of those excluded, over 3000). This group included studies that addressed the following:

- Adverse effects
- Aetiology
- Biological laboratory tests
- Case reports
- Case series
- Clinical evaluations
- Diagnostics
- Histology
- Miscellaneous epidemiology
- Morphology
- Non-atopic eczema
- Non-human studies
- Observational studies
- Pathogenesis
- Retrospective studies
- Severity scores
- Surveys
- Treatment commentaries
- Treatment investigations
- Treatment studies

Secondly, clinical trials that were not randomised, often referred to as Clinical Controlled Trials and abbreviated to CCTs. Thirdly, studies that were excluded after retrieval and analysis of the actual paper; although many of these included eczema patients, the eczema was unspecified, i.e., not clearly

atopic eczema, and/or the results of the AD patients were combined with patients that had other skin diseases such as psoriasis. These were all randomised clinical trials and are listed, with reasons for exclusion, in appendix 1. Because there were so many excluded topical steroid trials, these are listed under separate headings in appendix 1. In addition to excluded trials of eczema for 'other reasons', and trials of eczema that were excluded at an early stage because 'eczema' was unspecified, there is a category for excluded trials of topical steroids for eczema because there were so many.

3.3 ANTIHISTAMINES AND MAST CELL STABILISERS

3.3.1 Antihistamines

Theoretically antihistamines are thought to have a blocking effect on the histamine receptors in the skin, thereby reducing the itch, a common, debilitating symptom of AD. However, their role as an anti-itch treatment is unclear[39].

There are two types of antihistamine: sedative and non-sedative. More recently, the sedative type of antihistamines are thought to be more beneficial than the non-sedating type in atopic eczema by helping children and adults sleep at night, thereby reducing bouts of itching and scratching[35]. Whether or not they have an effect on the histamine receptors in the skin remains to be substantiated. Nevertheless, antihistamines *are* used in the treatment of AD and I was able to locate 20 randomised, controlled trials, which are summarised in Table 4.

Table 4 RCTs that have evaluated antihistamines in atopic eczema

Author and Date of study	Interventions	Population, sample size, duration of study	Trial design	Outcome measures	Main reported results	Quality of reporting	Notes
Berth-Jones *et al* 1989[58]	terfenadine 120mg twice daily vs placebo	28 patients age range 11-67 years study period 1 week	Crossover RCT	Excoriation and patient itch	No evidence of any difference between terfenadine and placebo	Method of randomisation and concealment unclear. Study described as double blind. No ITT analysis	Terfenadine double normal dose. Low power to detect carry-over effect in only 20 patients. No data in graphical form. First and last period data not presented separately
Doherty *et al* 1989[59]	acrivastine 8mg vs terfenadine 60mg vs placebo	49 patients age range 16-58 years study period 2 weeks	Parallel RCT	Patient-rated itch and doctor-rated itch	Acrivastine significantly reduced itching when compared with placebo according to the doctor's assessment (p=0.021). Both acrivastine (p=0.026) and terfenadine (p=0.037) improved the patient's condition significantly more than placebo	Method and concealment of randomisation unclear, study described as double blind.	Visual analogue data only given for day 7. Five dropouts (4 active, 1 placebo), no ITT analysis. Unclear what was being assessed and what was meant by "careful examination of the skin".

					according to the patient's assessment of the degree of benefit obtained. No significant differences were found between the two active treatments.		
Foulds *et al* 1981[60]	cimetidine + placebo vs sedative h_1+placebo vs cimetidine + h_1	21 patients age range 14-29 years study period 3x2 weeks	Multiple crossover RCT	Erythema, excoriation, patient-rated itch, physician global severity, patient global severity and % body surface area	Although it was found that there was a significant difference between individual patients for patient assessed day pruritis ($P<0.001$) and night pruritis ($0.01<P<0.025$) there was no difference between the treatment periods.	Method and concealment of randomisation unclear, study described as double blind. Only one loss to follow-up, no ITT analysis carried out.	No actual data given for clinical outcomes - only 'p' value for statistical comparisons
Frosch *et al* 1984[61]	cimetidine +chlorpheniramine vs chlorphreniramine + placebo vs placebo+placebo	18 patients age range 14-43 years study period 3x4 weeks	Multiple crossover RCT	Lichenification, patient itch, physician global severity, patient global severity	Analysis of cimetidine plus chlorpheniramine results for weeks 2, 3 and 4 for both day and night time patient assessed itch	Randomisation was conducted according to a Latin square, study described as double blind. Two dropouts - no ITT analysis carried	Baseline itch not given, therefore unable to calculate change. No standard errors given. Missing baseline data.

					compared to chlorpheniramine and placebo failed to show any significant difference.	out.	
Hamada *et al* 1996[62] (Japanese translation)	terfenadine 60mg twice daily + alclometasone propionate (0.1%) ointment twice daily vs placebo	64 patients age range 7-? Years study period 6 weeks	Parallel RCT	Erythema, excoriation, scaling, lichenification, papules/pustules, patient global severity assessment	Itching score and scratch marks were improved significantly. Physician 'improved' and 'markedly improved' was 89.3% in antihistamine and steroid group compared with 50% in the topical steroid only group.	Method and concealment of randomisation unclear, study described as double blind. No ITT analysis.	Used different topical steroids in each intervention and no oral placebo.
Hannuksela *et al* 1993[63]	three different doses of cetirizine 10mg, 20mg, and 40mg daily	178 patients age range 18+ years study period 4 weeks	Parallel RCT	Erythema, excoriation, scaling, vesiculation, patient-rated itch, doctor-rated itch, patient-rated sleep loss, physician global severity assessment, patient global severity	There was a non-significant difference between groups in patient assessed pruritis intensity at baseline. All groups improved significantly (P=0.005). This improvement was significantly more	Method and concealment of randomisation unclear. No ITT analysis carried out.	Possible benefit of cetirizine when used at four times normal dose, but at the expense of sedation. A high dropout rate of 51, 20 for side effects (mainly sedation) and 19 non-compliers, doesn't specify

				assessment	pronounced for cetirizine 40mg compared to placebo.		drug group.
Henz *et al* 1998[64]	Azelastine 4 mg Vs Cetirizine 10mg Vs placebo	74 patients with atopic eczema, 244 total including urticaria age range 17-67 years study period 2 weeks	Parallel RCT	Erythema, scaling, patient-rated itch, physician global severity assessment	Mean overall % response rate based on physician's global score was 36.4%, 25.0% and 27.3% in the azelastine, cetirizine and placebo groups respectively. Baseline data and exact numbers of atopic eczema patients in each group were not stated. Mean itching score dropped from 2.2 to 1.4 in the cetirizine group and from 2.2 to 1.2 in both azelastine and placebo groups (estimated from graphs).	Method and concealment of randomisation unclear. No ITT analysis carried out.	Neither drug reduced itching significantly more than placebo. Statistics not given for AE patients, no description of what constituted a response, placebo looks very impressive, clearly no difference in AE patients. High dropout rate of 37.
Hjorth *et al* 1988[65]	Terfenadine 60mg twice daily Vs	30 patients no age range data study period 2	Crossover RCT	Patient-rated itch	Terfenadine reduced severity of itch in	Method and concealment of randomisation	No outcome data given and no information

	placebo	weeks			approximately 52% of patients, 34% reported no change and 14% reported increased severity of itch. No data given for placebo.	unclear, study described as double blind. Unclear if any dropouts or withdrawals. Author since deceased.	whatsoever on placebo response.
Ishibashi *et al* 1989a[66] (Japanese translation)	E-0659 (Azelastine hydrochloride) 0.017mg/kg/day Vs Azelastine hydrochloride 0.07mg/kg/day Vs Azelastine hydrochloride 0.4mg/kg/day	157 patients general improvement rating (GIR), 168 patients overall safety rating (OSR), 159 patients general usefulness rating (GUR) age range 1-15 years study period 4 weeks	Parallel RCT	Erythema, excoriation, lichenification, pustules/papules, oozing/weeping, doctor-rated itch	No significant difference in general improvement rating, overall severity rating and general usefulness rating among the three dose groups. A significant difference in improvement ratio was found among three dose group in the signs if itch, papules, erythema, and lichenification.	No translated data available	No translated data available
Ishibashi *et al* 1989b[67] (Japanese translation)	E-0659 (Azelastine hydrochloride) 4mg/day and 2mg/day Vs	169 patients GIR, 179 patients OSR. No data available for GUR study period 4 weeks	Parallel RCT	Erythema, excoriation, lichenification, pustules/papules, oozing/weeping, doctor-rated itch	No difference in final general improvement rating or general usefulness rating among the three	No translated data available	No translated data available

	Ketotifen				groups. The effectiveness and usefulness in the treatment of atopic eczema were considered similar for the three groups. There was a significant difference in overall safety rating between the 4mg/day and 2mg/day groups. The safety rating was higher in the 2mg/day group than in the 4mg/day group. The overall safety rating showed no significant difference between the 4mg/day and ketotifen groups or the 2mg/day and ketotifen groups.		
Klein *et al* 1980[68]	Hydroxyzine 1.25mg/kg/day Vs	20 patients age range 2-16 years	Parallel RCT	Erythema, excoriation, patient-rated itch,	The group receiving hydroxyzine had a	Method and concealment of randomisation	Unstable data shown on a graph with inflationary

	Cyproheptadine 0.25mg/kg/day	study period 1 week		doctor-rated itch, physician global severity assessment	daytime percentage improvement of 32.14 ± 4.98 (mean ± S.E.M.) over their baseline pruritis for the entire week, which is significantly greater ($p<0.001$) than the percentage improvement for the cyproheptadine group of 6.21 ± 4.90.	unclear, study described as double blind. Not clear if any dropouts or withdrawals.	% scale but no actual data given.
Langeland *et al* 1994[69]	Loratadine 10mg Vs Placebo	16 patients age range 19-37 study period 12 weeks	Six consecutive crossover RCTs	Patient-rated itch	The study detected a significant effect of loratadine, as compared with placebo, on patient assessed pruritis during the day and night and severity of rash.	Method and concealment of randomisation unclear, study described as double blind (block randomised).	Complex design, six consecutive crossovers. Changes in pruritis on visual analogue scale - all small differences. No data for period or carry-over effects shown.
La Rosa *et al* 1994[70]	Cetirizine 5mg/day for 30kg body weight and under, 10mg/day	23 patients age range 6-12 years study period 8	Parallel RCT		Patient diary card scores showed a statistically significant	Method and concealment of randomisation unclear, study	Higher baseline scores in those on active treatments suggest that

	for over 30kg body weight Vs placebo	weeks			decrease in erythema and other cutaneous symptoms such as lichenification, in the cetirizine group. Improvement over baseline total mean global score of 230 for cetirizine reduced to 155 after 8 weeks treatment, and a baseline of 205 for placebo reduced to 180 ($p>0.05$) after 8 weeks treatment (estimated from graph).	described as double blind. Only one dropout (voluntary withdrawal).	regression to the mean could partly account for results.
Monroe 1992[71]	Loratadine 10mg once daily plus placebo twice daily Vs hydroxyzine 25mg three times daily Vs placebo three times daily	59 patients age range 18-65 years study period 1 week	Parallel RCT	Erythema, patient-rated itch	The daily pruritis score decreased 57% in the 14 patients treated with loratadine, 38% in the 14 patients treated with hydroxyzine, and 33% in the 4 patients treated with placebo.	Method and concealment of randomisation unclear, study described as double blind.	Patients excluded if unresponsive to antihistamines. No baseline values given. Very short study at 1 week.
Patel *et al* 1997[72]	Loratadine	118 patients	Parallel RCT	Erythema,	Loratadine	Method and	Study excludes

	10mg/day Vs Cetirizine 10mg/day	age range 12-65 years study period 2 weeks		excoriation, lichenification, patient-rated itch, doctor-rated itch, patient-rated sleep loss, physician global severity assessment, patient global severity assessment	reduced patients perceived severity of their overall condition by 20.8% at endpoint. Incidence of somnolence was 9% with cetirizine and 3% with loratadine.	concealment of randomisation unclear, study described as double blind. The report suggests 'intent-to-treat' but fails to carry it out.	non-responders before study started but not told how many. Unclear if either drug is of benefit in absence of placebo group.
Savin *et al* 1979[73]	Trimeprazine tartrate 20mg Vs Trimeprazine maleate 50mg Vs placebo	12 patients age range 23-38 years study period 3 nights over 4 weeks?	Unclear if parallel or crossover RCT	Patient-rated sleep loss	Neither of the drugs altered the likelihood of scratching bout beginning in wakefulness or in any stage of sleep. However, both drugs, especially trimeprazine, made sleep less broken, and the reduced time spent in stage 1 of sleep accounted for a modest reduction in the overall amount of scratching during the night.	Unclear if parallel or crossover study. Length of study unclear. Method and concealment of randomisation unclear, study described as double blind. Withdrawals or dropouts not mentioned in this study.	Unclear if the changes in sleep pattern helped the patient's eczema.
Savin *et al* 1986[74]	LN2974 15mg Vs	10 patients age range no data	Multiple crossover RCT	Patient-rated itch	No significant difference was	Method and concealment of	No actual data given.

	placebo	study period 10 days			detected between the limb movement times on placebo and on active treatment with LN2974. The difference between the mean scores of the visual analogue assessment of itching on placebo and on LN2974 did not reach statistical significance although tending to favour LN2974.	randomisation unclear, study described as double blind. Unclear if any withdrawals or dropouts.	
Simons *et al* 1984[75]	Hydroxyzine 1.4mg/kg Vs Hydroxyzine 0.7mg/kg	12 patients age range 1-14 years study period 4 days	Crossover RCT	Doctor-rated itch	The scores for atopic eczema severity and distribution were significantly reduced at the end of treatment for both doses of hydroxyzine ($P \leq 0.05$).	Method and concealment of randomisation unclear, study described as double blind. Unclear of any withdrawals or dropouts. Sample size unclear.	This trial was buried in the middle of a case-series. Only presented mean score at end of treatment rather than mean change in score. Itch data and baseline scores not given. Point of randomisation was after the

							single dose study. Far too small a study to establish equivalence effects.
Wahlgren *et al* 1990[76]	Terfenadine 60mg twice daily Vs Clemastine 2mg twice daily	25 patients age range 17-42 years study period 3 days	Crossover RCT	Patient-rated itch	No significant changes of difference in itch intensity between the three treatment periods (detected with Pain-Track), nor was there any difference in time awake without pruritis. No significant changes in itch magnitude appeared during each period (days 0-3).	Method and concealment of randomisation unclear, study described as double blind. No withdrawals or dropouts.	Very short trial of only 3 days - underpowered.
Zuluaga de Cadena *et al* 1989[77] (Colombian translated)	Hydroxyzine 25mg daily in three divided doses Vs Terfenadine 10mg daily in two divided doses Vs Astemizole 5mg	52 patients age range 2-6 years study period 4 weeks	Parallel RCT	Erythema, lichenification, vesiculation, pustules/papules, oozing/weeping, oedema	At the end of the 4 week evaluation period, 8 out of 15 patients on Terfenadine compared with 8 out of 17 patients on Astemizole and 6 out of 8 patients on	Method and concealment of randomisation unclear. Study described as single (investigative)-blind. No intention-to-treat analysis.	Outcome measures and their combination were quite complex. Small numbers and no placebo group.

	daily in one dose				Hydroxyzine had improvement in itch. Global improvement was noticed in 14 out of 15 cases on Terfenadine, 15 out of 17 cases on Astemizole and 7 out 8 cases on Hydroxyzine. Improvement in other outcome measures was similar between all 3 groups. Other laboratory measures were also recorded.		

3.3.2 Doxepin

Topical doxepin has been derived from the oral type of doxepin, which is a tricyclic antidepressant. Doxepin is a histamine antagonist for both H_1 and H_2 receptors and the theory behind the topical formulation is the idea that it might suppress the itch associated with AD.

Four RCTs assessing topical doxepin in AD were identified [78-81]:

Study 1

- Drake and Fallon *et al* 1994[78]
- 5% doxepin cream versus vehicle, 4 times daily
- 270 patients with AD
- study duration 7 days
- outcome measures
    - patient-rated itch
    - physician-rated itch
    - physician-reported eczema severity

Results

- Patient-rated itch via 100mm visual analogue scale (VAS) (0=no relief, 100=complete relief) - baseline for both groups was 0, after 7 days treatment the VAS was 68.6 for the doxepin group and 54.6 for the vehicle-only group
- Physician-rated itch was reported in 85% of patients taking doxepin compared to 57% of those treated by vehicle alone
- Physician-reported eczema severity was reported as 'better' in the doxepin group but no data was given

Study 2

- Breneman and Dunlap *et al* 1997[79]
- 5% doxepin cream versus vehicle

- 120 patients with AD or lichen simplex chronicus
- study duration 7-14 days
- outcome measures:
    - patient-rated VAS of pruritis severity and pruritis relief

Results

- 75% reported reductions in pruritis severity 15 mins post-treatment
- 85% reported reductions in pruritis severity 120 mins post-treatment
- there was no clinically or statistically significant difference in patient-assessed itch relief at the end of the 7-day RCT

Note

- the paper reported a mixture of atopic dermatitis and lichen simplex and did not separate the results

Study 3

- Berberian and Breneman *et al* 1999[80]
- 4 groups randomly allocated to 2.5% hydrocortisone, 0.1% triamcinolone acetonide, 2.5% hydrocortisone plus 5% doxepin cream or 0.1% triamcinolone acetonide plus 5% doxepin cream, 4 times daily
- 349 patients
- study duration 8 days
- outcome measures:
    - patient-rated itch via VAS
    - physician's global eczema severity assessment

Results

- Patient-rated itch in doxepin/hydrocortisone group versus hydrocortisone group was 77.8 and 68.3 respectively (VAS, 100=complete relief of itching). For doxepin/triamcinolone versus

triamcinolone groups, VAS was 94.9 versus 90.5, respectively ($p<0.05$) (baseline scores not given)

- Physician's global evaluation of eczema severity was not significantly different clinically or statistically

Study 4

- Drake and Cohen *et al* 1999[81]
- 5% doxepin hydrochloride cream versus 5% doxepin hydrochloride cream plus 0.025% triamcinolone acetonide
- 24 adults with AD
- study duration 7 days
- outcome measures:
    - pruritis severity scores (one of 6 itching assessment methods used in this study)

Results

- limited efficacy data given as mainly a pharmacokinetic study
- pruritis severity scores demonstrated statistically significant greater improvement in the doxepin/triamcinolone group at 8 days ($p=0.001$)

Note

- actual data for pruritis severity scores and other pruritis outcomes were not given

Adverse effects (for all studies)

- transient stinging or burning in doxepin-treated groups
- drowsiness in doxepin groups

Notes

- quality of reporting in all 4 studies was good for methods of randomisation, description of blinding and an intention-to-treat analysis was carried out in all studies

- all 4 RCTS were sponsored by the manufacturer of doxepin and were conducted by same group of investigators

3.3.3 Ketotifen

Ketotifen is a tricyclic benzocycloheptathiophene derivative with anti-anaphylactic and antihistamine activities. It is thought to play a role in IgE- and non-IgE-mediated mechanisms[82].

Two RCTs assessing ketotifen in AD were located, one in adults and one in children[83 84].

Study 1

- Falk 1993[83]
- ketotifen 1mg twice daily versus placebo
- 60 adults with AD
- study duration 3 months
- outcome measures:
  - itch
  - sleep loss
  - erythema
  - lichenification
  - overall efficacy of treatment

Results

- improvement of itch over baseline on a scale of 1-3 was 2.40 reduced to 1.20 for ketotifen ($p<0.01$) versus 2.30 reduced to 1.60 for placebo ($p<0.05$)

Study 2

- White and Macdonald *et al* 1988[84]
- 1-2mg ketotifen twice daily versus placebo
- 42 children (15 had AD)

- study period 4 months
- outcome measures:
    - parent-assessed diary cards for asthma symptom scores, plus night itch, day itch and redness of skin

Results

- no statistically significant beneficial effect of ketotifen was shown in asthma, allergic rhinitis or eczema

Adverse effects

- apart from slight drowsiness, no other adverse effects were reported

Notes

- The results of the Falk study[83] were difficult to interpret as no test of differences between the two treatments and no standard errors were given
- Method and concealment of randomisation were unclear, study described as double-blind
- Four dropouts, no intention-to-treat analysis
- White study[84] primarily evaluated ketotifen for asthma, with a sub-group of 15 children with eczema which was too small for meaningful analysis
- Method and concealment of randomisation were unclear, study described as double blind
- Withdrawals or dropouts not mentioned

3.3.4 Nedocromil sodium

Nedocromil sodium, the disodium salt of pyranoquinoline dicarboxylic acid, is a mast cell stabiliser mainly used in the treatment of asthma. It acts on the mucosal mast cells by preventing the release of inflammatory mediators, and blocks the late cutaneous reactions in mast cell-dependent allergic reactions.

Three RCTs evaluating nedocromil sodium in the treatment of AD were located[85-87].

Study 1

- Kemmett and Barneston 1987[85]
- 4% nedocromil sodium cream versus matching placebo
- 32 patients with AD
- study period 4 weeks
- outcome measures:
    - patient-assessed itch, redness and weeping
    - clinical assessment
    - IgE levels

Results

- No significant differences between nedocromil cream and placebo cream

Note

- No data given for results

Study 2

- van Bever and Stevens 1989[86]
- 4% nedocromil sodium versus vehicle only
- 26 adults and children with AD
- study period 4 weeks
- outcome measures:
    - itch
    - sleep loss
    - overall severity of skin lesions
    - skin examination for severity of skin lesions

Results

- no difference detected between the two treatments

Study 3

- Benton and McFarlane *et al* 1990[87]
- oral nedocromil sodium 100mg three times daily versus placebo
- 22 adults with moderate to severe AD
- study period 4 weeks
- outcome measures:
  - patient diary cards for itch, redness and weeping
  - clinician's overall opinion

Results

- no significant differences between active treatment and placebo

Adverse effects

- full blood counts and tests of renal and hepatic function to detect drug toxicity were all negative[87]
- one patient developed persistent diarrhoea, which ceased on withdrawal of drug[87]
- 17 episodes of flaring of symptoms, nine in the nedocromil sodium group[86]
- one patient reported dryness of skin, another reported furunculosis[86]

Notes

- all three studies were randomised but method and concealment of randomisation was unclear, all described as double blind
- Kemmett *et al* [85] was in abstract form only so little information was available and no data were given for results
- van Bever and Stevens[86] did not state whether daily score card was patient or doctor-assessed, and no actual data were given
- It was unclear how many patients were enrolled in the Benton *et al* study[87]

- studies were small and over short periods of time

3.3.5 Sodium cromoglycate

Sodium cromoglycate (SCG) is the salt of a bis-chromone carboxylic acid, often used in the treatment and prophylaxis of bronchial asthma, allergic rhinitis and other disorders associated with mast-cell degranulation. One mode of action of SCG is thought to be on inflammatory cells, where it inhibits various leukocyte functions, another is inhibition of histamine release from mast cells[88]. SCG is also thought to reduce intestinal permeability; increased intestinal permeability to macromolecules is thought to be one of the predisposing factors to food allergy in children with AD[89].

Ten RCTs of topical SCG and ten RCTs of oral SCG were identified [89-108] which are summarised in Tables 5 and 6.

Table 5 Oral sodium cromoglycate (also known as disodium cromoglycate and cromolyn) in atopic eczema

Author and date of study	Interventions	Population, sample size and study duration	Trial design	Outcome measures	Main reported results	Quality of reporting	Notes
Atherton *et al* 1982[99]	Oral SCG 100mg 4 times daily Vs placebo	29 patients age range 2-10 years study period 4 weeks	Crossover RCT	Patient-assessed itch and sleep loss. Physician-assessed erythema, vesiculation and/or crusting, excoriation and lichenification	No difference detected at 4 weeks between the effects of DSCG and placebo	Randomisation, blinding and four-week washout period appear adequate.	Small and short-term study.
Birkeland *et al* 1981[104]	Oral disodium cromoglycate (DSCG) 6mg three times daily Vs placebo	28 patients age range 19-48 years study period 6 weeks	Parallel RCT	Colour, scaling, infiltration, itching of the three most active eczematous regions. Total serum IgE. Reduction in disease activity	No significant changes were found between the severe and mild atopic eczema for number of regions involved at the first visit and reduction in disease activity during the trial. Serum IgE in relation to T and B cells shows non-significant differences in the figures in the severe and mild	Method and concealment of randomisation unclear, study described as double blind. Unclear whether any drop outs.	

					atopic dermatitis for T cells and B cells.		
Burks and Sampson 1988[103]	Oral cromolyn 30-40mg/kg/day Vs placebo	10 patients age range 3-15 years study period 1 week	Crossover RCT	Parent symptom diary cards for rash distribution, pruritis and urticaria	Sodium cromoglycate (40mg/kg/day) did not protect against food-induced symptoms in patients with atopic eczema and egg hypersensitivity	Method and concealment of randomisation unclear, study described as double blind.	Only ten children were studied and eight reacted to food challenge in this crossover study.
Businco *et al* 1986[101]	Oral SCG aqueous solution Vs placebo	31 patients age range 0.5-10 years study period 8 weeks	Crossover RCT	Parent-assessed diary cards for itching and sleep disturbance. Clinician-assessed redness, weeping, vesiculation, crusting, excoriations, lichenification	Increase in symptom score higher when patients were given DSCG than placebo	Randomisation , blinding and two-week washout period appear adequate.	Patients had history of food hypersensitivity. Small and short-term study.
Graham *et al* 1984[93]	Oral SCG 100mg 4 times daily Versus 200mg 4 times daily Vs placebo	29 patients age range 3-12 years study period 6 weeks	Crossover RCT	Patient diary card for pruritis, sleeplessness, severity and area of eczema Clinical assessment of area affected and	Mean eczema scores for severity and area not different between groups receiving SCG and placebo	Randomisation , blinding and two-week washout period appear adequate.	Small and short-term study. Patients had history of food hypersensitivity.

				severity Dryness and excoriation			
Kavli and Larsen 1981[100]	FPL 57787 (chromone carboxylic acid) 18mg 4 times daily Vs placebo	35 patients age range 15-42 years study period 2 weeks	Crossover RCT	Patient diary cards for itching, sleep loss, lichenification, excoriation and redness. Clinician-assessed disease extent and severity	A significant reduction in patient assessed itch was found for chromone carboxylic acid in the placebo, washout, chromone group ($p<0.05$) after 6 weeks treatment. Significant differences were found for lichenification, excoriation and redness in the placebo, washout, chromone group for clinically assessed signs ($p=0.05$). No significant differences were found between chromone followed by placebo groups at 3 weeks treatment.	Method and concealment of randomisation unclear, study described as double blind. Over half enrolled patients dropped out (n=18) mainly due to increased severity of atopic eczema or ineffective treatment, no intention to treat analysis carried out.	

Larsen and Larsen 1979[102]	FPL 57787 6mg 4 times daily Vs placebo	14 patients age range 18+ study period 6 weeks	Parallel RCT	General assessment of the eczema and severity of itch plus scaling, colour, lichenification	No statistically significant differences in the clinician's scores for any parameter.	Method and concealment of randomisation unclear, study described as double blind. No dropouts.	No results data given. Small sample over a short period of time.
Larsen and Jacobsen 1980[91]	FPL 57787 18mg 4 times daily Vs placebo	23 patients age range 18-41 study period 6 weeks	Crossover RCT	Clinician-assessed dryness, lichenification and excoriation	There were no statistically significant differences in the clinical assessments, in the patients' diary cards. Eleven patients preferred the active period, while 9 patients preferred the placebo period.	Method and concealment of randomisation unclear, study described as double blind. Three dropouts, no ITT. No results data given.	Small sample over a short period of time. Authors conclude "Our first study[102]gave some evidence that FPL 57787 might be effective in the treatment of AE". However, it gave no evidence of benefit. The later study used 3 times (18mg three times daily) the earlier dose of 6mg 3 times daily.
Lindskov and Knudson 1983[106]	Oral DSCG 200mg (adults)/ 100mg (children) 4 times daily Vs placebo	24 patients age range 4-37 study period 6 weeks	Crossover RCT	Patient- or parent-assessed day- and night-time itching and general severity of eczema Clinician-assessed	No significant differences between the two treatments in the patients' assessments	Cross-over trial with no wash-out period	Small study of 14adults and 10 children

				lichenification, eczema and overall disease			
Ventura *et al* 1996[89]	Oral DSCG 100-200mg/kg/day 4 times daily Vs placebo	83 patients age range 0.1-1.5 years study period 4 weeks	Parallel RCT	Clinician-assessed erythema, exudation, lichenification, eczema extension and itch	No difference in eczema score in the DSCG and placebo groups	Parallel group trial. Randomisation and blinding adequate	

Table 6 RCTs that have evaluated topical SCG in atopic eczema

Author and date of study	Interventions	Population, sample size	Trial design	Outcome measures	Main reported results	Quality of reporting	Notes
Ariyanayagum *et al* 1985[98]	4% SCG Vs placebo	46 patients age range 16-65 years study period 12 weeks	Parallel RCT	Patient diary card for pruritis, sleeplessness, severity of eczema and use of concomitant therapy Severity assessed on erythema, lichenification, vesiculation, dryness and excoriation	Mean eczema severity score reduced significantly at 12 weeks compared to 3 weeks in patients on DSCG but not on placebo. The same effects were seen with daytime itch and night-time itch.	Method and concealment of randomisation unclear, study described as double-blind	Short-term study of 12 weeks with an open label follow-up of one year
Croner *et al* 1981[96]	10% SCG w/w in white soft paraffin vs vehicle	22 patients age range 2-16 years study period 6 weeks	Parallel RCT	Patient diary cards for itch (day and night), sleep disturbance and severity of eczema on face, trunk, arms, legs	No significant group differences found except for less frequent use of steroids	Method and concealment of randomisation unclear, study described as double-blind	Small short-term study
Haider *et al* 1977[92]	10% SCG in white soft paraffin vs placebo	44 patients age range 3.5-14 years study period 12 weeks	Parallel RCT	Patient diary card for itch and sleep disturbance Physician-assessed inflammation, lichenification and cracking of the arms and legs	Significantly more withdrew for lack of effect from the placebo than the DSCG arms (16/21 versus 4/21)	Method and concealment of randomisation unclear, study described as double-blind	Small short-term study.

Hiratsuka *et al* 1996[108]	Topical SCG (concentration not given) Vs Beclamethasone dipropionate	43 patients age range 5-14 years study period 2 weeks	Parallel RCT	Patient diary cards for itching and sleep disturbance Physician-assessed inflammation, lichenification, cracking on 15 body areas	Equivalent to beclomethasone dipropionate in reducing eczema scores at 2 weeks	Method and concealment of randomisation unclear, study described as double-blind	Small short term study
Kimata *et al* 1990[90]	Cromolyn nebulizer solution Vs placebo	45 patients age range 8 mths to 3 yrs study period 4 weeks	Parallel RCT	Patient-assessed itch and sleep-loss Physician-assessed inflammation, lichenification, cracking	Itch scores, eczema scores and sleep scores all improved by week 2	Method and concealment of randomisation unclear, study described as double-blind	Small short term study
Kimata *et al* 1994[97]	SCG nebulizer plus oxatomide 1.5mg/kg/day Vs Placebo (water solution plus oxatomide)	53 patients age range 4-14 years study period 4 weeks	Parallel RCT	Patient-assessed itch and sleep-loss Physician-assessed lichenification, inflammation and cracking	Itch scores, eczema scores and sleep scores all improved with DSCG but not with placebo	Method and concealment of randomisation unclear, study described as double-blind	Small short term study
Kjellman *et al* 1986[105]	SCG 4% oil in water Vs placebo	40 patients age range 1-18 years study period 12 weeks	Parallel RCT	Patient diary cards for itch, sleep disturbance and overall severity (redness, vesiculation, crusting, excoriation, lichenification)	No significant change in itch scores or sleep disturbance reported	Method and concealment of randomisation unclear, study described as double-blind	Small short term study

Moore *et al* 1998[94]	Cromolyn sodium inhalation solution 0.21% Vs Placebo	26 patients age range 0.5-18 years study period 4 weeks	Crossover RCT	Physician-assessed erythema, vesiculation, crusting and cracking, scaling, lichenification	At 1 month cross over period, the group receiving DSCG first had a higher reduction in eczema scores than did those who received placebo first	Method and concealment of randomisation unclear, study described as double-blind	Small short term study
Pike *et al* 1988[107]	SCG oil in water cream Vs Placebo	36 patients age range 1-14 years study period 12 weeks	Parallel RCT	Physician-assessed diary charts recording pruritis, sleep disturbance	No numerical data reported	Method and concealment of randomisation unclear, study described as double-blind	Letter little detail given
Thirumoorthy *et al* 1978[95]	DSCG 10% in white soft paraffin Vs Placebo	11 patients age range 1-1.5 years study period 4 weeks	Right/left comparison RCT	Patient diary card for itch Clinical responses of the 2 sides assessed weekly by clinician and patient	No data given	Method and concealment of randomisation unclear, study described as double-blind	Letter little detail given. Eight patients only

3.3.6 Tiacrilast

Tiacrilast is a mast cell degranulation inhibitor. Mast cells have been identified as potentially significant in atopic eczema, hence, tiacrilast has been developed for topical application to eczema lesions in a single RCT:

Study 1

- Czarnetzki *et al* 1993[109]
- 3% tiacrilast hydrogel versus vehicle
- 37 adults with AD
- study duration 28 days
- outcome measures:
- composite scale of signs and itching (33% reduction in score from baseline for positive 'response')

Results

- 78% responded to the active drug compared to 75% with the vehicle (p=0.614)

Adverse effects

- generally well tolerated; one patient experienced burning sensation at the site of drug application

Notes

- method and concealment of randomisation were unclear
- 5 dropouts no reason given; no intention-to-treat analysis carried out
- lack of difference between active and vehicle although it was an under-powered study

3.4 ANTIMICROBIALS, ANTISEPTICS AND ANTIFUNGALS

Atopic eczema is prone to secondary infection by *Staphylococcus aureus,* a bacterium found in small quantities on some people's skin but found in much greater quantities on the skin of those with AD; less than 10% of those without AD have *Staph. aureus* on the skin compared to 75-100% of those with AD[110]. The bacteria can be found on 30-100% of AD uninvolved skin as well as AD involved skin, and is not necessarily clinically infected by the presence of *Staph. aureus*[39]. The transition from uninfected skin to infected skin is not clearly understood, and whether the bacteria migrate to the lesions from uninvolved skin or are spread by scratching, or indeed both, is not clear, but probable[39]. Nevertheless, AD is made worse by secondary infection of this type and requires immediate medical attention. Other types of infection that can be associated with AD are fungal such as *Candida* and viral such as *Herpes simplex*[111].

Ten RCTs were located that assessed antimicrobials, antiseptics or antifungals in the treatment of infected AD and are presented in Table 7.

Table 7 Antimicrobials, antiseptics and antifungals

Author and date of study	Interventions	Population and sample size	Trial design	Outcome measures	Main reported results	Quality of reporting	Notes
Salo *et al* 1988[112]	Oral erythromycin acistrate (EA) 400mg three times daily Vs Oral erythromycin stearate (ES) 500mg three times daily	42 patients age range 15-66 years study period 5-12 days Note: most had bacteriological isolates of *S.aureus* and four had combined *Staph/Strep* infection	Parallel RCT	Investigator and patient assessment of treatment efficacy on a five point Likert scale and side effects	Mean duration of treatment was 7.7 days in the EA group and 7.5 days and ES group. At the end of treatment, 75% and 83% of those in the EA and Es groups respectively were noted to show "good" or "very effective" improvement. Similar results according to patients. Gastrointestinal side effects similar in both groups	Method of randomisation and concealment unclear. No intention to treat analysis	Difficult to evaluate since two "actives" were being compared in the presence of inpatient care and potent co-treatment (topical steroids). The fact that 7 patients with clinically infected eczema did not have any bacteriological evidence of infection confirms the difficulty understanding the link between disease and bacteria
Weinberg *et al* 1992[113]	Oral cefadroxil 50mg/kg/day in two equal doses Vs Placebo	33 patients age range 0.5-12 years study period 2 weeks Note: all bacteriologically confirmed	Parallel RCT	Clearance of superinfection (assessed clinically), eczema severity, number of patients with positive cultures and global	Of 30 evaluable patients, all 4 in the cefadroxil group no longer had clinical evidence of superinfection at the end of the study compared	Method of randomisation and concealment unclear. No description of blinding. No intention to treat analysis	Results clearly in favour of cefadroxil for the children with infected atopic eczema. Poor quality of reporting.

		superinfected atopic eczema caused by *S.aureus* or mixed *Staph/Strep* infection		improvement	with 6 out of 15 in the placebo group. Number of patients with positive isolates fell from 4 to 4 and from 17 to 9 in the cefadroxil and placebo groups respectively. Physician-rated global improvement recorded marked or moderate improvement in 84% of cefadroxil compared with 53% of placebo-treated patients		
Ewing *et al* 1998[114]	Oral flucloxacillin 250mg daily or matched placebo four times daily	50 children with AD age range 1-16 years study period 4 weeks Note: none had any signs suggestive of bacterial infection	Parallel RCT	Change in bacteriological count of *S.aureus*, patient compliance, and composite eczema severity scores	Although mean *S.aureus* counts decreased significantly in those treated with flucloxacillin, clinical efficacy scores did not change between the two groups in any systematic way. The difference in bacteriological	Good description of randomisation and blinding, but no intention-to-treat analysis (5 dropouts by week 4)	An important study that did not find any evidence to support prolonged use of anti-staphylococcal antibiotics in those with clinically uninfected atopic eczema. Flucloxacillin only temporarily

					counts at 14 days after stopping treatment was no longer significant (p=0.32). Methicillin-resistant strains were commoner in those on flucloxacillin		changed skin colonization by *S.aureus*
Lever *et al* 1988[115]	Topical mupirocin ointment Vs placebo	49 patients age range2-56 years study period 2 weeks Note: all had relapsing AD without overt secondary skin infection	Crossover RCT (crossover period with a 2-week run-in, two 2-week crossover periods and a further 4-week follow-up)	Type and counts of bacterial isolates, composite clinical severity score and extent involved by disease. Patients' assessment of appearance, itch and sleep	Bacterial count for 45 evaluable patients was significantly reduced in those receiving topical mupirocin but not in the placebo group, although recolonization occurred in the 4-week follow-up period (17% of whom had developed a "new" strain that had not been previously isolated). For the first treatment period, total skin severity score fell from a mean of 69.9 to 68 in the placebo group	Method of randomisation and concealment unclear. No intention to treat analysis. No analysis of period or carry over effect. Results suggest a significant carry-over effect between first and second periods	Crossover design not ideally suited to a study of antibiotics with delayed actions on the skin. Some evidence of atopic eczema improvement in the first study period in favour of mupirocin. Concern for selection of resistant strains

					compared with a fall from 59.5 to 37.6 in the mupirocin group ($p<0.002$). Changes for surface area were not so marked. Patient assessments were statistically in favour of the mupirocin for the first treatment period		
Stalder *et al* 1992 [116]	Proprietary brand of chlorhexidine solution Vs 1:20,000 dilution of potassium permanganate solution	20 children age range 5 months to 9 years Study period 1 week Note: no detail given if they were clinically infected	Parallel RCT	Bacterial counts, composite clinical score and patient reported tolerance	Total severity score fell from 8.8 at day 0 to 5.7 at the end of the 7 days for chlorhexidine and from 11.1 to 8.8 for the permanganate group (p=0.63). Intensity and number of affected sites also showed very little difference between the two groups. Bacterial counts fell substantially in both groups but	Poor quality of reporting with very few methodological details	Difficult to interpret with such a tiny study and the comparison of two active treatments. Scanty methodological detail. The clinical tolerance data was the most useful

					they were not statistically significant (p=0.37) and baseline scores in the 2 groups were quite different. Clinical tolerance was "good" in both groups		
Sasai-Takedatsu *et al* 1997 [117]	Spraying infants with water twice a day for 1 week Vs Spraying infants with an acid electrolytic water (pH<2.7) using a spray gun	22 children age range 2-56 months with mild to moderate AD	Parallel RCT	Colony counts of *S.aureus*, composite grading score, and scores for itching and sleep disturbance	Colony counts decreased by around 50% in the active but not in the water group (although baseline scores were quite different). Global severity scores fell from 9 to 5 in the active group compared with a rise from 7 to 8 in the water group. Scores for itching and sleep disturbance also decreased in the active group but not in the water group	Although the study was described as randomised, there is serious cause to challenge this in the methods section whereby the authors state that the 22 patients were "arbitrarily divided by a referee physician into two groups of 11". Blinding also seems unlikely due to the acidic taste and sensation of the acid	Difficult to interpret the clinical data as the correct statistical comparison has not been done and because of the short duration of the study. Some serious concerns about the study quality. The ethics of spraying an acid onto young infants is also a cause for concern.
Harper 1995[118]	Proprietary bath emollient (Oilatum™) Vs	30 children age range 1-9 years study period 4	Crossover RCT of two 4-week treatment periods with a 2-week	Composite sign and symptom score (max. 100), patient recorded	Based on 26 evaluable patients, the change from	Method of randomisation was described, but no intention-to-	Both this study and the Holland *et al*[119] study are published in a

	Same bath emollient with two added antiseptics: 1. 6% w/w benzalkonium chloride 2. 2% triclosan (Oilatum Plus™) 15ml added to bath daily	weeks Note: all had recurrent infections and/or frequent exacerbation	washout period in between	global overall impression and global change scales	baseline score (baseline scores not given) was 9.0 for those using the antiseptic emollient compared with 2.7 for those with regular emollient at 4 weeks. Patient rated scores did not show any significant differences between the two treatments (data not shown in published paper)	treat analysis. Only statistical tests of change in scores from baseline for each treatment separately rather than the appropriate test of the difference in score changes between the two treatments	"round table" discussion document sponsored by the manufacturer. Difficult to interpret in view of the wrong statistical tests being used and missing patient-reported data. Re-analysis of data comparing the change in score between the two treatments at 4 weeks did not confirm any superiority of the antiseptic emollient
Holland *et al* 1995[119]	Standard proprietary bath emollient (Oilatum™) Vs Same bath emollient with two added antiseptics: 1. 6% w/w benzalkonium chloride 2. 2% triclosan	15 patients age range 4-34 years study period 4 weeks Note: all moderate to severe AD with *S.aureus* on their skin	Parallel RCT	Clinical scores of signs, symptoms, extent of disease and bacterial counts	At the end of 4 weeks treatment, clinical scores in the emollient/antiseptic group had fallen more than those in the emollient-only group, and were statistically significant. There was no	No description of randomisation process or intention-to-treat analysis. Although described as a parallel study patients were "paired for matching pre-treatment *S.aureus*	Difficult to interpret the lack of demonstration of efficacy in such a tiny study with high dropouts

	(Oilatum Plus™) added to bath daily				statistically significant difference in *S.aureus* counts between the 2 groups at the end of the treatment period. 5 dropouts in the emollient-only group	population densities	
Hizawa *et al* 1998[120]	Povidone-iodine solution to one arm daily Vs Nothing else on other side (emollients on both sides)	16 volunteers with AD age range 12-29 years study period 1 week Note: all with similar AD lesions in each elbow fold	Right/left investigator-blinded comparison	Physician-assessed before and after photographs and colony counts of *S.aureus*	Of 15 evaluable patients, physicians reported an improvement in the povidone-treated sites ($p<0.01$), but not on the control sites. Bacterial colonization was significantly reduced on the treated but not untreated site. No summary data of differences between treatments reported	Unclear method and concealment of randomisation. Investigator masking suspect since iodine stains the skin	Worth pursuing in a larger double-blind study since povidone-iodine is a low cost antiseptic with good anti-staphylococcal properties. This study is inconclusive in view of threat of unblinding, short duration, and failure to perform the appropriate statistical tests
Broberg *et al* 1995[121]	After a course of antibiotics, patients were allocated to a combination	60 patients age range 14-53 with AD affecting the head and neck of whom 83%	Parallel RCT	Modified SCORAD (a composite sign and symptom score) and	Of 53 evaluable patients, severity score fell from 58.6 at baseline to 33.2 after 4 weeks	No description of randomisation method, allocation concealment and	Despite widespread use of antifungals for AD affecting the head and neck,

	active against *Pityrosporum* yeasts (a cream containing the antifungal miconazole plus hydrocortisone applied twice daily to the head and neck and ketoconazole shampoo twice weekly) Vs plain hydrocortisone cream and shampoo base (emollients)	were positive for *P.ovale* on culture at start Study period 6 weeks		reduction in *P.ovale* counts	in the antifungal group compared with 60.1 at baseline to 22.9 in the standard group (differences between groups not statistically different). *P.ovale* colonization rates fell significantly in the antifungal group but not in the standard treatment group	no intention-to-treat analysis	this RCT does not suggest that there is any additional benefit over conventional treatment and that colonization by the yeast *P.ovale* may be a secondary phenomenon

3.5 COMPLEMENTARY MEDICINE

Complementary medicine is defined in this study as a group of therapeutic and diagnostic disciplines that exist largely outside the institutions where conventional health care is taught and provided[122]. Eight studies were located in total that assessed complementary medicine in the treatment of AD: 1 aromatherapy, 1 bioresonance, 4 Chinese herbal medicine, 1 hypnotherapy and biofeedback and 1 massage.

3.5.1 Aromatherapy

Aromatherapy is the therapeutic use of essential oils extracted from medicinal and aromatic plants, which are believed to have therapeutic effects on and within the body. One way of administering them is by massage, diltuted in carrier oil, directly onto the body [122].

Study 1

- abstract of a preliminary study
- Anderson *et al* 1998[123]
- counselling and massage with essential oils by both the therapist and the mother or the same treatment without essential oils
- 16 children with AD
- study period 8 weeks
- Outcome measures:
    - Parent assessed day-time irritation score, night time disturbance scores and general improvement scores

Results

- Statistically significant improvement of the eczema in the two groups of children following therapy, but there was no significant improvement shown between the experimental and control groups

- Correspondence with the author confirms the study was randomised, and that the full report will be available shortly. However, the full paper has not been published to date (September 2002) and the author hasn't responded to recent correspondence

3.5.2 Bioresonance

Bioresonance therapy, also called biophysical information therapy (BIT) has become popular as an alternative medical treatment for a variety of allergic diseases in Europe. Bioenergy is defined as the bioelectric magnetic field, which is unique to materials, and that bioelectric waves produced by people can have diagnostic and therapeutic purposes. The proponents of this theory claim that the main purpose of BIT is to give a strong impulse to spontaneous healing energies of the body for self-regulation. The ultra fine electro-magnetic waves of the patient's body, as well as their disturbances and presence of allergens, are purported to be transmitted for diagnosis and therapy using brass wire electrodes analysed by 'bioresonance apparatus'. This electronic instrument allegedly distinguishes between pathological and normal healthy waves from a patient. Pathological waves can be reversed electronically ('corrected to healthy ones') by the separator and transmitted back to the patient for a therapeutic effect. The use of such BIT is frequently accompanied by claims of complete cure for allergies[39]. One RCT was located that evaluated the efficacy of bioresonance in children with AD:

Study 1

- Schoni *et al* 1997[124]
- Bioresonance therapy versus placebo 'sham' bioresonance
- 36 children with AD
- study duration at least 4 weeks
- outcome measures:
    - disease severity score
    - sleep score
    - pruritis score

Results

- disease severity score reduced from 39.8 to 27.3 in the active group compared to a reduction from 35.3 to 26.6 for placebo group (p=0.23)
- there were no differences in active treatment and placebo for sleep scores
- pruritis score improved slightly in the active bioresonance group (p=0.12)

Adverse effects

- none reported

Notes

- blinding, randomisation and concealment of allocation were well described
- no intention-to-treat analysis carried out

3.5.3 Chinese herbal medicine

Chinese herbal medicine forms part of a system, which includes oral and/or topical Chinese herbs, acupuncture, diet, and exercise for both treatment and prophylaxis of disease. Medicinal plants of various kinds can be taken orally as a decoction by boiling them in water, usually a combination of several, and drinking the 'tea' produced, or as external applications directly to the skin. Prescriptions are individually determined based upon an overall assessment of the patient including pulse, appearance of tongue, and disease features, hence, standardised formulas are not generally prepared. Mode of action points towards anti-inflammatory and immunosuppressive properties by down regulating local T-cell mediated reaction[125].

A systematic review[126] of treatments for eczema with Chinese herbs was located which reported two randomised trials of atopic eczema [127-129]: an adult study and a child study. Adverse effects such as slight abdominal distension and headaches were highlighted in that review. The authors conclude that at present it is unclear whether Chinese herbal treatments of eczema do more good than harm.

In addition to these two trials a further two trials were identified [130 131], which evaluated oral Chinese herbal decoction compromising *Ledebouriella seseloides, Potentilla chinensis, Clematis armandii,*

Rehmannia glutinosa, Paenia lactiflora, Lophatherum gracile, Dictamnus dasycarpus, Tribulus terrestris, Glycyrrhiza glabra, Schizonepeta tenuifolia, except Sheehan[127] who used *Anebia clematidis* instead of *Clematis armandii.* All four randomised controlled trials are reported below:

Study 1

- Sheehan *et al* 1992[127]
- Chinese herbs decoction (as above) versus placebo 'inert' plant materials
- 47 children with AD
- study duration 8 weeks
- outcome measures:
  - erythema
  - surface damage (the net effect of papulation, vesiculation, scaling, excoriation and lichenification)
  - percentage area affected (maximum score 180)
  - patient preference

Results

- Median percentage changes of the clinical scores from baseline were 51% for Chinese herbs compared to 6.1% for placebo for erythema, and 63.1% and 6.2% change for surface damage in the herbs versus placebo groups respectively
- A one-year follow-up study of the children concludes that Chinese herbal medicine, in the medium term, proved helpful for approximately half the children who originally took part in the randomised controlled trial[132]

Study 2

- Sheehan *et al* 1992[128]
- Chinese herbs decoction (as above) versus 'inert plants' placebo, once daily
- Study duration not stated
- 40 adults with AD

- outcome measures:
    - Skin was assessed using a score of 0-3 for erythema
    - surface damage (the net effect of papulation, vesiculation, scaling, excoriation and lichenification)
    - percentage area affected (maximum score was 180)
    - patient subjective comments included itch, sleep loss and preference

Results

- Geometric mean total body score for erythema at the end of Chinese herbs treatment was 12.6 and at end of placebo phase was 14 (baseline scores not given). The geometric mean for surface damage at the end of Chinese herbs treatment was 11.3 compared to 111 at the end of placebo phase (baseline values not given)

Study 3

- Latchman *et al* 1996[131]
- Chinese herbs decoction (as above -finely ground) versus the same Chinese herbs in a new palatable form of freeze dried granules
- 18 patients with AD
- study period 8 weeks
- Outcome measures:
    - Skin was assessed using a score of 0-3 for erythema and surface damage

Results

- There was a significant reduction in erythema and surface damage compared with baseline ($p<0.001$). The groups showed no difference in clinical outcome between formulations

Study 4

- Fung *et al* 1999[130]
- Chinese herbs decoction as above versus 'inert plants' placebo

- 40 patients with AD
- Study period 8 weeks
- Outcome measures:
    - Scores based on the severity and extent of erythema, surface damage, lichenification, and scaling

Results

- There was a general trend of clinical improvement for both Chinese herbs and placebo
- There was no statistically significant treatment effect over placebo for all four clinical parameters, except for lichenification at week 4

Adverse effects

- Unpalatability of the herbs in both active and placebo groups was a common side effect causing 10 dropouts in Sheehan *et al* children study[127] and 8 dropouts in the Sheehan *et al* adult study[128]
- Other adverse effects included abdominal distension, headaches, transient dizziness, gastrointestinal upsets, one lichenoid eruption and one facial herpes
- There is a concern with Chinese herbs of potential hepatotoxicity, however, all the studies, except Latchman *et al*[131] carried out pre- and post-treatment liver function tests with no abnormalities detected

Notes

- All studies were randomised but method and concealment of allocation were not described
- All were described as double blind, except Latchman *et al*[131] where no blinding was mentioned
- No intention-to-treat analysis was carried out
- It is questionable whether the placebo plants are truly inert in the treatment of eczema
- The children study by Sheehan *et al*[127] reports large effects from Chinese herbal medicine highlighting a promising treatment of atopic eczema. This has not been replicated in the other studies, although they are all quite similar

- More randomised controlled trials with larger sample sizes over a longer period of time are needed

3.5.4 Hypnotherapy and biofeedback

Hypnotherapy and biofeedback used to develop relaxation techniques with or without mental imagery may be beneficial in the management of atopic eczema to distract from the symptoms associated with the itch-scratch cycle[133]. One RCT was located which addresses the use of these techniques in atopic eczema:

Study 1

- Sokel *et al* 1993[133]
- Hypnotherapy versus biofeedback versus 'placebo discussion' only
- 44 children with AD stabilised on topical and oral treatment in a 2-week run-in period
- study duration 20 weeks
- Outcome measures:
    - changes in the objective symptoms of erythema, surface damage and lichenification which resulted from attempts to reduce children's subjective experience of itching (and subsequent scratching) using: (1) relaxation which focused specifically on reducing itching (hypnotherapy); (2) relaxation which did not involve any direct imagery *per se* (biofeedback); (3) an 'attention placebo' group who were encouraged to discuss the eczema without any mention of symptom control

Results

- The children in the hypnotherapy and biofeedback groups showed a significant reduction from baseline in the severity of surface damage and lichenification compared with the control group. There was no difference between the two relaxation techniques. Erythema was not changed by the interventions

Adverse effects

- None were reported in this study

Notes

- Lack of blinding threatens the validity of the study
- The authors state that all the parents and children in the study were aware that the aim of the study was to help them with their symptoms further threatening the validity of the study. In particular, the 'attention placebo' was designed to avoid mentioning symptom control
- There were 4 dropouts but no explanation was given for reasons. No intention-to-treat analysis was carried out, hence, it is not clear what effect the high number of drop-outs had on the results

3.5.5 Massage therapy

It is possible that massage therapy might be beneficial in atopic eczema as a stress-reducing and enjoyable interaction between parent and child, by increasing peripheral circulation (which may be defective in atopic eczema) or by increasing compliance with topical treatments. One small RCT of massage therapy in young children has been identified:

Study 1

- Anderson *et al* [123]
- standard therapy with topical corticosteroids, emollients and antihistamines versus standard therapy plus a course of daily 20 minute massage following video demonstration
- 20 children with AD (mean age 3.8 years)
- study period 1 month
- Outcome measures:
    - Anxiety scores
    - Tactile defensiveness
    - Coping index
    - Scaling and excoriation

Results

- Parents in the massage group reported greater degrees of improvement in anxiety scores, tactile defensiveness, and a coping index when compared with the control group. Certain eczema activity signs (e.g. scaling and excoriation) improved statistically from baseline in the active group compared with only scaling in the control group, although statistical comparison of differences between the two groups was not done

Adverse effects

- None were reported in this study
- The cost of instruction by a therapist and video for one session was estimated at $30

3.6 DIETARY INTERVENTIONS IN THE TREATMENT OF ATOPIC DERMATITIS

3.6.1 Dietary manipulation

The role of the diet is a contentious issue in the treatment and prevention of atopic eczema. Firstly, in certain individuals, eating specific foods can cause pre-existing atopic dermatitis to worsen, and secondly, avoidance of selected foods can cause AD to improve, however, the second concept does not necessarily follow the first concept[134]. Even though there is evidence that diet plays a role in AD, it is not clear what specific foods are triggers in individuals and what benefit, if any, dietary manipulation plays in the treatment of AD.

Eight studies were located that assessed the role of dietary manipulation in the treatment of AD and are summarised in Table 8.

Table 8 Dietary manipulation in the treatment of AD

Author and date of study	Interventions	Population, sample size and study period	Trial design	Outcome measures	Main reported results	Quality of reporting	Notes
Atherton *et al* 1978 [135]	Egg and cow's milk exclusion diet (soya milk substitution) Versus Control diet with egg and cow's milk	36 children age range 2-8 years with AD study period 12 weeks	Crossover RCT Three 4-week periods. During the first and third periods patients were placed on egg and milk elimination diet and randomly allocated to a soya-based preparation or one containing egg and cow's milk	Eczema area and activity using an unpublished composite score, degree of adherence to diet and skin-prick tests	Of 20 children who completed the trial, 4 showed an improvement during the trial diet period, 6 showed no change and 1 showed deterioration. On control diet period, 3 showed improvement, 11 no change and 6 deteriorated. Itch was not statistically significant between the two groups	Method of randomisation and concealment unclear. Study described as double blind although some unblinding of parents cannot be excluded. No intention-to-treat analysis and high dropout rate (44%)	Improvements greater at end of first versus second period whatever the diet content - marked order effect. Soya milk (which itself can be allergenic in atopic eczema) used as "control" food
Munkvad *et al* 1984[136]	Elemental diet (amino acids, essential fatty acids, glucose, trace elements, sorbic acid and vitamins) Versus A blended diluted diet of foodstuffs consumed by	33 adults with AD covering more than 10% of the body, 4 of whom had a history of intolerance to one or more food elements Study period 3 weeks	Parallel RCT	Various unpublished extent and intensity signs scored between -3 and +3 Photographs before and after Patient itch and sleep-loss Various serum markers of	Of 25 evaluable patients, five out of 16 improved on the elemental diet compared to 4 out of 9 on the placebo diet. Itch, sleeplessness, antihistamine use and	Method of randomisation and concealment unclear. Unclear if the reported "double blinding" was successful in view of the different composition of the two diets. No	History of food intolerance in patients not confirmed during study. Small study of an intervention which is unpalatable, impractical and requires hospitalisation

	hospital inpatients			inflammation A 'major activity' score of >100 was defined as the criterion for a positive response to treatment	immunological tests were no different between the 2 groups	intention-to-treat analysis with a 24% dropout rate	and dietetic input
Cant *et al* 1986[137]	Exclusion diet of egg and cow's milk (with soya substitute) in mothers of infants with atopic eczema who were exclusively breast-feeding Versus Inclusion of egg and milk	19 mothers and babies with AD study period 12 weeks	Crossover RCT divided into three four-week periods. During 1st two periods, mothers excluded cows' milk, egg and other foods from their diet and were randomised in 1st or 2nd period for milk substitutes containing cow's milk and egg or soya. Normal diet in 3rd period	Combined area/intensity score (unpublished) with a maximum score of 60	Of 17 mothers completing the study, the activity scores decreased by 20% in four babies on soya and one on egg and milk. No statistically different mean scores between the two groups. Marked period effect in that children of mothers on normal diet in 3rd period continued to improve	Method of randomisation described. Concealment of allocation unclear. Study described as double blind although almost half mothers correctly identified substitutes. Attention-to-treat analysis was attempted	Well reported although very small study conducted alongside a before and after study. Soya used as control diet
Neild *et al* 1986[138]	Egg- and cow's milk-free diet (soya as substitute) Versus Normal diet	53 patients age range 1-23 years study period 18 weeks	Crossover RCT with three 6-week periods. During first and third periods, patients were placed on an egg and cow's milk exclusion diet and	Patient reported itch and sleep loss, use of co-treatments, composite score of area and intensity and skin prick tests	Of 40 evaluable patients, there was little difference for change in score (area, itch co-treatment use) between the treatment periods and none were	Method of randomisation and concealment of allocation unclear. Study reported as "double blind" although test substances might have tasted	High dropout rate due to diet too difficult to adhere to. Unclear if there was a period or carry-over effect. Confidence intervals suggested that if

			randomised to either soya or a milk containing egg and cow's milk		statistically significant	differently. No intention-to-treat analysis and high dropout rate (25%)	anything, patients did worse on the exclusion versus normal diet
Mabin *et al* 1995[139]	Three groups: i) few foods diet (eliminating all but five to eight foods) plus whey hydrolysate; ii) few foods diet plus casein hydrolysate; iii) remain on usual diet	85 children (median age 2.3 years) with AD that persisted despite conventional treatment and involving more than 12% of body. Breastfed children were excluded. Study period 6 weeks	Parallel single-blind RCT	Skin severity score incorporating extent and severity, and parental record of itch, sleep loss and global improvement	Of 46 evaluable patients, sixteen (73%) of the 22 controls and 15 (58%) of the 24 who received diet showed a greater than 20% improvement in skin severity score. Improvement in skin severity score in controls and daytime itch score in the whey hydrolysate group was statistically significant in the 12 statistical outcome comparisons made	Method of randomisation clearly described. Concealment of allocation unclear. Study described as investigator blind. No intention-to-treat analysis and very high drop out rate (46%)	Good description of patient flow and interventions. 35 out of 39 dropouts were in the diet group, illustrating the difficulty of adopting the few foods diet in even a motivated hospital group. No evidence to support benefit from diet and some evidence suggesting that control diet was better
Isolauri *et al* 1995[140]	Whey hydrolysate versus amino-acid derived formula containing no peptides	45 children who were not being breast fed, who had been fed substitute cow's milk for at least 6 months and who	Parallel RCT drawing patients from an initial study to determine cow's milk allergy	Atopic eczema severity (extent, intensity of signs and symptoms) measured by the SCORAD[141] system. Infant's	Weight gain and infant length was statistically less in the whey hydrolysate group. Eczema severity decreased	Method and concealment of randomisation allocation unclear. Randomised part of the study probably not	Highly selected population. Study mainly concerned comparison of growth in amino acid versus hydrolysate

		showed a positive reaction to a masked challenge with cow's milk study period 8 months		growth was also measured	from a SCORAD of 17 to 5 in 22 children on whey hydrolysate compared with a baseline of 21 to final score of 4 at 8 months in the amino acid group	blinded. No dropouts	formulae. Main statistical comparison of change in eczema severity between the 2 groups not reported in results although children in amino acid group had higher baseline score
Majamaa *et al* 1997[142]	Cows' milk elimination (extensively hydrolysed whey formula) with a probiotic (Lactobacillus GG) Versus Cows' milk elimination (extensively hydrolysed whey formula) without a probiotic (Lactobacillus GG)	27 infants with clinical history suggestive of cows' milk allergy who were confirmed as being sensitive to cows' milk by double-blind placebo controlled challenge. 19% of the children also had gastrointestinal symptoms. Study period 4 weeks	Parallel RCT	Atopic eczema severity measured by SCORAD[141]. No *a priori* statement of minimum clinically significant benefit	Of 27 evaluable children, the median SCORAD at baseline was 21 and 26 in the whey alone versus whey plus probiotic groups respectively. These decreased to 19 and 15 respectively at the end of 1 month	Method and concealment of randomisation allocation unclear. No blinding reported. No dropouts	Authors report statistical significance for the change in score from baseline to the end of the study separately for each intervention, but do not test the difference between the two treatments
Lever *et al* 1998[143]	Egg exclusion diet for young children as advised by a dietician versus general advice from a dietician	62 children all with positive IgE blood antibodies to egg, only seven of which had a history suggestive of egg allergy	Parallel RCT	Eczema severity as assessed by extent in % terms and a composite severity score in 16 body sites	Of 55 evaluable children, the area involved by eczema reduced from 19.6% to 10.9% in egg-free group compared	Method of randomisation unclear. Randomisation performed by same dietician who was giving	Study suggested that egg free diet in those with a positive RAST (radio-allergosorbent test) test to egg

	only	study period 4 weeks			with 21.9% to 18.9% in control group (p=0.02). Severity score reduced from 33.9 to 24.0 in the egg-free group compared with 36.7 to 33.5 in the control group (p=0.04)	the intervention. Parents unblinded. Assessor reported as blinded. No intention-to-treat analysis. Co-treatment use not reported	may be useful. Methodological concerns such as lack of randomisation concealment and increased motivation and ancillary care in intervention group could have resulted in bias

3.6.2 Supplementation with essential fatty acids (borage oil, fish oil and evening primrose oil)

Poly-unsaturated fatty acids are essential components of all cell membranes. There are two families of such essential fatty acids: *n*-6 (e.g. linoleic and arachadonic acid) and *n*-3 (e.g. eicosapentanoic acid). Some of these substances are precursors of a group of substances called eicosanoids, which may play an important part in the inflammatory and immunological processes of atopic eczema. Alterations in linoleic acid metabolism have been demonstrated in some patients with atopic eczema, suggesting that a defect in the enzymatic conversion of this essential fatty acid by δ-6-desaturase might be responsible for defects in the lipid barrier of the skin, a decreased postnatal maturation of T-lymphocytes, and the decreased production of anti-inflammatory metabolites in the skin. These observations are the rationale for dietary supplementation with essential fatty acids in atopic eczema. Such supplementation includes evening primrose oil, containing 8-10% gamma-linoleic acid (GLA), and more recently borage oil (containing at least 23% GLA). Topical use of evening primrose oil has also been tried. Fish oils are especially rich in *n*-3 fatty acids, and it has been suggested that these may compete with *n*-6 fatty acids in a way that might reduce the inflammatory components of atopic eczema[39].

Twenty three RCTs assessing essential fatty acids in the treatment of AD were located (5 borage oil, 4 fish oil and 14 evening primrose oil - 2 of which were duplicates of the same study[144, 145]). These are summarised in Tables 9, 10, 11 and 12.

Table 9 Borage oil, in the treatment of AD

Author and date of study	Interventions	Population, sample size and study period	Trial design	Outcome measures	Main reported results	Quality of reporting	Notes
Henz *et al* 1999[146] Translated study	Borage oil 500mg three capsules daily Versus Miglyol lipid as placebo three capsules daily	160 patients age range 14-65 study period 24 weeks	Parallel RCT	Costa scoring system[147]: erythema, excoriation, scaling, lichenification, vesiculation, pustules/papules, oedema, crusts, pigmentation/depigmentation, doctor-assessed itch, sleep-loss, multiple area assessment	The reduction in Costa score points was similar in the placebo and borage oil treated groups although improvement of individual symptoms over placebo was observed for erythema, vesiculation, crusting, excoriation, lichenification, and insomnia, but not for pruritis. (No data given). No statistically significant differences were noted between the two treatment groups regarding the primary efficacy criterion 'corticosteroid dosage until response'	Method and concealment of randomisation not stated, study described as double blind, success of blinding not recorded. No intention -to-treat analysis	Authors state that all previous evening primrose oil studies look at 8-10% gammalinolenic acid, whereas borage oil looked at 23% gammalinolenic acid concentration. Significant effect shown in subgroup (*post hoc*) of best compliers and whose blood changed. No overall difference in main comparison

					(P=0.8949). Significant benefit shown in a sub-group of 'good compliers'		
Borrek *et al* 1997[148] Translated study	Borage oil Versus Corn seed oil	24 patients age range 3-17 years study period 14 weeks	Crossover RCT	Costa[147]: erythema, excoriation, scaling, lichenification, vesiculation, pustules/papules, oedema, crusts, pigmentation, doctor-assessed itch, sleep loss, multiple area assessment	After 10-14 weeks of treatment there was no improvement of the eczema with active treatment compared to placebo. Both groups showed improvement while taking placebo. This result could be seen in the objective investigations (Costa-Score, 3 times per treatment period) as well as in the daily patient's documentation. The patients whose eczema has improved with borage oil (n=10) had no special characteristics, so that authors could	No data at present	Small study which showed no difference between active drug and placebo. Awaiting translation for methodological quality

					not identify any responder-type		
Buslau & Thaci 1996[149] Translated study	Borage oil 2g two capsules daily Versus Palm oil as placebo 1g two capsules daily	50 patients age range not given study period 12 weeks	RCT design not stated	ADASI[150]: Erythema, scaling, excoriation, oozing/weeping, inflammation and patient-assessed itch	Of the 32 evaluable patients, 14 out of 18 patients (78%) in the borage oil group compared with 6 out of 14 (43%) patients in the palm oil group showed a significant improvement in ADASI score compared with baseline	Awaiting full translation. No intention to treat analysis carried out and large dropouts	Unclear what a 'significant improvement' meant to patients in terms of magnitude of response
Valsecchi *et al* 1996[151]	Borage oil 500mg capsule containing 80mg gamma-linoleic acid, linoleic acid, palmintic acid, oleic acid and stearic acid Versus Liquid paraffin as placebo	31 patients age ranges 2-11 and 15-38 study period 14 weeks	Parallel RCT	Erythema, excoriation, scaling, lichenification, vesiculation, pustules/papules, doctor-assessed itch, area assessment	There was no statistically significant difference (p=0.165) between the mean reduction from baseline clinical score of the placebo (48.4) and the gamma linoleic acid (GLA) group (70.8). Mean baseline score was higher in the GLA group at 281.0 compared	Method and concealment of randomisation not stated, blinding not stated, no intention -to-treat analysis. Published as a letter only	No difference between the 2 groups but study under-powered to detect modest benefits

					with 251.3 in placebo		
Bahmer & Schafer 1992[152]	Borage oil two capsules 500mg three times daily Versus Palm oil in similar dose	12 patients age range 20-48 years study period 4 months	Parallel RCT	ADASI scoring system[150]	Using within-patient change in ADASI score, 5 out of 7 patients treated with borage oil showed a favourable effect compared with one out of five treated with palm oil	No data available	Pilot study awaiting full translation

Table 10 Fish oil in the treatment of AD

Author and date of study	Interventions	Population, sample size and study period	Trial design	Outcome measures	Main reported results	Quality of reporting	Notes
Gimenez-Arnau *et al* 1997[153]	Eicosapentaenoic acid plus docosahexanoic acid (fish oil) Versus Linoleic acid (vegetable oil)	48 patients mean age 24.2 study period 12 weeks	Parallel RCT	Doctor-assessed itch, rule of nines area assessment[154] Rajka score[155]	Only 6-week results presented for all 3 groups due to high drop out rate in vegetable oil and placebo groups. This showed a 75% reduction in median Rajka scores in the fish oil group compared with 5.3 in the placebo and 8.8 in the vegetable oil groups ($p<0.001$). Baseline scores not given	Method and concealment of randomisation unclear, study described as double blind. No mention of withdrawals or dropouts	Very scant methods and results data
Soyland *et al* 1994[156]	Fish oil, 6 capsules daily Versus Corn oil 'placebo'	145 patients age range 18-64 study period 4 months	Parallel RCT	Erythema, dryness, scaling, lichenification, induration, patient-assessed itch, doctor-assessed itch	The mean clinical score for the 6 parameters evaluated by the physicians showed an improvement from 4.4 to 3.1 (30%, $p<0.001$) in the fish oil	Method and concealment of randomisation unclear, study described as double blind. Twenty four withdrawals/drop outs, no intention-to-treat analysis	Large study with no hint of any difference of response between the 2 groups

					group, and from 4.2 to 3.2 (24%, $p<0.001$) in the corn oil group. No significant differences between the two groups for any outcome	carried out	
Bjorneboe *et al* 1989[157]	Translation not available						
Bjorneboe *et al* 1987[158]	Fish oil ten capsules daily versus Olive oil as 'placebo'	31 patients age range 16-56 study period 12 weeks	Parallel RCT	Erythema, excoriation, scaling, lichenification, oozing/weeping, patient-assessed itch	The total patient's symptom score showed significantly greater improvement in the experimental group compared to control group mean change 11.3 and 1.3 respectively, baseline scores not given ($P<0.02$). The physician assessed scores showed no statistically significant difference between the groups	Method and concealment of randomisation unclear, study described as double blind. Eight withdrawals and dropouts, no intention-to-treat analysis carried out.	Discrepancy of outcomes between patients and physicians. Multiple outcomes

Table 11 Oral evening primrose oil (EPO) in the treatment of AD

Author and date of study	Interventions	Population, sample size and study period	Trial design	Outcome measures	Main reported results	Quality of reporting	Notes
Hederos & Berg 1996[159]	Epogam™ (500mg EPO, 40mg GLA, 10mg vitamin E) Versus Placebo (500mg sunflower oil plus 10mg vitamin E)	60 patients age range 1-16 years study period 16 weeks	Parallel RCT	Erythema, excoriation, dryness, scaling, lichenification, crusts, doctor-assessed itch, sleep loss, physician-assessed global severity	Both groups of patients were substantially improved with respect to baseline but no significant differences between EPO and placebo groups were observed. The mean % improvement from baseline for patient's global assessment was 10.0 and 7.1% for Epogam and placebo respectively. The corresponding % improvement for physician-assessed global improvements were 11.0 and 4.8% for EPO and placebo respectively	Method and concealment of randomisation unclear. Study described as double blind. No size differences between 2 groups. Intention-to-treat analysis carried out, 2 withdrew in EPO group	Well described study
Biagi *et al* 1994[160]	EPO high-dose	51 patients	Parallel RCT	Erythema,	There was a trend	Randomisation	Benefit only in

	0.5g/kg/day Versus Low-dose EPO 50% mix 0.5g/kg/day plus placebo capsules (olive oil and 10mg vitamin E) Versus Placebo capsules	age range 2-8 years study period 8 weeks		excoriation, scaling, lichenification, vesiculation, pustules/papules, oedema, crusts	towards improvement in the low dose group, which approached significance (p=0.077) and a significant improvement in the high dose group compared to placebo (p=0.046) for overall physician-rated severity. There were no significant changes for the symptoms of itch and for the extent of disease in the EPO group compared to placebo	and concealment not stated, blinding not elaborated on or tested for. No intention-to-treat analysis, 3 dropouts	higher dose group and for one out of 3 main outcome measures regardless of whether children were atopic or not
Humphreys *et al* 1994[161]	EPO 500mg plus vitamin E 10mg, 12 capsules daily Versus Liquid paraffin 300mg plus 10mg vitamin E	58 adult patients study period 16 weeks	Parallel RCT	Erythema, scaling, lichenification, doctor-assessed itch, physician-assessed global severity, patient-assessed global severity	23 out of 27 patients taking active treatment showed an improvement in their clinical score for erythema by the end of the treatment period compared with 11 out of 23 in the	Method and concealment of randomisation unclear, blinding unclear No intention-to-treat analysis carried out, (6 dropouts) good description of dropouts though.	Well-described study but 3 groups a little confusing. Baseline severity very different in EPO group than placebo but this was adjusted in analysis

					placebo group. The results for surface damage were very similar, 12 out of 23 in the placebo group showing an improvement in clinical score, compared with 23 out of 27 in the EPO group. No benefit for lichenification	Statistics well described.	
Berth-Jones & Graham-Brown 1993[162]	Epogam™ 500mg (contains GLA) Versus Efamol Marine™ 107mg (contains fish oil) Versus Placebo (olive oil)	43 patients age range 7-12 years study period 16 weeks	Parallel RCT	Leicester[163]/Costa severity score[147]: erythema, excoriation, dryness, scaling, lichenification, cracking, vesiculation, oedema, crusts, doctor-assessed itch, sleep loss, patient-assessed global severity, rule of nines area assessment[154]	At 16 weeks, the mean (SE; number of patients) improvements in Leicester scores were 8.48 (2.85; 33) for patients on Epogam™, 2.54 (2.89; 35) for patients on Efamol Marine™, and 7.15 (2.88; 34) for those on placebo. On neither active regimen was mean improvement significantly different from	Method and concealment of randomisation unclear. Study described as double blind. No intention-to-treat analysis (21 dropouts). Well reported study otherwise	No improvement in Epogam™ or Efamol Marine™ singly or combined, similar in children and adults

					placebo at 16 weeks (p=0.74 for Epogam™, 0.26 for Efamol Marine™)		
Bordoni *et al* 1987[164]	Efamol™ 0.5g/day Versus Olive oil placebo	24 patients age range 2-4 years study period 4 weeks	Parallel RCT	Erythema, excoriation, scaling, lichenification, vesiculation, oedema, inflammation, doctor-assessed itch, sleep loss	After 4 weeks, the symptoms of patients treated with Efamol™ significantly improved (p<0.01), in placebo treated children the clinical status remained largely unchanged	Method and concealment of randomisation unclear, "doctor unaware of which patients receiving which treatment" suggests single blind study. Dropouts not mentioned - presume intention-to-treat analysis.	Efamol™ suggested benefit, very short-term study. High dose capsules for children
Schalin-Karrila *et al* 1987[165]	EPO (360mg linoleic acid, 50mg oleic acid, 45mg gamma-linoleic acid) four capsules twice daily Versus Placebo 500mg liquid paraffin	25 patients age-range 19-31 years study period 12 weeks	Parallel RCT	Dryness, inflammation, doctor-assessed itch, physician-assessed global severity, area assessment	In the EPO group, a statistically significant improvement was observed in the overall severity and grade of inflammation (p<0.001) from baseline and a significant reduction in the surface area involved as well as dryness and itch compared	Randomisation method and concealment method not mentioned, success of blinding not recorded, yet possible that placebo group could have bowel problems given they had 4g of liquid paraffin daily. No intention-to-treat	Authors concluded that EPO superior for global severity; inflammation, dryness, itch

					with baseline ($p<0.01$). Patients in the placebo group showed a significant reduction in inflammation compared with baseline ($p<0.05$). Unclear if there was a comparison of change in clinical scores between the 2 groups	analysis (one from EPO, not mentioned in placebo group). EPO group started off more severe	
Bamford *et al* 1985[166]	EPO 2-4 capsules twice daily <15 years of age EPO 6-8 capsules twice daily >15 years of age Versus Placebo 500mg liquid paraffin and 10 IU vitamin E	154 patients age range 2-15 and 16-66 study period 3 months	Crossover RCT	Erythema, excoriation, scaling, lichenification, oozing/weeping, patient-assessed itch, area assessment	No significant effect on erythema, scaling, excoriation, lichenification, or overall severity in 123 patients with atopic eczema of average severity while they took oral doses of evening primrose oil (2 or 4gm in children, 6 or 8gm in adults). Actual data shown graphically in 4 figures	Method and concealment of randomisation unclear, study described as double blind. Thirty-one dropouts, no intention-to-treat analysis carried out. Study very clearly written up.	Good information on how many patients were approached and how compliance was checked. Later correspondence by company accused authors of mixing up tablets
Wright 1985[167]	Translation not available						

Wright & Burton 1982[168]	Efamol™ (360mg linoleic acid, 45mg gamma-linoleic acid divided into three different doses for adults and two different doses for children) Versus Placebo (500mg liquid paraffin)	99 patients age range 0.8-11 years and 15-58 years study period 12 weeks	Crossover RCT	Erythema, scaling, doctor-assessed itch, physician-assessed global severity, patient-assessed global severity	In the low dose groups itch was the only symptom that responded better to EPO than placebo. In the high dose groups the patient assessments showed that the EPO was significantly superior to the placebo with regard to itch ($p<0.003$), scaling ($p<0.002$), and general impression of severity ($p<0.01$). The doctor's assessments also showed a beneficial effect of the active treatment on the overall severity of the condition ($p<0.002$). The other symptom scores showed the same trend but failed to reach statistical significance	Random method and concealment method not mentioned, success of blinding not recorded. No intention-to-treat analysis, 16 adults and 3 children dropped out. Only itch improved in low dose groups whereas most improved in high dose groups	Published separately twice

Lovell *et al* 1981[169]	Efamol™ (500mg EPO plus 45mg GLA) Adults 4 capsules twice daily, children 2 capsules twice daily Versus Liquid paraffin	32 patients age range 1.5-4 years and 14-32 years study period 3 weeks each	Crossover RCT	Doctor's assessment and patient's assessment	Doctor's assessment baseline 6.26 (±0.24) reduced to 5.27 (±0.38) after EPO and 5.64 (±0.38) after placebo. Patient's assessment baseline 5.96 (±0.16) reduced to 5.02 (±0.37) after EPO and 5.54 (±0.38) after placebo	Method and concealment of randomisation unclear, study described as double blind	Clinical significance of a change in score from 5.96 to 5.02 not clear

Table 12 Topical evening primrose oil (EPO) in the treatment of AD

Author and date of study	Interventions	Population, sample size and study period	Trial design	Outcome measures	Main reported results	Quality of reporting	Notes
Gehring *et al* 1999[170]	Study 1: EPO in an amphiphilic oil-in-water emulsion Versus Vehicle (20% miglyol) Study 2: EPO in a water-in-oil emulsion Versus Vehicle (liquid paraffin)	20 patients in each study age range 19-42 years study period 4 weeks	Two within-person right/left forearm parallel studies	Objective laboratory measures of skin barrier function including transepidermal water loss (TEWL), skin hydration and irritation after sodium lauryl sulphate provocation	In study 1, barrier function assessed in various ways improved in both groups equally. In study 2, the author's claimed that there was evidence of a stabilising effect of the active preparation above vehicle, yet the graphs for skin hydration and TEWL and irritation potential do not suggest any clinical or statistical differences at the end of the 4 week study	Method and concealment of randomisation not described. No intention-to-treat analysis. Study described as double blind.	This study described two different studies. In study 1, an EPO oil-in-water emulsion was compared to vehicle in a right/left forearm comparison in 20 participants, and in study 2, an EPO water-in-oil emulsions was compared against a different vehicle in 20 different participants. The authors then make inferences about one emulsion compared against the other without any direct data to support this. The authors' conclusions are not supported by their data. The

							study shows the general improvement of barrier function that occurs with oil applied to the skin, but provides no evidence of efficacy of EPO above vehicle
Ferreira *et al* 1998[145] and Ferreira *et al* 1998[144] (duplicates of the same study)	Emollients containing 10% GLA Versus Borage oil (24% GLA) Versus Rose hip oil (35-40% GLA) Versus Atoderm™ emollient without EFAs	23 patients age range 3-15 years study period 4 months	Parallel RCT	Xerosis and doctor-assessed itch	Clinical assessment of xerosis and pruritis revealed improvement in all 4 groups, slightly more pronounced in the 3 gamma linoleic acid (GLA) groups. None of the changes statistically significant	Method of concealment of randomisation unclear, no mention of blinding. Two dropouts/withdrawals, no intention-to-treat analysis carried out.	To be included, eczema had to be in remission, those who had eczema flare became failures. No hint of a dose/benefit between the different concentrations of EPO
Anstey *et al* 1990[171]	EPO cream in a water-in-oil emulsion Versus E45™ emollient cream	12 patients age range 4-46 years study period 14 days	Within person right/left arm parallel RCT	Erythema, dryness, scaling, lichenification, infiltration, patient-assessed itch, physician-assessed global severity, patient-assessed global severity	Analysis of results revealed a significant difference between the two groups in the mean absolute change in patient scores over the 14-day period (p=0.006) and	Method and concealment of randomisation unclear, study described as double blind. Marked discrepancy between patient and doctor assessment may	A very small sample over a very short time of only 2 weeks, but acknowledged as a pilot study

					also in percentage change over 14 days (p=0.021). In both cases the change was positive, indicating improvement in eczema and that EPO was the better cream. There were no significant differences for change in doctor's assessment	suggest unblinding. One dropout, no intention-to-treat analysis carried out	

3.6.3 Vitamin and mineral supplementation

Pyridoxine

Study 1

- Mabin *et al* 1995[172]
- Pyridoxine (vitamin B_6) versus placebo
- 48 children with AD
- study duration 4 weeks
- outcome measures:
  - skin severity scores
  - daytime itch
  - nocturnal itch

Results

- There was an increase in median skin severity score in the pyridoxine group from 92.3 at the beginning of the trial to 109.0 at the end of the 4 week study duration
- There was a decrease in median skin severity score in the placebo group from 125.5 at the beginning of the trial to 77.0 at the end of the trial
- The difference between the median change in skin scores was 29.2 (95% confidence interval (CI) ranging from a benefit with pyridoxine of 19.5 to a benefit with placebo of +85.0)
- There was no statistical difference for scores of skin severity, daytime itch or nocturnal itch
- 16% in both groups felt that their skin was overall better according to parental observation

Adverse effects

- no serious adverse effects were described
- one child developed an non-specific erythematous rash while taking pyridoxine
- one child reported to be more itchy than usual while taking placebo

Notes

- a well reported study with method of randomisation, allocation concealment and blinding clearly described
- no intention-to-treat analysis carried out
- no adjustment of the different baseline scores was made

Selenium and vitamin E

Study 1

- Fairris *et al* 1989[173]
- 600μg selenium versus 600μg selenium plus 600IU vitamin E versus placebo
- 60 adults with AD
- study duration 12 weeks
- outcome measures:
  - severity score based on inflammation, lichenification, scaliness
  - venous blood to measure selenium concentrations
  - punch biopsy to measure selenium in skin

Results

- there was a significant increase in the concentration of selenium in whole blood and the activity of selenium dependent glutathione peroxidase in platelets in selenium-only group and selenium plus vitamin E and an increase in the concentration of vitamin E in plasma in selenium plus vitamin E group
- mean severity score fell from 21.0 at baseline to 4.7 in the selenium only group, from 21.8 at baseline to 15.3 in the selenium plus vitamin E group, and from 20.4 to 14.5 in the placebo group
- no significant difference between the three groups in the severity of eczema or the concentration of selenium either before or after the 12 weeks of supplementation
- the authors conclude that selenium enriched yeast supplement was absorbed and bioavailable, it does not enter the skin or produce a worthwhile improvement in AD

Adverse effects

- none reported

Notes

- method of randomisation described
- no intention-to-treat analysis performed

Vitamin E and vitamin B_2

Study 1

- Hakakawa & Ogino 1991[174]
- vitamin E 100mg plus vitamin B_2 versus vitamin E 100mg versus vitamin B_2
- 59 patients with AD
- study duration 4 weeks
- outcome measures:
    - physician-assessed overall usefulness and global rating

Results

- response was greater in the vitamin E plus vitamin B_2 than in the vitamin E or vitamin B_2 groups

Notes

- difficult to interpret without placebo control
- difficulties in blinding and *post hoc* subgroup analysis of dry skin subtypes at different time intervals bring validity of this study into question

Zinc supplementation

Study 1

- Ewing *et al* 1991 [175]
- oral zinc sulphate 185.4mg/day versus placebo
- 15 children with AD
- age range 1-16 years

- study period 8 weeks
- outcome measures:
    - severity scores for erythema
    - surface area score

Results

- virtually no difference in score between zinc supplementation and placebo and nothing statistically significant

Adverse effects

- none reported

Notes

- no description of randomisation and allocation concealment
- no intention-to-treat analysis carried out

3.7 MISCELLANEOUS INTERVENTIONS

3.7.1 Nitrazepam

A benzodiazepine, nitrazepam is often used for nighttime sedation. The idea of using such a drug for those with AD is linked to the symptom of itch, which can keep a patient awake at night and unable to function during the day[176]. One RCT of nitrazepam was located:

Study 1

- Ebata *et al* 1998[177]
- Nitrazepam 5mg versus placebo
- 10 adults with AD
- study duration 3 successive nights
- crossover with 4 day washout period
- outcome measures:
    - nocturnal scratching - percentage of total scratch time (bouts of scratching lasting more than 5 seconds measured by infrared video)

Results

- total scratch time in nitrazepam group was 6.5% compared to 5.4% in placebo group (statistically significant)
- frequency of bouts of scratching slightly less in nitrazepam group, however, mean duration of bouts was longer in nitrazepam group (statistically significant)
- no change to degree of itching and condition of AD during the study

Adverse effects

- none reported in this study

Notes

- small study
- method of randomisation and allocation concealment not recorded

3.7.2 Papaverine

In atopic eczema phosphodiesterase levels in mononuclear cells are raised. Papaverine is a phosphodiesterase inhibitor, which is why it has been used in the treatment of AD. Two RCTs assessing the use of papaverine in AD have been located:

Study 1

- Berth-Jones & Graham-Brown 1990[178]
- Papaverine hydrochloride 100mg four times daily or 60mg four times daily in children versus placebo
- 50 patients
- mean age 25.6 years
- study period 4 weeks
- outcome measures:
  - patient-assessed itch
  - doctor-assessed extent and severity of disease (clinical score)

Results

- mean itch score in last 7days of each treatment period was 58.6 for papaverine compared to 55.7 for placebo (max. score 140)
- clinical score was 178 and 176 in active and placebo phases respectively

Adverse effects

- no serious adverse effects reported

Notes

- baseline scores not given

Study 2

- Shupack *et al* 1991[179]
- papaverine hydrochloride 150-300mg three times daily versus placebo
- 30 adults with AD
- age range 18 and over
- study duration 2 weeks
- outcome measures:
    - itching
    - patient-assessed global evaluation
    - physician-assessed global evaluation

Results

- no statistically significant advantage over placebo for papaverine hydrochloride

Adverse effects

- three patients on papaverine hydrochloride had abnormal liver function tests
- nausea occurred in 46% of patients in active treatment compared to 27% taking placebo (not statistically significant)

Notes

- method of randomisation and concealment of allocation unclear
- no intention-to-treat analysis performed
- abnormal liver function tests are cause for concern

3.7.3 Ranitidine

Ranitidine is a histamine type-2 receptor antagonist that modifies the immune system by inhibiting histamine activity. It has been used in the treatment of gastric ulcers and those treated with ranitidine that also had AD improved. One RCT of ranitidine was located for the treatment of AD:

Study 1

- Veien *et al* 1995[180]
- Ranitidine 300mg twice daily versus placebo
- 47 adult patients with hand eczema and AD
- study duration 4 months
- outcome measures:
  - composite score of signs of eczema

Results

- composite sign score reduced from a mean of 10.17 to 4.91 in the active treatment group versus 10.58 to 7.46 in the placebo group (p=0.07)
- 17 out of 23 patients on ranitidine reported 'clearing' or 'marked alleviation' compared with 8 out of 24 on placebo (p=0.02)

Adverse effects

- non reported

Notes

- method of randomisation and concealment of allocation not clear
- intention-to-treat analysis was carried out

3.7.4 Salbutamol

Animal studies show that β_2-adrenoreceptor agonist, of which salbutamol is a type, can reduce inflammation[181]. One study of salbutamol in the treatment of AD in humans was located:

Study 1

- Archer & MacDonald 1987[181]

- Salbutamol ointment (1% base in white soft paraffin, twice daily) plus a placebo oral tablet with oral salbutamol (a slow release spandet 8mg twice daily plus white soft paraffin placebo ointment twice daily) versus a placebo spandet and white soft paraffin only
- 20 adults with AD
- study period 2 weeks
- outcome measures:
  - itching
  - number of affected zones
  - skin thickening, vesiculation, epidermal change and redness

Results

- no statistically significant or clinically useful changes shown

Adverse effects

- 5 withdrawals, 3 of which were due to adverse effects
- 5 patients taking oral salbutamol and 1 patient on topical salbutamol reported tremor
- systemic absorption of topical salbutamol was found in two patients

Notes

- method of randomisation, concealment of allocation and blinding not described
- no intention-to-treat analysis carried out

3.7.5 Suplatast tosilate

Rebound phenomenon, a severe flare-up after discontinuation of a topical steroid, can occur in people with AD that have been treated for long periods of time with potent and very potent topical steroids[15]. One RCT was located that compared an anti-allergic drug, suplatast tosilate, which down-regulates IgE production and related cytokines, versus bufexamace ointment, a non-steroidal anti-inflammatory ointment, in the prevention of rebound phenomenon from topical steroids in the treatment of AD:

Study 1

- Kimata 1999[182]
- Oral suplatast tosilate 400mg/day and bufexamace ointment versus bufexamace ointment
- 32 patients with AD
- study period 2 weeks
- outcome measures:
    - occurrence of rebound phenomenon

Results

- 15 patients in the control group experienced rebound phenomenon after 2 weeks compared to 17 patients in active drug group
- several cytokines increased in the control group but not in the active group

Adverse effects

- none reported

Notes

- small study that was unblinded making it prone to investigator bias
- 'rebound phenomenon' not defined
- a larger RCT required that is double blind, over a longer period, with clinical outcome measures and a vehicle-only comparison group[39]

3.7.6 Theophylline

Theophylline is a phosphodiesterase inhibitor, which increases cAMP levels. The theory behind using this drug in the treatment of AD is based on patients with AD having a defect in their β-receptors leading to low levels of cAMP within cells[183]. One RCT was located that looked at theophylline in the treatment of AD:

Study 1

- Ruzicka1980[183]
- Theophylline/ethylenediamine 300mg versus placebo
- 14 adults with AD
- study period 2 weeks
- outcome measures:
  - sleep disturbance
  - AD symptom score

Results

- mean symptom score was 1.82 versus 1.68 in the active and placebo groups respectively
- sleep disturbance was 5 out of 14 nights versus 4.4 out of 14 night for the active and placebo groups respectively

Adverse effects

- none reported

Notes

- small study of short duration
- very brief reporting of methodology section making it difficult to interpret

3.8 NON-PHARMACOLOGICAL TREATMENTS FOR ATOPIC DERMATITIS

3.8.1 Detergents

Anecdotal evidence suggests detergents used to wash clothes that contain enzymes can irritate the skin encouraging people with AD to use non-biological washing powders instead to avoid unnecessary skin aggravation or irritation[184]. One RCT was located that assessed detergents with enzymes against detergents without enzymes:

Study 1

- Andersen *et al* 1998[185]
- Detergent containing enzymes of high concentration versus detergent without enzymes
- 26 adults with AD
- mean age 25 years
- study duration 1 month
- outcome measures:
  - SCORAD[141]
  - Patient-reported itch
  - Patient-reported eczema activity

Results

- No difference between detergents: SCORAD score for both control and active was 29 (95% CI -4 to +5 on a scale of 108)
- Patient-reported itch 1.3 for both enzyme and non-enzyme detergent
- Patient-reported eczema activity 1.4 for both enzyme and non-enzyme detergent

Adverse effects

- Patients were patch tested at the end of the study for contact dermatitis caused by enzymes and no patients responded positively
- Blood tests did not show specific blood IgE against the enzymes

Notes

- Small study
- Not sponsored by pharmaceutical industry

3.8.2 Clothing

Certain fibres such as wool can irritate eczematous skin. The National Eczema Society advise people to wear cotton clothing because it is believed to be less irritant to sensitive skin such as atopic eczema. Three RCTs were located that assessed certain types of clothing in AD patients:

Study 1

- Diepgen *et al* 1990[186]
- Four poncho-like shirts of varying fibre roughness (one of which was cotton, the others of which increased in weight and fibre roughness)
- 55 patients with AD versus 31 control patients without AD
- outcome measures:
  - itching or discomfort due to repeated wearing of the shirts measured by a points scale (10=max. comfort, 1=max. discomfort)

Results

- the people that wore cotton had a comfort score of 8.4 compared to 7.3, 3.6 and 3.3 for the other types of fibre (estimated from graph)
- the difference between the cotton and the other fibres was significant for the latter 2 groups

Adverse effects

- none reported

Notes

- the roughness of the shirts brings the blinding success of the study into question

- there are many fibres, natural and synthetic that weren't tested, therefore a larger study testing other smooth fibres is required before conclusions can be drawn

Study 2

- Diepgen *et al* 1995[187]
- Garments made from seven different fabrics including jersey-knits (polyester filament yarn, cotton, polyester staple fibres) and warp-knits (polyester filament yarns, matt, round)
- 20 patients with AD
- study duration: each garment was worn for 4 days under standardised conditions
- outcome measures:
    - comfort assessed by a visual analogue scale

Results

- comfort was statistically significantly higher for warp-knits compared to jersey knits but there was no difference between fabrics made of cotton and polyester

Adverse effects

- none reported

Notes

- it was not clear if the study was randomised however after meeting face-to-face with the author at a dermatology conference (British Association of Dermatologists 2000), randomisation was positively confirmed

Study 3

- Seymour *et al* 1987[188]
- Cloth nappies versus cellulose core nappies containing absorbent gel material
- 85 babies with AD
- age range <20 months

- study period 26 weeks
- outcome measures:
  - overall grade of eczema on the body
  - nappy rash

Results

- for overall grade of AD there was no clinical or statistical difference between the different types of nappy
- the group that used the cellulose nappy with absorbent gel material had significantly less nappy rash compared with the other groups ($p<0.05$)

Adverse effects

- none reported

Notes

- randomisation, concealment of allocation and blinding not clearly described

3.8.3 House dust mite hyposensitisation

Hyposensitisation is a technique used to induce an immunological and clinical tolerance to allergens that might be playing a role in allergic disease by repeated and progressive exposure to increasing amounts of allergen[39]. Three RCTs were located that assessed hyposensitisation with house dust mite allergen:

Study 1

- Glover & Atherton 1992[189]
- Tyrosine-absorbed extract of house dust mite injections versus placebo injections
- 26 children with AD who had positive house dust mite skin-prick tests
- study duration 8 months
- outcome measures:

- clinical scores:
    - redness
    - skin thickening
    - surface damage

Results

- clinical scores improved in both groups however there was no statistically significant difference between the active and placebo groups
- 7 from the active treatment group were followed up for a further 6 months and were randomly allocated to active treatment or placebo: redness and skin thinning got worse in the control group, the scores of which were statistically significant

Adverse effects

- discomfort at injection site
- there is evidence to suggest, in rare circumstances, desensitisation can cause anaphylactic shock, which is life threatening. This is based on desensitisation with bee sting or hay fever allergy[39]

Notes

- lack of statistical significance could be due to lack of power or a large placebo effect from injections[39]

Study 2

- Galli *et al* 1994[190]
- Oral hyposensitisation to house dust mite versus conventional therapy and house dust mite reduction measures
- 16 children with AD
- outcome measures:
    - change in clinical score

Results

- active treatment group improved but this was not clinically or statistically significant

Adverse effects

- none mentioned

Notes

- small study
- conventional treatment and house dust mite reduction measures as a control may explain why there was a lack of treatment effect

Study 3

- Wen *et al* 1992 [191]
- weekly injections of allergenic extract versus a partially purified extract versus saline placebo
- 56 patients with AD
- study duration 12 months
- outcome measures:
    - unspecified clinical score

Results

- data presented in graphical form only showed a reduction in clinical score for all three groups

Adverse effects

- discomfort of injections

Notes

- no statistical tests performed
- minimal methodological details given

3.8.4 House dust mite reduction

The majority of people with AD have a sensitivity to environmental allergens, which can be identified via raised IgE antibodies in the blood. Research evidence suggests 70% of atopic patients patch-tested are allergic to the house dust mite which is classed as an environmental allergen[192]. It makes sense therefore to assess the effect of reducing this allergen as a treatment for AD. Five RCTs assessing house dust mite (HDM) reduction were located, however 2 were the same study published twice, hence are reported together as study 2 below:

Study 1

- Colloff *et al* 1989[193]
- natamycin (spray HDM killer) versus placebo spray with and without vacuum cleaning
- 20 adults with AD
- study period 4 months
- outcome measures:
    - clinical improvement in the eczema symptom score

Results

- there was no significant clinical improvement in the natamycin group
- mean symptom score (max. 288) in the active group fell from 55.2 to 38.6 versus 45.2 to 35.8 for no natamycin and no vacuum cleaning group

Adverse effects

- none reported

Notes

- method of randomisation and concealment of allocation not reported
- no intention-to-treat analysis carried out

Study 2

- Tan *et al* 1996[194] and Friedmann *et al* 1998 (duplicate publication of the same study)
- GoreTex® (Intervent, UK) bedding covers, benzyltannate spray to kill mites and denature their allergens (*Der p1*) and a high-filtration vacuum cleaner versus plain cotton bedcovers, placebo spray and a standard upright vacuum cleaner with a poor filtration performance
- 60 patients (30 children and 30 adults)
- study period 6 months
- outcome measures:
  - concentration of HDM allergen (*Der p1)* in bedroom carpet
  - surface area involvement of AD
  - composite severity score (max. score 108)

Results

- both groups showed a dramatic reduction in HDM allergen (*Der p1)* concentration in bedroom carpets
- composite severity score reduced slightly in both groups but marginally more in the active group (12.6 units reduction for active group and 4.2 units for placebo group)
- the active group had more severe AD to begin with therefore additional statistical analysis was carried out that allowed for baseline scores and initial HDM antigen levels which showed a mean difference of 4.2 in change of score (95% CI 1.7 to 6.7 units, p=0.008) between the two treatments
- further statistical analysis showed changes in bedroom HDM allergen concentrations largely accounted for the treatment effect
- subgroup analysis was carried out that suggested only children had a clinically and statistically significant improvement

Adverse effects

- none reported

Notes

- method of randomisation and concealment of allocation not clear
- no intention-to-treat analysis carried out
- impressive length of study at 6 months giving time to reflect the relapsing and remitting features of AD

Study 3

- Endo *et al* 1997[195]
- room floors, mattresses and quilts cleaned thoroughly as explained and demonstrated by a team of mite specialists versus a less intensive clean with vacuum suction reduced to 50%
- 30 children with AD
- study duration 12 months
- outcome measures:
  - mite numbers
  - clinical score (unspecified)

Results

- there was a statistically significant reduction in mite numbers for room floors only in the active cleaning group
- clinical scores were significantly improved in the active group but not the 'placebo' group

Adverse effects

- none reported

Notes

- parents were unblinded
- physician was blinded when carrying out clinical score assessment
- clinical scores were in graphical form only and difficult to interpret accurately

Study 4

- Nishioka *et al* 1998[196]
- quilts and mattresses encased in microfine fibres versus simple cleaning measures only
- 57 Japanese infants with AD that were not allergic to house dust mite (blood tests at the start of the study used to confirm this)
- study duration 1 year
- outcome measures:
    - none reported in the actual paper
    - authors of the study were contacted who reported outcome measures as 'clinical outcomes'

Results

- authors reported no difference between the two groups at the end of the study for clinical outcomes via *post hoc* correspondence

Adverse effects

- none reported

Notes

- method of randomisation, concealment of allocation and blinding methods not described
- no clinical outcomes recorded in the published paper
- had to take authors word for results on clinical outcomes

3.8.5 Parental education

Part of the mainstay of treatment in clinical practice today is a combination of explanation and discussion, emollients and topical corticosteroids[197]. It was therefore encouraging to find an RCT assessing the impact of education and information on eczema to the parent of a child with eczema:

Study 1

- Broberg *et al* 1990[198]

- conventional treatment by a dermatologist versus conventional treatment by a dermatologist plus a nurse lesson which included general information about AD and environmental control, information and demonstration of topical treatment and discussion of realistic expectations
- Parents of 50 patients aged 4 months to 6 year 2 months with AD
- Study duration 3 months
- Outcome measures:
    - Mean eczema score (max. score 96)

Results

- A baseline mean score of 26.4 fell to 7.1 in the conventional care plus education group compared to a fall from 21.3 to 10.8 for the conventional care only group ($p<0.05$)
- individual scores for the education group were lower than the control groups individual scores (statistically significant)

Adverse effects

- none reported

Notes

- baseline scores were different and were not adjusted for in the comparison
- unblinded study
- no intention-to-treat analysis carried out

3.8.6 Psychological interventions

AD can be linked to several psychological problems including anxiety and depression which can lead to low self esteem, lack of confidence and habitual scratching[199, 200]. This may be linked to social and peer pressures such as the media and the beauty industry where 'perfect skin' is the desired 'norm'. This can cause added stress and distress in the atopic's life promulgated by stigma, bullying, impaired social skills and negative judgement by others[201]. From another psychological perspective, those with AD have been found to scratch habitually even when the eczema isn't itchy for reasons such as stress

and attention seeking behaviour. This damages the skin further and exacerbates the condition[200]. Three RCTs were located that assessed psychological interventions of 3 different kinds:

Study 1

- Melin *et al* 1986[202]
- two sessions of habit-reversal treatment plus hydrocortisone cream versus hydrocortisone cream only
- 17 patients with AD
- age range 19-41 years
- study period 28 days
- outcome measures:
  - global eczema score
  - self-assessed annoyance
  - scratching episodes

Results

- for global eczema score there was a mean reduction of 67% in the habit-reversal plus hydrocortisone group compared to 37% mean reduction for the hydrocortisone-only group ($p<0.05$)
- self-assessed annoyance was reduced more in the active group
- mean percentage reduction of scratching episodes was 79% in the active group compared to 49% in the hydrocortisone-only group ($p<0.01$)

Adverse effects

- none reported

Notes

- unblinded
- method of randomisation and allocation concealment not described

Study 2

- Noren & Melin 1989[203]
- application of betamethasone (a potent topical cortiscosteroid) plus habit-reversal for the first 3 weeks followed by hydrocortisone cream (a mild topical corticosteroid) plus habit-reversal for the remaining 2 weeks versus application of hydrocortisone plus habit-reversal for the entire study period versus application of betamethasone for 3 weeks then hydrocortisone for 2 weeks versus application of hydrocortisone cream for the entire study duration
- 45 patients with AD
- mean age 24.8 years
- study duration 5 weeks
- outcome measures:
  - total skin status
  - scratching

Results

- significant differences were reported between behaviour therapy groups and steroid-only groups for total skin status
- there was a reduction in scratching of 65% in the hydrocortisone-only group, 74% in the betnovate then hydrocortisone group, 88% in the hydrocortisone plus habit-reversal group and 90% reduction in the betnovate and hydrocortisone and habit-reversal group

Adverse effects

- none reported

Notes

- unblinded
- method of randomisation and allocation concealment not described

Study 3

- Ehlers *et al* 1995[204]
- autogenic training as a form of relaxation therapy (ATP) versus cognitive-behavioural treatment (BT) versus a standard dermatological educational programme (DE) versus combined DE and BT (DEBT)
- 14 patients with AD
- study period 3 months of intervention (with one-year follow-up for relapse)
- outcome measures:
  - skin severity lesion score
  - itching
  - global skin severity

Results

- mean skin severity lesion score after one year fell from 29.5 to 28.8 in the DE group, 33.7 to 19.8 for the ATP group, 31.0 to 20.7 for the BT group and 35.4 to 25.8 for the DEBT group
- for mean severity of itch there were no significant differences in change
- improvement in global skin severity was greatest in DEBT group

Adverse effects

- none reported

Notes

- A blinded study, however, the method of randomisation and allocation concealment were not described in detail
- No intention-to-treat analysis carried out

3.8.7 Salt baths

Anecdotal reports point towards an improvement in some people's AD while on holiday abroad where swimming in the sea, de-stressing and sunlight play a part of daily life. The Dead Sea appears to

greatly benefit people with various skin diseases such as psoriasis and eczema but it is unclear what its role is in AD[205]. Whether it is the salty seawater, sun or de-stressing that helps the eczema or a combination of all three is unclear at present. In addition, salt water or saline solution is a mild antiseptic, which could explain why some people's eczema improves while on holiday but again without robust evidence it is difficult to differentiate between sun, sea and de-stressing. It was encouraging therefore to find an RCT that evaluated deep-sea salt versus saline, yet disappointing to not find a trial that compared salt baths to ordinary baths:

Study 1

- Adachi *et al* 1998[206]
- Sterilised, heated to 65°C deep-sea water sprayed on the body before home bathing and washed away after 10 minutes daily versus physiological saline using the same process
- 100 patients with AD
- aged 15 years and over
- study period 1 week
- outcome measures:
    - doctor-assessed global evaluation
    - skin signs

Results

- reduction in doctor-assessed global evaluation and skin signs for both groups after one week by a small amount only, none of which were clinically or statistically significant changes

Adverse effects

- none reported

Notes

- short duration
- well reported study

- limited due to use of two potentially active treatments

3.8.8 Ultraviolet light

As previously mentioned, some people find sun exposure helps their eczema, however, like the chapter on salt baths (3.8.7), it is difficult to isolate the sun from other anecdotally beneficial factors on holiday such as swimming in salt water and generally relaxing. There are however therapeutic reports that suggest UV light may be beneficial in the treatment of eczema[207]. Observational evidence and experimental findings suggest UV light has an effect on the Langerhans cells, contact sensitisation, releasibility of inflammatory mediators, release of neuropeptides from the skin and many other effects[208].

UVA, UVB or PUVA are the three main types of UV light used to treat atopic eczema that is unresponsive to conventional treatment:

- UVA - rays closest to the visible spectrum, able to pass through glass and are the least harmful to the skin[209]
- UVB - the rays responsible for nearly all biological effects following sunlight exposure including tanning, burning and skin cancer[209]
- PUVA - UVA plus the addition of the photoactive drug, Psoralen, which is taken orally or mixed in the bath. Psoralen enhances UVA radiation. Its role in the treatment of psoriasis is proven but is unclear in AD[210]

Six RCTs were located that assessed UV light in the treatment of atopic eczema, which are presented in Table 13.

Table 13 UV light in the treatment of atopic dermatitis

Author and date of study	Interventions	Population, sample size and study period	Trial design	Outcome measures	Main reported results	Quality of reporting	Notes
Der-Petrossian *et al* 2000[211]	Narrow band UVB versus bath PUVA 1mg/L as 8-MOP three times per week	12 patients with severe/chronic AD with a mean age of 27 years ± S.D of 11.3 years 6 weeks duration	Prospective, randomised, single blind half side comparison	Patient rated (PR) itch and sleep loss (VAS 0-10cm) as part of SCORAD[141], doctor-rated (DR) global severity, DR global changes of modified SCORAD for 8 signs and symptoms	Baseline scores of 100% SCORAD for bath-PUVA and UVB reduced by 65.7% for bath-PUVA treated side and 64.1% for UVB treated side (p=0.48)	Study described as randomised, and investigator blinded. No intention-to-treat analysis carried out. 2 withdrawals, one due to exacerbation of AD, an another due to a differential response in terms of less erythema reactions to the bath-PUVA side	A small study, which took care to ensure that both treatments were given in equal doses. Big falls in SCORAD scores for both treatments with little difference between the two
Reynolds 1999[212]	Narrow-band UVB (up to max. of 1.2 J/cm^2) versus UVA (up to max of 15 J/cm^2) or placebo (visible light) all twice weekly (mild to moderate topical steroids plus emollients)	73 adult patients with moderate to severe AD 12 weeks duration	Prospective, randomised, double blind parallel study	5 clinical features at 6 separate body sites plus itch and sleep loss (VAS), and extent of disease recorded by one observer	The proportion of patients reporting reduction in itch over 24 treatments was 90% (p=0.02) for narrow-band UVB, 63% for UVA and 53% for placebo (p=0.02 compared with placebo). Changes	Study described as randomised (in balanced blocks), controlled, and double blind. No intention-to-treat analysis	Published in abstract form only at time of report. Only 47 out of 73 patients completed study. Study possibly partly unblinded due to lack of pigmentary changes on one side and burning

					for sleep loss failed to reach statistical significance		in others
Krutmann *et al* 1998[213]	High dose UVA1 40J/ cm^2 once daily versus once daily fluocortolone 0.5% cream or ointment versus UVA-UVB minimal erythema dose-dependent once daily	53 patients acute severe exacerbation of AD 10 days duration	Prospective, randomised, parallel study	Costa scoring system[147]: erythema, oedema, vesicles, exudation, crusts, excoriations, scales, lichenification, pruritis, loss of sleep on a 7-point scale (0=no lesion, 6=extremely severe)	Improvement over baseline for total clinical score: High-dose UVA1 baseline of 56 reduced to 26, fluocortolone baseline of 60 reduced to 35 and UVA-UVB baseline of 60 reduced to 42 (all after 10 days treatment) ($p<0.0001$) Mean reduction in total disease activity was 9.7 for 21 evaluable patients on narrowband UVB, 4.8 on UVA and 0.4 on placebo, the change significant at the 5% level for narrow band UVB versus placebo only	"A randomisation sequence generated by random numbers". No blinding. No withdrawals or dropouts	Very short duration. Results had to be estimated from graphs. Useful to have a comparison with topical steroids. Study suggests superiority of high dose UVA over a topical steroid
Jekler 1992 [214]	Mixed UVA (74%) and UVB	30 patients with mean age of 24.8	Prospective, randomised	Patients assessed for pruritis,	A decrease from baseline score of	Described as randomised but	This paper also presents the two

	(26%) versus UVB 3 times per week	years and mean disease duration of 20.5 years 8 weeks duration	left/right parallel study	lichenification, scaling, xerosis, vesiculation, excoriations, erythema and an overall evaluation on a score of 0-3 (none to severe) healing evaluated on a scale of 3 to -1 (3=healed, -1=worse)	10.8 to 5.2 for UVAB and 6.1 for UVB (p=0.002 for difference in scores between treatments). 21/24 patients reported mild burning with UVB which was sever in 6 patients compared with 3 episodes of mild burning with UVA/B (none severe)	method unclear. No blinding. No withdrawals or dropouts	studies reported in Jeckler 1988 in more detail. A further 3 small left/right comparison studies are also described comparing UVA versus UVB and low dose UVB versus UVA/B, and UVA versus UVA/B, but it is unclear if these were RCTs
Krutmann *et al* 1992[215]	High doseUVA1 (0-40J/ cm^2 once daily) versus UVA-UVB therapy (up to 30mj/ cm^2 UVB and 7.5j/ cm^2 UVA daily	25 young adults with AD and definite atopy 15 days duration	Prospective, randomised, parallel study	Costa scoring system: erythema, oedema, vesicles, exudation, crusts, excoriations, scales, lichenification, pruritis, loss of sleep on a 7-point scale (0=no lesion, 6=extremely severe)	A decrease from baseline of 53 (overall score) to 14 after UVA1 (p<0.001 against comparator change). Comparative data for UVA-UVB not given but shown in graphical form only. UVA-UVB 52 at baseline changed to 38 (estimated from graph)	Described as "randomly selected patients" but method unclear. Author contact confirmed "treatments randomly allocated". No blinding. No dropouts or withdrawals	Unclear if patients randomised but confirmed by authors
Jekler & Larko	UVA (average 8.1	33 patients with	Prospective,	Patients assessed	Improvement	Described as	Both treatments

1991[216]	mW/cm^2) versus UVB (0.85 mW/cm^2) 3 times per week	mean age of 23.3 years. Mean disease duration of 19.6 years 8 weeks duration	randomised left/right parallel study	for pruritis, lichenification, scaling, xerosis, vesiculation, excoriations, erythema and an overall evaluation on a score of 0-3 (none to severe). Healing evaluated on a scale of 3 to -1 (3=healed, -1=worse)	from mean baseline of 10.3 (range 6-18) for clinical signs (total score) decreased to 5.5 for UVA and 6.4 for UVB. Pruritis scored separately with baseline of 2.2 improving to 1.1 after UVA and 1.3 after UVB	single blind and randomised but methods unclear. Differential tan on UVA side of the body likely to have unblinded study. 12 withdrawals and dropouts, no description given, no intention-to-treat analysis	induced large improvements compared with baseline, with some small statistically significant change in favour of UVA. Most patients preferred UVA
Jekler & Larko 1988[217] Study 1	Thrice weekly UVB (20-153mJ/cm^2 up to 63-816mJ/cm^2) versus placebo (visible light) 3 times per week	17 patients over the age of 15 years, most of whom had skin type III (tans easily, seldom burns) 8 weeks duration	Prospective, randomised, controlled left/right parallel study	Patients assessed for pruritis, lichenification, scaling, xerosis, vesiculation, excoriations, and erythema. Variables assessed on a scale of 0-3, plus a global assessment	Improvement from baseline of 1.5 (mean) to 0.7 for UVB and 1.4 for placebo for overall clinical response ($p<0.001$) Thus the total score was significantly lower for the UVB treated side	Described as randomised but method unclear. Blinding unlikely due to mild burning on UVB-treated side. No intention-to-treat analysis	Unclear if randomisation referred to side of active/placebo treatment or whether to type of minimal erythemal dose. Large (11/17) dropouts due to "intercurrent disease" and lack of time for treatments
Jeckler & Larko 1988[217] Study 2	Thrice weekly UVB given at 80% of minimal dose required to produce redness (minimal erythemal dose -	25 patients with mean age of 25.9 years, most with skin type III 8 weeks duration	Randomised right/left side parallel study	Same as for study 1 above	Clearing or considerable improvement in 15/25 on high dose UVB versus 16/25 with low dose (not	Methods very scanty. Randomisation unclear. Probably unblinded. No intention-to-treat analysis	Further details of study found in Jeckler 1992[214]. This study of high versus low dose UVB suggested very little

	MED) versus UVB at 40% of MED				statistically significant)		difference between the two treatments

3.9 OTHER TOPICAL AGENTS

3.9.1 Ascomycin derivatives

Also known as SDZ ASM 981, more recently pimecrolimus which is the active constituent, and marketed as Elidel®, this new type of drug is a cell-selective cytokine inhibitor, developed for the treatment of inflammatory skin diseases such as AD. Ascomycin is derived from a natural substance produced by the fungus *Streptomyces hygroscopicus var. ascomyceticus.* Its mode of action is on the T-cells that produce cytokines, which mediate the inflammation, redness and itching associated with AD[218].

Four RCTs were located that assessed ascomycins in the treatment of AD[219, 220, 221].

Study 1

- van Leent *et al* 1998[221]
- topical ascomycin 1% cream twice daily versus placebo twice daily
- 34 adults with AD
- length of study 21 days
- outcome measures:
  - severity score
  - lesion clearance

Results

- 71.9% decrease in baseline score in the twice daily group compared to 10.3% in the placebo group ($p<0.001$)
- 37.7% reduction in baseline score in the once daily group compared to 6.2% in the placebo group ($p=0.002$)
- total clearance of lesions was achieved in 15 patients in the twice daily group compared to none in the placebo group
- no patients achieved total clearance of lesions in once daily group for active treatment or placebo

Study 2

- Luger *et al* 2001[220]
- 0.05%, 0.2%, 0.6% and 1% SDZ ASM 981 cream versus vehicle
- 260 patients aged 18 years and over
- 3 weeks duration
- outcome measures:
    - Eczema Area Severity Index (EASI)[222]
    - Pruritis on a scale of 0-3
    - Patient-rated improvement

Results

- A clear dose-response relationship for SDZ ASM 981 was evident, with 0.2%, 0.6% and 1.0% SDZ ASM 981 creams all being significantly more effective than vehicle (P= 0.041, 0.001 and 0.008, respectively) in terms of baseline to end-point changes in EASI and pruritis score
- The 1% cream was the most effective SDZ ASM 981 concentration
- Betamethasone valerate was more effective than the SDZ ASM 981 creams tested in this study
- The efficacy plateau was not reached with the SDZ ASM 981 creams within 3 weeks treatment

Adverse effects

- Most common adverse effects reported were application site reactions described as burning, feeling of warmth, stinging, smarting, pain and soreness

Notes

- Intention-to-treat analysis was carried out but there was no description given of the method of randomisation and allocation concealment (blinding)

Studies 3 and 4

- Eichenfield *et al* 2001[219]
- Two independent RCTs reported together with pooled results

- Pimecrolimus 1% versus vehicle
- 403 patients aged 1 to 17 years
- study duration 6 weeks
- outcome measures:
    - Primary efficacy parameter was IGA score (the IGA represents an overall evaluation of dermatitis performed by the investigator at every visit. IGA scores utilize a 6-point scale, ranging from 0 (clear) to 5 (very severe disease). IGA scores measure disease severity based on morphology, without referring back to baseline state
    - Secondary efficacy parameters were the EASI score severity of pruritis, and overall AD disease control

Results

- A significantly higher proportion of patients treated with pimecrolimus than vehicle were clear or almost clear of disease signs, as classified by IGA, at every post baseline visit. At the final visit (day 43), 34.8% of the pimecrolimus-treated patients were rated as clear or almost clear of disease, compared with only 18.4% of patients in the vehicle group ($P \leq 0.05$)
- EASI scores were lower in the active treatment group at the first assessment on day 8 and at each subsequent post baseline visit
- At each post baseline visit and at the final visit, significantly more pimecrolimus-treated patients reported mild or no pruritis than did patients treated with vehicle

Notes

- Randomization and allocation concealment not detailed
- No intention-to-treat analysis carried out

3.9.2 Emollients

Essentially emollients are moisturisers that add moisture to the skin and/or prevent excess loss of moisture from the skin. According to Cork[223], a leading UK Consultant Dermatologist and strong advocate of emollients for the treatment of AD, emollients help to repair the broken skin barrier in

eczema. They act like an artificial mortar (fat) that fills the gaps between the skin cells. Being a 'fat', emollients waterproof the skin cells, which, as a result, fill up with water and swell making them plump, hydrated and supple. Emollients, therefore, temporarily restore the defective skin barrier if applied frequently enough and if also used as replacements for soaps/detergents that dry out eczematous skin further. There is also a belief that emollients can protect the skin from allergens in the environment including bacteria such as *Staph.aureus*[223], thus having a preventative as well as a protective mechanism.

One would expect there to be many RCTs assessing the efficacy of such an important treatment in AD. However, only five trials were located that met the inclusion criteria of this thesis:

Study 1

- Kantor *et al* 1993[224]
- oil-in-water emollient (Moisturel™) once daily cream (study 1) or lotion (study 2) versus water-in-oil emollient (Eucerin™) once daily cream (study 2) or lotion (study 2) (both groups applied hydrocortisone 2.5% cream once daily to affected areas)
- 50 patients of all ages
- study period 3 weeks
- outcome measures:
    - independent physician-assessed:
        - redness
        - scaling/crusting
        - itching
        - burning/stinging
    - global eczema severity

Results

- Study 1: Global eczema severity fell from 1.28 to 1.00 in the Eucerin cream group compared to a fall from 1.92 to 0.96 in the Moisturel cream group (n=25)

- Study 2: Global eczema severity fell from 1.91 to 0.68 in the Eucerin lotion group compared to a fall from 1.91 to 0.91 in the Moisturel lotion group (n=22)
- Differences from baseline were statistically significant but differences between the two emollients were not

Adverse effects

- One patient experienced a burning sensation after application of oil-in-water emollient

Notes

- Short duration study of poor quality

Study 2

- Hanifin *et al* 1998[225]
- emollient (Cetaphil™) three times daily plus twice-daily topical steroid (desonide lotion 0.05%) versus twice daily desonide lotion only
- 80 patients with AD
- study period 3 weeks
- outcome measures:
  - 7 symptoms and signs on a scale of 0-9, max. score 63 (total score)
  - investigator-assessed global severity

Results

- total reduction in score for desonide lotion alone was 70% from a baseline of 24.23 compared to a reduction of 80% from baseline score of 24.4 for desonide plus emollient (p<0.01)
- 10% of desonide-only patients showed complete clearing of eczema compared to 11% in the combined emollient and topical steroid group

Adverse effects

- 14% patients in desonide-only group reported stinging or burning after application of the treatment compared to 12% in combination group

Note

- short duration of poor quality

Study 3

- Wilhelm & Scholermann 1998[226]
- emollient containing 10% urea versus vehicle base as 'placebo'
- 80 patients with sub acute AD and associated dry skin
- study duration 4 weeks
- outcome measures included:
  - skin redness
  - induration
  - summary score of signs and symptoms
  - outer skin moisture measurement (capacitance meter)

Results

- there was a 70% improvement in skin redness in group treated with 10% urea preparation compared to 30% improvement in vehicle-only group
- outer skin moisture measurement showed a statistically significant increase in hydration in the 10% urea group compared to vehicle-only group

Adverse effects

- four patients reported transient (short duration) burning in the urea group

Notes

- short duration study of poor quality

Study 4

- Andersson *et al* 1999[227]
- a 'new' emollient cream containing 5% urea compared to an established emollient cream containing 4% urea and 4% sodium chloride
- 48 adults with AD
- study duration 30 days
- outcome measures:
  - physician-assessed clinical disease severity scale (max. score 1600)
  - patient-assessed visual analogue scale for dry skin (max. score 14 meaning 'no dry skin')
  - biometric measurements of water content or water loss through the outer layer of the skin

Results

- clinical disease severity improved for both creams which was statistically significant but not statistically significant *between* the two creams
- visual analogue scale for dry skin changed from 7.5 baseline score to 10 for 'new' cream compared to a change of 7 to 9 for established cream
- biometric measurements not statistically significant between the two creams

Adverse effects

- none reported

Notes

- actual data not given. The data that was given was difficult to read and interpret
- poor quality study

Study 5

- Larregue *et al* 1996[228]
- 6% ammonium lactate in an emollient cream base versus cream base only
- 46 children aged 6 months to 12 years with AD

- study duration 30 days
- outcome measures:
    - pruritis
    - redness
    - dryness
    - desquamation
    - lichenification
    - hyperkeratosis
    - presence of papules

Results

- there was a reduction in lichenification, hyperkeratosis and dryness in both groups but slightly more in ammonium lactate group, statistically significant for lichenification half way through study and for erythema at end of study

Adverse effects

- none reported

Notes

- only some of outcome measures reported
- poor quality study

3.9.3 Lithium succinate

A different form of eczema to atopic eczema, seborrhoeic eczema, has been linked to an infection known as malassezia (pityrosporum). Treatment with lithium succinate has been effective in the treatment of seborrhoeic eczema[229]. One RCT was located that assessed the use of this drug in the treatment of AD:

Study 1

- Anstey & Wilkinson 1991[230]
- 8% lithium succinate ointment versus placebo ointment
- 14 patients with AD (mean age 16 years)
- study duration 2 weeks
- outcome measures:
  - overall impression of eczema
  - global severity

Results

- slight improvement was seen at the end of the study for overall impression and global severity compared to baseline scores for both active and placebo, the scores of which were virtually the same for both groups
- no statistically significant changes between the 2 groups

Adverse effects

- one patient developed contact allergy to the ointment which was later found to have been due to the wool alcohol content of the ointment

Notes

- method of randomisation and concealment of allocation not described
- study described as double-blind
- No intention-to-treat analysis carried out
- Very small study published as correspondence only

3.9.4 Tacrolimus ointment

Tacrolimus originates in transplantation where it is used orally to help prevent organ rejection by suppressing the immune system. In recent times this drug has been developed as a topical treatment for atopic dermatitis, where it is referred to as an immunomodulator. In brief, it has a modulating effect on the immune system in the skin whereby it reduces the inflammation, redness and itching

associated with AD[231]. From a pharmacodynamic perspective tacrolimus is believed to control atopic dermatitis by inhibiting T lymphocyte activation, altering cell surface expression on antigen-presenting dendritic cells and modulating the release of inflammatory mediators from skin mast cells and basophils. Of these, the inhibition of T lymphocyte activation is thought to be the primary mechanism of action. Tacrolimus forms complexes with immunophilins (FK-506 binding proteins (FKBPs)), primarily FKBP12, which then bind to and competitively inhibit the activity of calceneurin. This prevents up-regulation of the signal-transduction pathways in T-cells and thus inhibits the transcription of genes for interleukin (IL)-2, IL-3, IL-4, IL-5, granulocyte-macrophage colony-stimulating factor, tumour necrosis factor-α and interferon-γ. Several of these cytokines play significant roles in the pathophysiology of AD[232].

Seven RCTs have been published in full to date (September 2002)[233-238], two of which are reported in the same paper[233]. Five compared tacrolimus ointment with vehicle ointment[233 234 237 238], and two with hydrocortisone (1% acetate in children, 0.1% acetate in adults)[235 236], which are presented in Table 14.

Table 14 Tacrolimus ointment in the treatment of atopic eczema

Author and date of study	Interventions	Populations, sample size, duration of study	Trial design	Outcome measures	Main reported results	Quality of reporting	Notes
Reitamo *et al* 2002 (a)[236]	0.03% vs 0.1% topical tacrolimus vs 0.1% hydrocortisone butyrate	571 adults age range 16-70 years study period 3 weeks	Parallel RCT	Patient-rated itch on a 10cm VAS, physician-rated global severity, changes in individual signs (erythema, edema-induration-papulation, excoriations, lichenification), mEASI score used to calculate the above	The mEASI mAUC as a % of baseline showed that averaged over the 3-week course of treatment, patients had a median improvement of 53% with 0.03% tacrolimus, 63.5% with 0.1% tacrolimus and 63.9% with hydrocortisone butyrate. There was no statistically significant difference between 0.1% tacrolimus and 0.1% hydrocortisone butyrate; however, the lower improvement in mEASI for 0.03% was statistically	Good description of randomization and blinding. Intention to treat (ITT) analysis was carried out on all patients who were randomized and received at least one application of study ointment. One patient in the hydrocortisone butyrate group never received treatment therefore the ITT population was 570 adults	mEASI baseline scores not given. Patient-rated itch data not given or mentioned in the results

					significant when compared to that of 0.1% tacrolimus (P<0.001), or hydrocortisone butyrate (P=0.002)		
Reitamo *et al* 2002 (b)[235]	0.03% vs 0.1% topical tacrolimus vs 1% hydrocortisone acetate ointment	560 children age range 2-15 years study period 3 weeks	Parallel RCT	Patient-rated itch on a 10cm VAS, physician-rated global severity, changes in individual signs (as above)	The mEASI mAUC as a percentage of baseline showed 0.03% and 0.1% tacrolimus ointment to be significantly more effective than 1% hydrocortisone acetate ointment (P<0.001), and 0.1% tacrolimus ointment to be more effective than 0.03% tacrolimus ointment (P= 0.006)	Good description of randomization and blinding. Intention to treat (ITT) analysis was carried out on all patients who were randomized and received at least one application of study ointment.	Baseline mEASI scores not given. Patient-rated itch data not given or mentioned in the results
Paller *et al* 2001[234]	0.03% vs 0.1% topical tacrolimus vs vehicle control	351 children age range 2-15 years study period 12 weeks	Parallel RCT	Patient-rated itch but no details given, patient-rated global severity but no details given, physician-rated global severity,	Both concentrations of tacrolimus ointment were significantly more effective than vehicle for all measured efficacy	Method of randomization and allocation concealment not described. ITT carried out	Baseline mEASI scores not given

				changes in individual signs (physician-assessed) as above	parameters. No statistically significant differences between the two tacrolimus ointment concentrations were observed for any efficacy parameter		
Hanifin *et al* 2001 Study 1[233]	0.03% vs 0.1% topical tacrolimus vs vehicle control twice daily	304 adults study period 12 weeks	Parallel RCT	Patient-rated itch 10cm VAS, physician-rated global severity, changes in individual signs (as above)	For physician-rated global severity the overall success rate (≥ 90% improvement in disease status) was significantly (P<0.001) higher for tacrolimus ointment-treated patients than for vehicle-treated patients. Patient-rated pruritis scores showed significantly greater improvement compared with vehicle (P<0.001)	Method of randomization and allocation concealment not described. ITT carried out	
Hanifin *et al* 2001 Study 2[233]	0.03% vs 0.1% topical tacrolimus vs vehicle control	328 adults study period 12 weeks	Parallel RCT	Patient-rated itch 10cm VAS, physician-rated	For physician-rated global severity the	Method of randomization and allocation	

	twice daily			global severity, changes in individual signs (as above)	overall success rate (≥ 90% improvement in disease status) was significantly ($P < 0.001$) higher for tacrolimus ointment-treated patients than for vehicle-treated patients. Patient-rated pruritis scores showed significantly greater improvement compared with vehicle ($P<0.001$)	concealment not described. ITT carried out	
Boguniewicz *et al* 1998[237]	0.03% vs 0.1% vs 0.3% topical tacrolimus vs vehicle control	180 children age range 7-16 years study period up to 22 days	Parallel RCT	Patient-rated itch 10cm VAS, patient-rated global severity, physician-rated global severity, changes in individual signs (as above)	Patient-rated itch had a median percent improvement from baseline to end of treatment of 88.7% for 0.03% tacrolimus, 73.6% for 0.1% tacrolimus, 77.1% for 0.3% tacrolimus and 50.5% for vehicle. The mean percentage improvement for mEASI score was	Method of randomization described, study described as double blind but concealment of allocation not described. ITT analysis carried out. Overall one of the better written studies	Pruritis baseline scores given, which is rare

					72% for 0.03% tacrolimus, 77% for 0.1% tacrolimus and 81% for 0.3% tacrolimus compared to 26% for vehicle (P<0.001)		
Ruzicka *et al* 1997[238]	0.03% vs 0.1% vs 0.3% topical tacrolimus vs vehicle control	215 adults and children age range 13-60 years study period 3 weeks	Parallel RCT	Primary end point was change in score 1 (the sum of the scores for erythema, edema and pruritis) in the treated area. Secondary endpoint change from baseline in score 2 (score 1 plus the sum of the scores for oozing or crusting, excoriations, and lichenification of involved skin and dryness of noninvolved skin in the treated area. Patient-rated itch 10cm VAS and sleep loss, patient-rated global severity,	A significant difference was observed among the treatment groups in the change in score 1 between baseline and the end of treatment (P<0.001). Changes between baseline and the end of treatment for score 2 also differed slightly among the 4 treatment groups (P<0.001). Global assessment showed a significantly higher proportion of patients in each of the tacrolimus groups than in the vehicle group had	Method of randomization and concealment of allocation not described. ITT carried out	Data not given for patient-rated itch

				physician-rated global severity	completely resolved or markedly improved symptoms (P<0.001)		

3.9.5 Topical coal tar

It has long been recognized that tars can have a soothing effect on inflamed skin, and they are a traditional remedy in some countries for skin diseases such as eczema and psoriasis[15]. Tars contain hundreds of chemicals, some of which have medicinal effects, most of which have never been identified. The principal tars for treatment of skin disease in the UK come either from coal (coal tar) or from shale containing fossilized fish (ichthammol). It is not as common these days to apply coal tar to eczema, nevertheless, it is still used by some clinicians. One RCT was identified that assessed coal tar in the treatment of AD:

Study 1

- Niordson & Stahl 1985[239]
- Coal tar preparation (Clinitar™ cream) versus conventional 1% crude coal tar in the same cream
- 27 patients with AD (mainly children)
- study period 4 weeks
- outcome measures:
  - infiltration
  - redness
  - skin thickening
  - scratch marks
  - dryness

Results

- all signs of eczema listed above reduced by 50% in both groups at the end of treatment
- there were no statistically significant differences between the two groups

Adverse effects

- 4 patients reported stinging and itching, 2 with coal tar cream and one from use of both treatments. Patch testing confirmed an allergic reaction
- it is not clear how safe coal tar application to the skin is as it may be carcinogenic[240]

Notes

- unblinded
- method of randomisation and concealment of allocation not described
- no intention-to-treat analysis
- the title of this study is 'Treatment of psoriasis with clinitar cream: A controlled clinical trial'[239] however the study is entirely assessing atopic eczema
- coal tar is not cosmetically acceptable as it has a strong unpleasant odour, and it can be very messy

3.10 SYSTEMIC IMMUNOMODULATORY AGENTS

3.10.1 Allergen-antibody complexes of house dust mites

Many people with atopic disease are sensitive to house-dust mites and often have high levels of anti-house dust mite antibodies in their blood. Injections of complexes of house dust mite allergen (*Der p 1*) with antibodies have been used to treat asthma and shown clinical improvement in the treated patients[241]. Two RCTs of allergen-antibody complex of house dust mite were located but on closer inspection were duplicates of the exact same study published one year apart:

Study 1

- Leroy *et al* 1992 and Leroy *et al* 1993[241 242]
- house dust mite allergen-antibody complex injections versus placebo
- 24 adults with AD that were sensitive to house dust mite
- 4 months study
- outcome measures: disease intensity and itch

Results

- there was an improvement in disease intensity in the active treatment group which was statistically significant (1000 to 612 compared to 1000 to 859 for active and placebo scores respectively)
- % mean reduction in itch reduced from 3.3 to 2.2 and 3.3 to 2.6 in active and placebo groups respectively

Adverse effects

- delayed-type inflammatory action at injection site and itching were experienced in 6 patients (4 from active and 2 from placebo)

Notes

- method of randomisation and concealment of allocation was unclear, study was described as double blind

3.10.2 Cyclosporin

Cyclosporin (CyA) is an immune suppressant derived from a fungus. It was first discovered in the early 1970s for the prevention of organ rejection in transplant patients. In the late 1970s it was introduced to dermatology for the treatment of psoriasis and later became available for AD. It is reserved for those unresponsive to conventional treatment due to the serious side effects associated with this powerful drug, such as kidney damage. CyA mechanism of action is on the immune system where it dampens down allergic and immune responses, such as, inhibiting the production of cytokines by lymphocytes. Cytokines act as messengers to 'switch on' other lymphocytes which in those not affected by AD or other immune diseases, are essential for immunological and allergic reactions of a healthy immune system[6].

Twelve RCTs assessing CyA in the treatment of AD were located which are presented in Table 15.

Table 15 Cyclosporin in the treatment of AD

Author and date of study	Interventions	Population and sample size	Design, description and duration	Outcome measures	Main reported results	Quality of reporting	Notes
Topical Cyclosporin							
de Rie *et al* 1991[243]	Cyclosporin 10% topical gel Versus placebo	8 patients, 3-55 years of age	Left/right comparison RCT of 3 weeks duration	ADSI scoring system (presume it is same as ADASI [150]): pruritis, erythema, exudation, excoriations, lichenification	Only 2 patients showed a moderate improvement (≤25%) of the lesions treated, without detectable cyclosporin (CsA) trough levels. Detectable CsA levels were only found in two irresponsive patients treated with the 10% CsA suspension gel (11 and 18 ng/ml). No adverse events found	Method of randomization and concealment of allocation not described. Study reported as 'double-blind'	Very small study(8 patients) of only 3 weeks duration
de Prost *et al* 1989[244]	Cyclosporin 10% topical gel Versus placebo	20 patients with stable AD, age-range 2-29 years	Left/right comparison RCT of 2 weeks duration	Observer-assessed pruritis, erythema, vesicles and oozing, crusts, xerosis and lichenification	The comparison of each criterion at the end of treatment revealed a statistically significantly greater improvement for all criteria in the	Method of randomisation and concealment of allocation not described and only mentioned in abstract. Study described as double blind	Small study of very short duration (2 weeks)

					CsA group compared with the placebo group. The most marked difference concerned the criteria of pruritis, vesicles and crusts. The mean overall score on day 14 was 6.2 ± 3.9 in the CsA group versus 9.6 ± 3.9 in the placebo group ($p<0.005$)		
Oral Cyclosporin							
Harper *et al* 2000[245]	Max. of 5 mg/kg/day continuously Versus Oral cyclosporin max. of 5mg/kg/day given as intermittent 3 month course	43 patients with severe AD, age range 2-16 years	Parallel RCT of 12 months duration	Patient-rated itch, irritability, sleep-loss and global severity. Doctor-rated global severity using SASSAD score[246]. Doctor-rated extent using rule of nines[154]. Renal function and blood pressure	Significant improvements were seen in all efficacy parameters at every time-point, however, there were no significant differences seen between treatment groups at any time point	Method of randomisation and concealment of allocation not described. Study described as double blind	
Cordero Miranda *et al* 1999[247] Spanish translation	Cyclosporin oral transfer factor in escalating does (units not specified)	23 patients aged 3-40 years	Parallel RCT of 6 months duration	Physician-assessed erythema, 'eczema', lichenification,	No data available	No data available	No data available

	Versus Hydrocortisone 1%			itch, oedema. Global physician's assessment every 15 days			
Zurbriggen *et al* 1999[248]	Cyclosporin (Sandimmun™) 4-4.5mg/kg/day Versus Cyclosporin (Neoral™) 4-4.5mg/kg/day	14 patients with severe AD aged 20-64 years	Crossover RCT of 8 weeks duration	Area assessment plus severity assessment at six sites plus itch and sleep loss (authors reference Sowden *et al* 1991[249] for details of outcome measures)	The improvement under Neoral therapy was significantly higher than with Sandimmun (disease activity p=0.047; extent of disease p=0.016). At end of study both formulations yielded similar improvement in the patient's condition	Method of randomisation and allocation concealment not described. Study described as double-blind	Small study
Zonneveld *et al* 1996[250]	Cyclosporin 5-3mg/kg/day (A) Versus Cyclosporin 3-5mg/kg/day (B)	78 patients with severe long-standing AD. Age range 18-70 years	Parallel, open RCT of 10 months duration	Area assessment plus severity assessment of 6 body regions for erythema, lichenification, vesicles/papules, dryness/scaling, cracking/fissuring, excoriation plus patient-assessed itch and sleep loss plus patient and physician global	Cyclosporin showed an efficacy of 59.8% in group A and 51.7% in group B assessed by severity score. Assessed in terms of an area score, these figures were 48.7% and 40% respectively	Method of randomisation and allocation concealment not described. Study was open	Long-term study, which assessed side-effects as well as efficacy. CyA appeared safe and well tolerated by end of study period

				assessment			
Munro *et al* 1994[251]	Cyclosporin 5mg/kg/day Versus placebo	Phase 1: 24 patients with chronic AD aged 19-48 years Phase 2: 17 patients from phase 1 re-randomised to reduction of either the dose of CyA given daily or the frequency with which the 5mg/kg dose was given	Crossover RCT of 8 weeks duration	Composite scale for erythema, excoriation and lichenification using rule of nines[154] plus itch and sleep loss	Phase 1: All patients showed a reduction in the extent and severity f eczema on CyA compared with placebo, and all expressed a preference for the active treatment. Improvement was greatest for area, erythema, excoriation and itch Phase 2: improvement comparable to phase 1 for both groups	Method of randomisation and allocation concealment not described. Study described as double-blind. No ITT analysis carried out	Study suggests amount of CyA required to maintain AD is less than amount required to reach remission
van Joost *et al* 1994[252]	Cyclosporin 5mg/kg/day Versus placebo	46 patients with AD aged 17-68 years	Parallel RCT of 6 weeks duration	Physician-assessed severity in six regions for 10 signs plus physician-assessed extent of disease plus physician-assessed itch and sleep loss plus patient-assessed global severity	Mean improvement in disease severity score of 55% compared with baseline after 6 weeks. In placebo treated group mean % difference showed worsening (4%). Difference between the CyA and placebo	Method of randomisation and concealment of allocation was not described. The study described as double-blind	No notes to add

					groups was statistically significant		
Salek *et al* 1993[253]	Cyclosporin 5mg/kg/day Versus placebo	33 patients with severe AD aged 17-56 years	Crossover RCT of 16 weeks duration	Disease activity, disease extent, patient-assessed itch and sleep loss, patient-assessed health-related quality of life. UKSIP[254] and EDI scores used	There was a close correlation ($p<0.05$-$p<0.01$) between the UKSIP and EDI scores. In contrast, there was either no correlation, or only a very poor correlation, between the quality of life parameters and clinical measures of extent and activity of eczema	Method of randomisation and concealment of allocation not described. Study described as double-blind. No ITT analysis carried out	Reported results are all correlations between quality of life and clinical assessment, no actual outcome data given on clinical assessment. When CyA was stopped relapse was rapid
Allen 1991[255]	Cyclosporin 5mg/kg/day versus placebo	33 patients with severe AD aged 17-56 years	Crossover RCT of 16 weeks duration	Erythema, purulence, excoriation or crusting, dryness or scaling, cracking or fissuring and lichenification at 6 body sites, extent of disease, patient-assessed sleep-loss and itch	Estimated from graph: baseline extent of disease % score for both groups was 70%: Placebo/CyA treatment sequence maintained score of 70% for placebo, reducing to 25% for CyA, compared to CyA/Placebo group which	Method of randomisation and concealment of allocation not described. Study described as double-blind. No ITT analysis carried out	This study, Sowden study below and Salek study above are all the same study reported in three different ways by different lead authors but same group

					reduced to 35% for CyA and back up to 70% for placebo		
Sowden *et al* 1991[249]	Cyclosporin 5mg/kg/day Versus placebo	33 patients with severe AD aged 17-56 years	Crossover RCT of 16 weeks duration	Erythema, purulence, excoriation or crusting, dryness or scaling, cracking or fissuring and lichenification at 6 body sites, extent of disease, patient-assessed sleep-loss and itch, patient and doctor global assessments	Patients in both treatment sequences showed a rapid improvement in both disease activity and extent of disease on CyA	Method of randomisation and concealment of allocation not described. Study described as double-blind. No ITT analysis carried out	See above note
Wahlgren *et al* 1990[256]	Cyclosporin 5mg/kg/day Versus placebo	10 patients with stable, moderate or severe AD aged 22-42 years	Crossover RCT of 10 days duration	Patient-assessed itch, physician-assessed severity at 20 areas. Various lab tests	CyA significantly reduced the itch intensity, the eczema score and the consumption of topical hydrocortisone	Method of randomisation and concealment of allocation not described. Study described as double-blind. No withdrawals or dropouts	Very small study (n=10) of short duration

3.10.3 Levamisole

One RCT was located that assessed levamisole in the treatment of AD. This drug enhances the immune system where it stimulates white blood cells, in addition to showing antiparasitic properties in veterinary medicine where it is used for helminthic parasites in animals. The theory behind its use in AD is that it may increase cell-mediated immune response, which is thought to be decreased in this skin disease and have an effect on secondary infection, which is frequent in AD.

Study 1

- White & Hanifin 1978[257]
- Levamisole hydrochloride versus placebo, amount according to body weight
- 36 patients with AD, aged 4-64 years
- study period 6 months
- outcome measures:
    - patient's objective improvement
    - frequency of infections
    - physician prediction of active treatment
    - composite clinical scores
    - immunological markers such as IgE changes

Results

- 6 out of 11 patients in the active group noticed improvement compared to 6 out of 15 in the placebo group
- mean percentage improvement in an undefined composite sign score was 44% versus 16% in active and placebo groups respectively

Adverse effects

- one patient developed urticaria and another developed nausea and vomiting while taking levamisole

Notes

- good quality study with clear description of blinding
- no intention-to-treat analysis carried out

3.10.4 Platelet-activating factor (PAF) antagonist

PAF has been used experimentally to induce itch and contact urticaria as it is a potent inflammatory reaction mediator. The theory behind using PAF antagonist in AD is to have the opposite effect to PAF, thereby reducing or stopping the itch and inflammation[258]. One RCT was located that assessed PAF antagonist in the treatment of AD:

Study 1

- Abeck *et al* 1997[258]
- PAF antagonist topical solution versus vehicle placebo
- 44 patients with AD
- study period 28 days
- outcome measures:
  - improvement of lesions treated
  - itching

Results

- for active treatment 57% 'responded' (undefined) compared to 61% for placebo group
- based on 36 evaluable patients, 18 of active group and 17 of placebo group showed marked improvement or total clearing on lesion site
- there was a lack of difference between the active and placebo groups for itch improvement, which was statistically significant on day 14 but not at end of study on day 28

Adverse effects

- skin dryness and skin burning sensation immediately after application of active treatment in 14 out of 15 patients

- contact dermatitis developed in one person and severe erythema in another

Notes

- randomisation and concealment of allocation were poorly described
- intention-to-treat analysis carried out

3.10.5 Interferon-gamma

Most, but not all, people with AD have increased IgE in their blood (see Chapter 1, section 1.2.2.2), which is one of the immunological abnormalities expressed in this skin disease. Recombinant interferon-gamma has an inhibiting effect on IgE synthesis by human peripheral blood lymphocytes *in vitro*[39]. Based on this, interferon-gamma has been assessed as a potential treatment for AD in humans by two RCTs:

Study 1

- Hanifin *et al* 1993[259]
- Subcutaneous injections of recombinant interferon-gamma 50μg/m^2 once daily versus placebo injections
- 83 patients with severe atopic eczema
- age range 2-65 years
- study period 12 weeks
- outcome measures:
    - physician-assessed global improvement
    - patient/parent-assessed global improvement
    - redness
    - scratch marks
    - induration
    - itching
    - dryness
    - lichenification

Results

- greater than 50% physician-assessed global improvement was seen in 45% of patients receiving active treatment compared to 21% receiving placebo (p=0.016)
- greater than 50% patient/parent-assessed global improvement was seen in 53% of patients receiving active treatment compared to 21% receiving placebo (p=0.002)
- there was a statistically significant 30% reduction in redness and scratch marks for the active treatment group and a non-statistically significant 30% reduction in induration, itching, dryness and lichenification

Adverse effects

- 60% experienced headache in the active treatment group, 32% muscle aches and 39% chills compared to 28%, 12% and 5% respectively for those receiving placebo (an analgesic was taken to try and prevent the above side effects)
- white blood cell count fell in 5 patients, however, this normalised as treatment continued and 7 patients had mild elevated liver transaminase levels, all these patients were receiving active treatment

Notes

- the patients randomised to active treatment were significantly older than those allocated to placebo
- concealment of allocation was not clear but there was a clear description of the generation of randomisation sequence and intention-to-treat analysis was carried out
- the therapeutic and adverse effects of interferon-gamma could have compromised blinding

Study 2

- Jang *et al* 2000[260]
- high dose (1.5 million units/m^2) interferon gamma versus low dose (0.5 million units/m^2) interferon gamma versus placebo administered via subcutaneous injections three times per week

- 51 patients with severe AD
- age range 18-42 years
- study period 12 weeks
- outcome measures:
    - clinical improvement (composite score of signs and surface area)

Results

- clinical improvement was 'markedly' better in the two active treatment groups compared to placebo ($p<0.05$) but there was not a marked difference between the two active treatments

Adverse effects

- three patients taking active treatment dropped out due to AD flare-ups (n=2) and abnormal liver function tests (n=1)
- 54% in active treatment group experienced flu-like symptoms of fever and muscle-aches even though analgesics were taken to counteract this

Notes

- method of randomisation and concealment of allocation were not described, there was no mention of blinding and no intention-to-treat analysis was carried out
- adverse effects for placebo group not given

3.10.6 Thymic extracts and their synthetic derivatives

Thymomodulin, Thymostimulin and Thymopentin

Impaired T lymphocyte cell function and sustained serum IgE levels have been described consistently in atopic eczema. This, along with observation that patients with primary T cell immunodeficiency such as Wiskott-Aldrich syndrome have elevated IgE and lesions identical to atopic eczema, has prompted researchers to explore the therapeutic value of agents that promote the differentiation and function of mature lymphocytes. Initial work on calf thymic extracts given as an elixir or injection (thymomodulin and thymostimulin) was superseded by synthetic pentapeptides (thymopentin) given

by injection. Thymomodulin is calf thymus acid lysate given orally in syrup form. Thymostimulin is a mixture of heat-stable polypeptides extracted from calf thymus and given by injection. Thymopentin is a synthetic pentapeptide corresponding to some of the amino acid sequences of human thymopoetin, the hormone responsible for promoting differentiation and function of mature lymphocytes[39]. The adverse effects and notes are reported together in this section.

Thymomodulin

Two RCTs were located that assessed tyhmomodulin in the treatment of AD:

Study 1

- Fiocchi *et al* 1987[261]
- thymomodulin syrup 3mg/kg/day versus placebo
- 12 children with AD
- length of study: 6 months
- outcome measures:
    - 'clinical signs' including extent of disease

Results

- improvement was seen in several of the clinical signs for active treatment

Study 2

- Cavagni *et al* 1989[262]
- thymomodulin syrup 120mg/day versus placebo
- 19 children with AD and food allergy - all of which followed a restriction diet
- study period 90 days
- outcome measures:
    - 'clinical signs'

Results

- significant improvement was seen in one of the clinical signs - excoriation
- re-challenge with restricted foods was better tolerated by the active treatment group

Thymostimulin

Two studies were located that assessed thymostimulin in the treatment of AD:

Study 1

- Staughton *et al* 1983[263](abstract only)
- thymostimulin 1.5mg/kg twice weekly versus placebo
- adults with AD (numbers not given)
- 10 weeks duration
- outcomes: reduction in disease severity

Results

- non-statistically significant reduction in disease severity (values not given)

Study 2

- Harper *et al* 1991[264]
- Thymostimulin 1.5mg/kg twice weekly versus placebo
- 29 young adults with AD
- 10 weeks duration
- outcome measures:
    - composite severity scale
    - patients-assessed itch
    - sleep loss

Results

- active treatment groups severity reduced by 20% from baseline score compared to 1% for placebo group (p=0.008)

- no statistically significant differences were seen for patient-assessed itch and sleep loss

Thymopentin

Four RCTs assessing thymopentin in the treatment of AD were located:

Study 1

- Kang *et al* 1983[265]
- thymopentin 50mg injections three times weekly versus placebo injections
- 18 patients with AD, mean age 33 years
- 6 weeks study
- outcome measures:
  - 'compound' score (max. score 18)

Results

- mean score improvement was 2.38 compared to 0.82 for active and placebo respectively ($p<0.05$)
- 'good' improvement was reported in 5 out of the 8 patients that took active treatment compared to 2 out of the 10 that received placebo

Study 2

- Leung *et al* 1990[266]
- Thymopentin 50mg injections versus placebo
- 100 young adults with moderate-to-severe AD
- 6 weeks study
- outcome measures included itch and global severity

Results

- 66% of patients experienced improvement of itch in the active treatment group compared to 40% of patients in the placebo group ($p=0.02$)
- global severity showed a statistically significant improvement for the active treatment group

Study 3

- Stiller *et al* 1994[267]
- thymopentin 50mg injections three times weekly versus placebo
- 39 adults with severe AD
- 12 weeks study
- outcome measures: total severity score (max. score 3) and patient-assessed improvement

Results

- total severity score improved in the active group from a baseline of 2.19 to 1.68 at the end of the study period compared to placebo which was 2.18 at baseline and 2.02 at end of study (statistically significant)
- patient-assessed improvement was 3.11 at baseline which reduced to 2.78 at end of study compared to 3.00 and 2.92 for placebo

Study 4

- Hsieh *et al* 1992[268]
- All patients received thymopentin 50mg injections three times weekly for 6 weeks then were randomised to either thymopentin or saline injections to assess the efficacy of thymopentin by withdrawal
- 16 children with AD
- 6 weeks study
- outcome measures: withdrawal as 'surrogate' evidence of efficacy via severity score (max. 15, where 15=most severe)

Results

- total severity score 6.0 after first 6 weeks and 12.8 after second 6 weeks for placebo group compared to a fall from 5.8 at end of first 6 weeks to 4.0 at end of second 6 weeks for active treatment group ($p<0.001$; estimated from graph)

Adverse effects

- no information reported in Fiocchi, Cavagni, Staughton, Kang or Hsieh studies
- Harper trial reported one withdrawal due to development of alopecia areata
- Dropouts in the Harper trial were very high towards the end of the study
- Local swelling at site of injection was reported in the Leung study
- Nearly all patients in the Stiller study experienced adverse effects in both placebo and active treatment groups which were unspecified

Notes

- Reporting was generally poor with none bar Leung *et al* describing randomisation procedure, allocation concealment, success of blinding and none at all carrying out an intention-to-treat analysis
- This form of treatment was discontinued about 10 years ago for reasons that are unclear but could be due to the fact that injections are probably not an acceptable treatment for AD particularly considering the majority of those with the disease are children

3.10.7 Immunoglobulin

Initially used to treat nasal and eye allergies, immunoglobulin was assessed in the treatment of AD via one small RCT, published in French and translated by someone other than the author of this thesis but following a protocol developed by the author:

Study 1

- Pons-Guiraud 1986[269]
- Immunoglobulin intramuscular injections versus albumin injections, administered as a course of 10 injections over 3 months
- 47 patients aged between 2 and 37 years
- outcome measures: eczema extent, and signs of AD including erythema, oedema, itching and lichenification

Results

- 72.8% of the 22 patients receiving active treatment experienced an improvement in their eczema compared to 36% of the 25 in the albumin group
- itching, lichenification and lesions were all statistically significantly improved

Adverse effects

- none mentioned

Notes

- randomisation, allocation concealment and blinding poorly described. It was unclear if an intention-to-treat analysis was carried out

3.10.8 Transfer factor

Transfer factor is an extract from white blood cells and is thought to play a role in cellular immunity. Cellular immunity may be impaired in AD[39], therefore, transfer factor has been assessed in AD via one RCT which was translated from Spanish by someone other than the author of this thesis, but following a protocol developed by the author:

Study 1

- valdes Sanchez *et al* 1991[270]
- transfer factor intramuscular injections versus placebo injections
- 24 adult patients with AD
- 8 weeks study
- outcome measures: immunoglobulin levels and T-lymphocytes in the blood plus physician-assessed global severity

Results

- 50% of patients in the active treatment group experienced 'major' improvements compared to 33% in the placebo group, not statistically significant: 95% CI around the 17% difference between the 2 treatments ranged from -22% (i.e. a 22% difference in favour of placebo), to a +55% in favour of transfer factor

Adverse effects

- none reported

Notes

- method of randomisation was clearly described, and reported as double-blind. Method used to conceal allocation was not given

3.11 TOPICAL CORTICOSTEROIDS AND ORAL STEROIDS

As discussed in chapter 1, section 1.5, topical corticosteroids are part of the mainstay of treatment for AD and have been for the past 50 years due to their ability to reduce inflammation, redness and itching in the majority of people with the condition[36]. Topical steroids, as they are commonly shortened to, are available in different potencies, which range from mild to very potent with the least potent that will control a patient's eczema prescribed in the first instance. The potency prescribed may or may not increase depending on several factors such as location of eczema, severity of eczema and age of patient, indeed, different potencies may be prescribed for different areas of the body[15]. Topical steroids are not usually prescribed as a continuous treatment but more as a method of getting the eczema under control along side emollients with regular breaks in use when emollients only are used[15].

The most important activity of topical steroids is their anti-inflammatory effect, which is achieved through vasoconstriction, decreased capillary permeability, and inhibition of leukocyte proliferation and migration[271]. A major side-effect of prolonged use of topical steroids is their anti-proliferative activity, which can cause skin atrophy or 'skin thinning'. The aim therefore is to achieve maximum activity and minimal side effects, which is often why the least potent steroid is prescribed first and only increased in potency if control is not achieved[36]. A total of 149 trials of topical steroids in the treatment of AD were located. However, 65 had to be excluded from this study as they did not meet the inclusion criteria, the main reason being that they did not give a clear description of the eczema being studied or atopic eczema was mixed with other dermatoses and not separated in the results. The excluded trials are in appendix 1. A total of 85 trials on the use of topical steroids in the treatment of AD were finally included and are assessed in tables 16-23. Table 24 summarises the trials that assessed oral steroids in the treatment of AD.

Table 16 Topical corticosteroid versus placebo in the treatment of AD

Author and date of study	Interventions and comparator	Population and sample size	Design, description and duration	Outcome measures	Main reported results	Quality of reporting	Notes
Brock & Cullen 1967[272]	0.5% triamcinolone acetonide once daily in flexible collodion versus 'flexible collodion' placebo once daily	40 patients in total, 2 AD patients	Prospective, randomised, double blind parallel study	Lesion improvement	Out of 2 AD patients 1 found active site better and 1 found neither site better	Method and concealment of randomisation unclear, study described as double blind, no withdrawals or dropouts	Scant details. Patient preference study gives little indication of magnitude of effect
Gehring & Gloor 1996[273] German study translated	Twice daily water-in-oil emulsion for 2 weeks versus water-in-oil emulsion plus1% hydrocortisone for 1 week followed by the emulsion only in the second week	69 patients with atopic dermatitis	Prospective, randomised, double-blind parallel-group study for 2 weeks	Doctor assessed erythema, patient assessed roughness and itching. Other biological measures	Both groups improved substantially for all parameters. Trend toward greater improvement in hydrocortisone groups but not statistically significant	69 patients enrolled, 12 did not meet all study criteria yet 63 were used in final assessment	The study demonstrates the large vehicle/placebo response in atopic eczema trials
Vanderploeg 1976[274]	0.05% betamethasone dipropionate ointment twice daily versus vehicle placebo	36 patients with moderate to severe atopic dermatitis	Prospective, randomized, double blind study of 3 weeks duration	Amount of scale, erythema, pruritis, thickness of lesions and crusting on a 0-4 scale (0=none, 4=very severe) Global evaluation (<25%= worse to 100%= excellent)	Improvement over baseline for mean total symptom score was 11.4 for dipropionate and 11.2 for placebo decreasing to 1.6 for dipropionate and 8.4 for placebo at week 3 ($p<0.0001$)	Method and concealment of randomisation unclear, study described as double blind 'code', 3 dropouts, no intention-to-treat analysis (ITT)	Large treatment effect

Roth & Brown 1978 [275]	Hydrocortisone valerate cream 0.2% versus placebo three times daily	20 atopic eczema patients	Prospective, randomised, left, right, parallel study of 4 weeks duration	Pruritis, erythema, scaling, excoriation, lichenification, Overall condition and severity of disease	No actual data given for hydrocortisone valerate versus placebo. "75% of the patients showed excellent improvement or were better with the hydrocortisone valerate cream compared to 20% with the placebo. Overall ratings at the end of the therapy showed hydrocortisone valerate to be significantly more effective than the placebo ($p<0.001$)"	Method and concealment of randomisation unclear, study described as double blind. Withdrawals and dropouts not mentioned	Difficult to estimate magnitude of benefit without actual data
Sudilovsky *et al* 1981 [276]	0.1% halcinonide cream once daily plus cream base placebo twice daily versus cream base placebo three times daily	58 atopic eczema patients	Prospective, randomised, right, left, parallel study of 3 weeks duration	Comparative and absolute therapeutic responses: erythema, oedema, and changes in size of thickness of lesions. Physician global response	Of 54 evaluable patients at week 3, 4 (24%) were markedly improved for halcinonide comparative clinical response versus 1 (2%) for placebo patients ($p<0.001$)	Method and concealment of randomisation unclear, study described as double blind, 4 dropouts/ Withdrawals, no ITT	Patients with a previous history of poor response to topical corticosteroids were excluded
Lupton *et al*	Halcinonide	233 patients with	Prospective,	Therapeutic	In Halcinonide	Method and	Big treatment

1982[277]	ointment 0.1% versus three times daily versus ointment base placebo three times daily	mild, moderate and severe atopic dermatitis	randomized, double blind paired comparison study of 2 weeks duration	response of lesions on each side evaluated as excellent, good, fair or poor. Lesion resolution evaluated for lesion size, erythema, oedema, transudation and lichenification. Therapeutic response 4-point scale (4=excellent, 1=poor)	group 64% excellent, 21% good, 10% fair and 5% poor response. In placebo group 23% excellent, 21% good, 36% fair and 20% poor response	concealment of randomisation unclear, study described as double blind. 19 lost to follow up, no ITT	effect. Short duration of only 4 weeks does not take into account relapse and remit nature of AD
Sefton *et al* 1984[278]	Hydrocortisone valerate 0.2% ointment twice daily versus vehicle placebo	64 patients with mild to moderate atopic dermatitis	Prospective, randomised, double blind left right parallel study of 2 weeks duration	Pruritis, erythema, scaling, papulation, lichenification and vesiculation. Global evaluation using an analogue scale 0-100 (100 most severe)	Mean global evaluation severity scores on 0-100 analogue scale: hydrocortisone valerate baseline score of 34.6 decreasing to 10.3 and placebo baseline score of 34.1 decreasing to 28.9 after 14 days treatment ($p<0.01$)	Method and concealment of randomisation unclear, study described as double blind (identical coded tubes) 3 dropouts, no ITT	Six trials described in this paper (3 RCTs) only one of which had not been published elsewhere
Wahlgren *et al* 1988[279]	Betamethasone dipropionate 0.05% cream	30 adult patients with persistent atopic dermatitis	Prospective, randomised, double blind	Intensity of pruritis using Pain-Track.	"No pruritis" on days 3-4 was 35.8% during	Method and concealment of randomisation	Very short duration (4 days) using a novel

	twice daily versus base cream placebo twice daily	and chronic pruritis	crossover study of 4 days duration	Distribution and activity of eczema determined, excoriations counted	betamethasone and 21.5% during placebo therapy (p=0.0062)	unclear, study described as double blind, 4 dropouts, no ITT	approach to measure itch
Stalder *et al* 1994[280]	Desonide once daily versus excipient once daily	40 children with atopic dermatitis	Prospective, randomised, double blind parallel study of 7 days duration	Global physician score based on extent and severity of lesion. Local lesion score based on target area. Various bacteriological assessments	66.7% desonide group showed improvement or resolution compared with 15.8% in the placebo group (p<0.001). *S. aureus* density decreased by log 2.2 compared with log 0.6 in the placebo group (p<0.05)	Method and concealment of randomisation unclear, study described as double blind. No mention of withdrawals and dropouts	Paper suggests that use of topical steroids alone have a big impact on bacterial colonisation
Lebwohl 1996[281] Study 1	Fluticasone propionate ointment 0.005% versus placebo 'vehicle'	203 patients with atopic eczema	Prospective, randomized, parallel study of 29 days duration	Patient's self-assessment of treatment efficacy. Physician's gross assessment, severity scores of 5 signs and 1 symptom	Patient's self-assessment at day 29, 81% (n=74) found fluticasone excellent or good versus 37% (n=28) found vehicle excellent or good. Drug related adverse events were rare	Method and concealment of randomisation unclear, study described as double blind. Large number of withdrawals and dropouts n=101. No intention-to-treat analysis performed	Unclear why 2 identical large multi-centre trials conducted and repeated concurrently
Lebwohl 1996[281] Study 2	Fluticasone propionate ointment 0.005% versus placebo	169 patients with atopic eczema	Prospective, randomized, parallel study of 29 days duration	Patients self-assessment of treatment	Patient's self-assessment at day 29, 84% (n=63) found fluticasone	Method and concealment of randomisation unclear, study	Unclear why 2 identical large multicentre trials conducted and

	'vehicle'			efficacy. Physician's gross assessment, severity scores of 5 signs and 1 symptom	excellent or good versus 48% (n=26) found vehicle excellent or good. Drug related adverse events were rare	described as double blind. Large number of withdrawals and dropouts n=80. No intention-to-treat analysis	repeated concurrently
Sears *et al* 1997[282]	Hydrocortisone butyrate 0.1% cream versus cream base placebo once daily	194 patients with atopic dermatitis	Prospective, randomised, double blind parallel study of 14 days duration	Seven disease signs (infiltration, scaling, erythema, lichenification, vesicles, papules, and excoriation) were evaluated on a four-point scale: 0=absent, 3=severe) Pruritis evaluated separately on same 4-point scale. Overall improvement on a 7-point scale (1=cleared, 7=worse) and global treatment efficacy on a 4-point scale (1=good and 4=poor)	Seven sign lesion scores improvement over baseline of 9.4 for hydrocortisone butyrate reduced to 2.67 at day 14, and placebo baseline of 9.95 reduced to 6.69 at day 14.	Method and concealment of randomisation unclear, study described as double blind. 26 dropouts, no ITT	Large study with big treatment effects
Maloney *et al* 1998[283]	Clobetasol propionate 0.05% cream twice daily versus vehicle	81 patients with moderate to severe atopic dermatitis	Randomised, double blind parallel study of 43 days duration	Physician gross assessment based on % improvement of	Gross assessment at day 43 showed 78% of clobetasol treated patients	Method and concealment of randomisation unclear, study	Baseline scores not given

	placebo twice daily			target lesion plus changes from baseline in mean severity scores for erythema, pruritis, induration/papulation, lichenification, erosion/oozing/crusting, and scaling/dryness and for total signs and symptoms	were good, excellent or cleared compared to 33% of placebo treated patients	described as double blind. 20 dropouts, no ITT	

Table 17 Topical steroid versus another topical steroid in the treatment of AD

Study	Interventions and comparator	Study population and sample size	Design, description and duration	Outcome measures	Main reported results	Quality of reporting	Notes
Binder & McCleary 1972 [284]	Fluocinonide cream 0.05% four times daily versus betamethasone valerate cream 0.10% four times daily	10 atopic eczema patients	Prospective, randomised, left right parallel study of 2 weeks duration	Lesion improvement	Fluocinolone was superior to betamethasone in 70% of patients	Table of randomised numbers used. Study described as double blind No withdrawals or dropouts	Difficult to interpret magnitude of effect
Almeyda & Fry 1973[285]	10% urea and 1% hydrocortisone versus cream 0.1% betamethasone 17-valerate cream	50 atopic eczema patients	Prospective, randomised, left, right, parallel study of 3 weeks duration	Lesion response: excellent, good, none, deterioration	Mean response of good or excellent outcome 76% urea hydrocortisone and 78% betamethasone 17-valerate	Method and concealment of randomisation unclear. Study described as double blind. No withdrawals or dropouts	Study which claimed equivalence of a very mild corticosteroid preparation against a potent one. Study grossly under-powered to establish equivalence
Leibsohn & Bagatell 1974[286]	Halcinonide cream 0.1% three times daily versus betamethasone 17-valerate cream 0.1% three times daily	9 patients with atopic dermatitis	Prospective, randomised. Left right parallel study of 3 weeks duration	Decrease of lesion size, reduction in erythema, oedema, transudation, lichenification and scaling, relief of pruritis and pain	An excellent or good response was recorded in 63% halcinonide patients and 38% betamethasone patients for overall evaluation of therapeutic response	"Randomized according to patient's study number" Study described as double blind. 1 lost to follow-up, no ITT	Study of 88 patients with mixed dermatoses, some responding differently to the treatment
Almeyda & Burt 1974[287]	Hydrocortisone 1% UHc powder-	36 adults and children with	Prospective, randomised, left,	Clinical condition assessed as	97% 'excellent' or 'good'	Method and concealment of	Another study which assumes

	cream versus 0.1% betamethasone 17-valerate	mild, moderate and severe atopic eczema	right, parallel study of 4 weeks duration	excellent if completely cleared and good if partially cleared, no improvement and deterioration	improvement for hydrocortisone 1% and 94% 'excellent' or 'good' improvement for betamethasone	randomisation unclear. Study described as double blind. No withdrawals or dropouts	that no evidence of a statistical difference is the same as therapeutic equivalence
Lundell & Koch 1974[288] German translated study	0.1% fluprednylidenace ate versus 0.25% fluocortolone	42 patients with severe atopic dermatitis	Prospective, randomised, left, right, parallel study of 4 weeks duration	Erythema, scaling, weeping, itching (composite score "therapeutic index")	Good effect for both preparations; fluprednylidenace tate significantly better than fluocortolone after 2nd week; "therapeutic index" 0.96 versus 0.86 after 4 weeks	Method and concealment of randomisation unclear, study described as double blind. 3 withdrawals/ dropouts, no ITT	Difficult to interpret treatment effect without placebo control
Bjornberg & Hellgren 1975[289] Swedish translated study	0.25% Desoximetasone cream twice daily versus 0.1% Betamethasone valerate cream twice daily	22 patients with atopic dermatitis and 24 patients with psoriasis	Prospective, randomised, double-blind controlled side-to-side comparison for 1-2 weeks	0-5 scale assessment of skin morphology. Scoring of superior treatment (a>b, or b>a or a=b)	For atopic dermatitis patients: Desoximetasone treated side was rated superior 11 times; Betamethasone treated side rated superior 8 times; no difference 3 times	Randomisation unclear	Very short duration
Bleeker 1975[290]	Halcinonide 0.1% cream Twice daily Versus clobetasol	27 moderate to severe atopic eczema patients	Prospective, randomized, left, right, parallel study of 2 weeks duration	Lesions assessed for decrease in erythema, oedema, transudation,	92% 'excellent' or 'good' overall clinical response for both halcinonide and	"Table of random assignment". Study described as double blind. No dropouts or	No placebo arm

	propionate 0.05% cream twice daily			lichenification, scaling, pruritis and pain	clobetasol	withdrawals	
Morley 1976[291]	0.05% clobetasone butyrate cream or ointment twice daily versus 0.0125% flurandrenolone cream or ointment twice daily	71 atopic eczema patients children only	Prospective, randomised, left, right, parallel study of 1 week duration	Clinician assessed lesions as healed, improved, static or worse plus clinician/patient preference for right/left side	No data on clinician-rated healing of lesions given. Patient preference data only reported which indicated a non-statistically significant preference in favour of clobetasone butyrate	Method and concealment of randomisation unclear, implies double blinding (neither clinician nor patient aware of identification), no withdrawals or dropouts	No data to indicate magnitude of treatment effect
Savin 1976[292]	Betamethasone dipropionate ointment 0.05% versus hydrocortisone ointment 1% twice daily	27 patients with atopic dermatitis 26 moderate, 1 very severe	Prospective, randomized, parallel study of 3 weeks duration	Clinical effectiveness: excellent(>75%) good (50-75%), fair (25-50%), poor (<25%)	50% betamethasone 'excellent' or 'good' response compared to 22% hydrocortisone	Method and concealment of randomisation unclear, study described as double blind. 5 dropouts, no ITT	Clear categorical data and separation of atopic eczema and psoriasis
Yasuda 1976[293]	Hydrocortisone 17-butyrate 0.1% Locoid ointment versus triamcinolone acetonide 0.1% ointment or hydrocortisone acetate 1% ointment	144 atopic dermatitis patients	Prospective, randomised, left, right, parallel study of 7 days duration	Decrease in erythema, scaling, oedema, subjective symptoms such as pruritis and burning sensation and improvement of lesions	Hydrocortisone 17-B superior to triamcinolone 10%, comparable 16%, inferior 3%. Hydrocortisone 17-B superior to hydrocortisone acetate 16%, comparable 9%	"table of numbers assured randomisation". Study described as double blind. 7 dropouts, 32 "not yet evaluated" hence no ITT	Well reported with useful data on placebo and psoriasis groups

					and inferior 3%		
Mali 1976[294]	Betamethasone dipropionate cream versus locacorten 0.02% twice daily	16 atopic dermatitis patients from a total of 66 "steroid responsive dermatoses"	Prospective, randomized, parallel study of 3 weeks duration	Much better, slightly better, no change, slightly worse, much worse	19% betamethasone group 'much better' compared to 4% Locacorten group ($p>0.10$)	Method and concealment of randomisation unclear, study described as double blind, 16 withdrawals, unclear from which group	Useful to have data separated by diseases but only 16 AE patients
Bluefarb *et al* 1976[295]	Diflorasone diacetate 0.05% cream versus flucinonide 0.05% cream twice daily	210 atopic/neurodermatitis patients	Prospective, randomised, parallel study of 3 weeks duration	Degree of therapeutic response 1-25%, 26-50%, 51-75%, 76-100% clinical resolution, no change in severity or deterioration of lesions	Improvement over baseline >50% improvement: 71% for both diflorasone and fluocinonide	Method and concealment of randomisation unclear, study described as double blind. 9+ withdrawals, no ITT	Some reservation on whether atopic/ neurodermatitis is the same as atopic eczema
Roth & Brown 1978[275] Study 1	Hydrocortisone valerate cream 0.2% versus betamethasone valerate cream 0.1% three times daily	19 atopic eczema patients	Prospective, randomised, left, right parallel study of 4 weeks duration	Symptoms pruritis, erythema, scaling, excoriation, lichenification Overall condition and severity	74% showed clear or excellent improvement for both hydrocortisone valerate and betamethasone valerate	Method and concealment of randomisation unclear, study described as double blind. Withdrawals and dropouts not mentioned	Under-powered study
Roth & Brown 1978[275] Study 2	Hydrocortisone valerate cream 0.2% versus hydrocortisone cream 1% three times daily	29 atopic eczema patients	Prospective, randomised, left, right parallel study of 4 weeks duration	Symptoms pruritis, erythema, scaling, excoriation, lichenification Overall condition	No actual data given for this study. "Overall judgement of the response to the two medications	Method and concealment of randomisation unclear, study described as double blind.	Difficult to evaluate without any data

				and severity	(defined as cleared, excellent, good, no effect, or worse) showed hydrocortisone valerate to be statistically superior to hydrocortisone ($p<0.05$)	Withdrawals and dropouts not mentioned	
el-Hefnawi *et al* 1978[296]	Halcinonide-neomycin-amphotericin ointment 0.1% versus hydrocortisone 1% ointment	5 atopic dermatitis patients	Prospective, randomised, left, right parallel study of 3 weeks duration	Subjective and objective evaluations of responses. Global evaluation	100% improved or cleared for both halcinonide and hydrocortisone (cleared: 80% and 60% respectively)	"Pre-designed randomization chart". Study described as double blind. Withdrawals and dropouts not mentioned	Very few atopic eczema patients mixed up with other inflammatory skin diseases
Fisher & Kelly 1979[297]	Fluocinonide 0.05% emollient cream three times daily versus betamethasone valerate 0.1% cream three times daily	107 atopic eczema patients	Prospective, randomised, left, right parallel study of 3 weeks duration	Clinical response relative to status of lesion	Mean clinical response 4.5 for fluocinonide and 4.38 for betamethasone on a scale of 1-5 where 5=excellent or clear	"Randomization correlated with sequential numbers". Study described as double blind, 11 withdrawals/drop outs, no ITT	Suspect randomisation method
Ramelet & Mauracher 1982[298]	Betamethasone dipropionate 0.05% versus diflucortolone valerate 0.3% twice daily	12 adults with resistant atopic dermatitis	Prospective, randomised, parallel study of 14 days duration	Physician assessed erythema, induration, scaling, crusting, pruritis, excoriation, and pain. Physician global assessment	For overall therapeutic efficacy 83% had cleared or marked improvement in both betamethasone and diflucortolone groups	Method and concealment of randomisation unclear, study described as double blind, no dropouts or withdrawals	Very small number of patients over very short period of time

				of therapeutic response % improved			
Sefton & Kyriakopoulos 1983[299] Study 1	Hydrocortisone valerate ointment 0.2% versus betamethasone valerate 0.1% ointment three times daily	68 mild to moderate atopic eczema patients	Prospective, randomised, left, right parallel study of 4 weeks duration	Investigator assessed pruritis, erythema, scaling, papulation, lichenification, vesiculation on an analogue scale of 1-100 (100 being most severe)	Improvement over baseline for hydrocortisone 44.1 reduced to 12.6 betamethasone 43.4 reduced to 10.7	"allocation ... by a restricted randomization process... in coded identical tubes" 14 initially lost to follow up, plus 3 from this part of study, no ITT carried out	Magnitude of efficacy of 0.2% hydrocortisone valerate similar to that of a potent preparation
Sefton & Kyriakopoulos 1983[299] Study 2	Hydrocortisone valerate ointment 0.2% versus triamcinolone acetonide 0.1% ointment three times daily	37 mild to moderate atopic eczema patients	Prospective, randomised, left, right parallel study of 4 weeks duration	Investigator assessed pruritis, erythema, scaling, papulation, lichenification, vesiculation on an analogue scale of 1-100 (100 being most severe)	Improvement over baseline for hydrocortisone 46.4 reduced to 15.6 triamcinolone 47.9 reduced to 14.5	"allocation ... by a restricted randomization process... in coded identical tubes" 14 initially lost to follow up, plus 1 from this part of study, no ITT carried out	3 studies described in same paper
Sefton & Kyriakopoulos 1983[299] Study 3	Hydrocortisone valerate ointment 0.2% versus flucinolone 0.025% ointment t.i.d.	26 mild to moderate atopic eczema patients	Prospective, randomised, left, right parallel study of weeks duration	Investigator assessed pruritis, erythema, scaling, papulation, lichenification, vesiculation on an analogue scale of 1-100 (100 being most severe)	Improvement over baseline for hydrocortisone 27.1 reduced to 4.7 fluocinolone 26.9 reduced to 4.6	"allocation ... by a restricted randomization process... in coded identical tubes" 14 initially lost to follow up, plus 1 from this part of study, no ITT carried out	3 studies described in same paper
Lassus 1983[300]	Alclometasone dipropionate	40 children with atopic eczema	Prospective, randomised,	Erythema, induration,	76-100% improvement or	Method and concealment of	Useful to have outcome data

	cream 0.05% twice daily versus hydrocortisone butyrate cream 0.1% twice daily		parallel study of 2 weeks duration	pruritis. Physician global evaluation of improvement	"marked-cleared" was seen in 40% of alclometasone patients and 35% of hydrocortisone patients	randomisation unclear, study described as double blind. No withdrawals or dropouts	presented as categories
Bagatell *et al* 1983[301]	Alclometasone dipropionate cream 0.05% versus hydrocortisone cream 1.0% three times daily	249 atopic eczema patients	Prospective, randomised parallel study of 3 weeks duration	Erythema, induration, pruritis. Investigator global evaluation.	71% alclometasone patients showed cleared or marked improvement compared to 69% for hydrocortisone patients	Method and concealment of randomisation unclear, study described as double blind. 20 withdrawals/ Dropouts, no ITT carried out	Although written up as a study supporting superiority of the newer alclometasone, there is not much difference when % markedly improved or clear is evaluated
Van DelRey *et al* 1983[302] Spanish translation	Alclometasone cream 0.05% versus hydrocortisone butyrate	30 patients over 12 years old, more than one year disease duration and resistant to treatment	Parallel double-blind prospective randomized trial lasting 3 weeks	Doctor assessed erythema,, hardening of the skin and scaling. After treatment improvement evaluated on a scale 1-6 where 1= 100% improvement	Both treatments gave similar results of efficacy. Total sign score fell from 7.20 to 1.00 in the alclometasone group and from 7.14 to 0.93 in the hydrocortisone group.	Described as double blind and randomized but method not clear One patient excluded from hydrocortisone group as he had seborrhoeic dermatitis.	Difficult to establish equivalence in such a small study.
Harder & Rufli 1983[303] Swiss translated paper	Diflorasonediacetate 0.05% ointment once daily versus Betamethasone 17 valerate 0.1%	98 patients with "eczema" (probably atopic eczema but this is not specified in the paper)	Prospective, randomised, single-blind parallel-group study for 3 weeks	Improvement as assessed by: erythema, oedema, lichenification, induration, scaling,	(Only summary data reported) Both groups achieved good results. No significant difference	26 drop-outs (detailed description given), no intention -to-treat analysis	One of the first studies to evaluate once daily application versus more frequent application of a standard treatment

	ointment twice daily			excoriation, itching, exulceration; each assessed with 4 point scale	between groups		
Konzelmann & Harms 1983[304] Swiss translated paper	Diflorasone diacetate 0.05% cream once daily versus betamethasone dipropionate 0.1% cream	120 patients with "acute or sub acute eczema"	Prospective, randomised, open parallel-group study for 3 weeks	Improvement assessed by doctor on 5-point scale 0-100% improvement	85% of all patients showed grade 4 improvement (75-100%), no significant difference between groups	18 drop-outs which were not assessed	Similar to above study
Duke *et al* 1983[305]	Alclometasone dipropionate ointment 0.05% twice daily versus clobetasone butyrate ointment 0.05% twice daily	68 atopic eczema patients	Prospective, randomised parallel study of 3 weeks duration	Clinical score erythema, induration, pruritis, and physician global assessment	75% improvement in alclometasone group compared to 68% improvement in clobetasone group for mean clinical score	Method and concealment of randomisation unclear, "blind evaluator technique" suggests single blind study. No ITT	A small equivalence study
Lassus 1984[306]	Alclometasone dipropionate cream 0.05% twice daily versus clobetasone butyrate cream 0.05% twice daily	43 atopic eczema patients	Prospective, randomised parallel study of 2 weeks duration	Erythema, induration, pruritis and physician global evaluation of improvement	85% improvement for alclometasone group compared to 86% improvement for clobetasone group for 3 signs	Method and concealment of randomisation unclear, study described as double blind. No withdrawals or dropouts	Little difference in treatment effect
Veien *et al* 1984[307]	Hydrocortisone 17-butyrate (Locoid) cream 0.1% versus hydrocortisone	40 atopic eczema patients	Prospective, randomised, left, right parallel study of 4 weeks duration	Global severity of all lesions	Complete clearance of skin symptoms was found in 60% hydrocortisone	Method and concealment of randomisation unclear, study described as	Treatment benefit of hydrocortisone butyrate increased as study progressed

	(Uniderm) 1% cream				17-butyrate treated patients compared to 30% hydrocortisone 1% treated patients	double blind. No withdrawals or dropouts	
Nolting 1985[308] German translation	Betamethasone dipropionate 0.05% versus desoximetasone 0.25% ointment	33 AE patients with resistant or severe disease in a trial which also included psoriasis patients	Prospective, randomised, parallel RCT of 2 weeks duration	Physician global rating	41% and 53% had clearance in the betamethasone versus desoximetasone groups respectively ($p>0.05$)	Method and concealment of randomisation unclear, study described as double blind. No ITT	Numbers of AD patients too small to make any specific comments
Rajka & Verjans 1986[309]	Hydrocortisone 17-butyrate (Locoid) 0.1% fatty cream versus desonide (Apolar) 0.1% ointment twice daily	30 moderate to severe atopic dermatitis patients	Prospective, randomised, left, right, parallel study of 4 weeks duration	Investigator assessed global severity and severity grades of erythema, induration and scaling	Mean global severity score over baseline of 2.8 reduced to 1.3 for hydrocortisone and 1.7 for desonide ($p<0.05$)	Method and concealment of randomization unclear, study described as double blind. No dropouts	Scaling scores not given on 9 out of 30 patients because they did not experience scaling throughout the trial
Majerus & Reiffers-Mettelock 1986[310]	Halometasone 0.05% cream or ointment versus betamethasone valerate 0.1% cream or ointment twice daily	75 atopic dermatitis patients	Prospective, randomised, parallel study of 3 weeks duration	Inflammation, crusting, scaling, lichenification, excoriation, induration, exudate, pruritis, pain (healing, improvement, failure)	Healing was reported in 70% of patients with halometasone cream, 60% with halometasone ointment compared to 90% on betamethasone cream, and 80% on betamethasone ointment	Method and concealment of randomization unclear, study described as double blind. 33 dropouts/ withdrawals, no ITT	RCT of mixed inflammatory dermatoses
Ulrich 1991[311]	0.05%	165 patients with	Prospective,	1. clinical	1. clinical	Randomisation	One of authors

German translation	Halomethasone cream twice daily versus 0.25% Prednicarbate cream twice daily (both topical corticosteroids)	active episode of atopic dermatitis suitable for exclusively topical treatment	randomised, double- blind parallel group study for two weeks	effectiveness (doctor assessed, 5 point scale) 2. onset of clinical effectiveness (doctor assessed) 3. side effects 4.cosmetic acceptability (patient assessed 5 point scale)	effectiveness: no significant difference between groups 2. onset: no difference at day 1 or 4 between groups 3. side effects: non e reported 4 cosmetic acceptability: 51% Vs 46% rated it "excellent", not sign difference	criteria unclear. Authors tried to create subgroup of "severely affected patients", probably retrospectively. They then claim significant advantage for Halomethasone in severely affected patients	was an employee of the company which produces Halomethasone cream
Haneke 1992[312] (Germany) Study 1	0.1% methylprednisolone aceponate ointment once daily versus 0.1% betamethasone valerate twice daily	94 adults with atopic dermatitis	Prospective, randomised, left, right, parallel study of 4 weeks duration	Patient and doctor global assessments. Doctor assessed 11 signs and symptoms	No actual data given for once daily methylprednisolone versus twice daily betamethasone	Method and concealment of randomisation unclear. Study described as double blind, no ITT	Results of all 3 studies impossible to disentangle
Haneke 1992[312](Germany) Study 2	0.1% methylprednisolone aceponate ointment twice daily versus 0.1% betamethasone valerate twice daily	94 adults with atopic dermatitis	Prospective, randomised, left, right, parallel study of 4 weeks duration	Patient and doctor global assessments. Doctor assessed 11 signs and symptoms	No actual data for twice daily methylprednisolone versus twice daily betamethasone given	Method and concealment of randomisation unclear. Study described as double blind, no ITT	Results of all 3 studies impossible to disentangle
Rampini 1992[313] Study 1	Methylprenisolone aceponate 0.1% cream twice daily	80 children with atopic dermatitis	Prospective, randomised, parallel study of 3	Objective and subjective symptoms of	97.3% Methylprenisolone patients	Method and concealment of randomization	Three studies of three different comparisons in

	versus prednicarbate 0.25% cream twice daily		weeks duration	erythema, exudation, scaling, hyperkeratosis, itching, burning. Global therapeutic response	achieved complete healing or distinct improvement compared to 100% prednicarbate patients	unclear, study described as double blind. 2 dropouts/ withdrawals, no ITT	different age groups
Rampini 1992 [313] Study 2	Methylprenisolone aceponate 0.1% once daily ointment versus prednicarbate 0.25% cream twice daily	120 children with atopic dermatitis	Prospective, randomised, parallel study of 3 weeks duration	Objective and subjective symptoms of erythema, exudation, scaling, hyperkeratosis, itching, burning. Global therapeutic response	96.3% Methylprenisolone patients achieved complete healing or distinct improvement compared to 98.1% prednicarbate patients	Method and concealment of randomization unclear, study described as double blind. 12 dropouts/ withdrawals, no ITT	Three studies of three different comparisons in different age groups
Ottevanger *et al* 1992[314]	Momethasone furoate once daily versus hydrocortisone 17-butyrate twice daily	96 atopic dermatitis patients	Prospective, randomised, parallel study of 6 weeks duration	No information given	85% momethasone patients significantly greater improvement versus 71% hydrocortisone group (p=0.0025)	Method and concealment of randomisation unclear, study described as investigator blind. Dropouts/ withdrawals no data given	Published in abstract form only
Gelmetti 1994[315] Italian translation	0.025% budesonide cream versus 0.1% alclometasone dipropionate twice daily	40 children with atopic dermatitis	Prospective, randomised, parallel study of 2 weeks duration	Percentage of patients who were good or excellent. Composite scale of signs and symptoms and tolerability	83% good or excellent for budesonide versus 94% good or excellent for alclometasone. (No formal	Method and concealment of randomisation unclear, blinding unclear, no ITT	No final analysis. Very similar effects, small numbers over very short term

					statistical comparison done)		
Jorizzo *et al* 1995[316]	Desonide 0.05% ointment versus hydrocortisone 1% ointment twice daily	14 children with atopic dermatitis	Prospective, randomised, parallel study of 5 weeks duration	Physician global improvement, erythema, lichenification, excoriations, oozing and crusting, induration and papules. Pruritis assessed subjectively	68% desonide patients and 40% hydrocortisone had clearing or marked improvement at 5 weeks	Method and concealment of randomization unclear, study described as investigator blind. 2 dropouts/ withdrawals, no ITT	Study followed up by a longer 6 months follow-up study which did not show any signs of skin thinning in either group
Camacho 1996[317] Spanish translation	0.25 % prednicarbate cream versus 0.2% flucortolone monhydrate cream twice daily	49 outpatients with atopic dermatitis aged 19-65 years	Prospective, randomised, double blind parallel right/left comparison of 3 weeks duration	Itch, erythema, eczema, vesicles/papules, and lichenification, on a scale of 0-3. Also physician and patient global evaluation of whether one side better than the other	Physicians rated the prednicarbate side better in 12 patients, the flucortolone side better in 7 patients and no difference in 16 patients (p=0.30) at the end of 3 weeks. 80% of patients recorded 'good to excellent' improvement on the prednicarbate side compared with 63% for the flucortolone side (p=0.10). No statistical difference between signs and	Randomisation method and concealment not described. Stated to be double-blind. No intention to treat analysis (14/49 dropouts)	Sponsored study of very short duration. Dropouts were not included in analysis which is worrying given the high dropout rate (29%) and the fact that at least two dropped out because they worsened

					symptoms were noted. Stinging similar in both groups		
Lebwohl *et al* 1999[318]	0.1% mometasone furoate cream once daily versus 0.2% hydrocortisone valerate cream twice daily	219 children with moderate to severe atopic dermatitis	Prospective, randomised, parallel study of 21 days duration	Investigator assessed 7 signs and symptoms on a 0-3 scale (0=none, 3=severe) and global assessment % improved	Mean improvement in severity score (no baselines given) at day 21 (% of patients with 100% clearance), 87.4% for mometasone and 79.7% for hydrocortisone valerate at day 21	Method and concealment of randomisation not clear, study described as evaluator blind	Unclear if the once daily versus twice daily cream was blinded (probably not). End points given but unclear what they are
Thomas *et al* 2002[52]	0.1% betamethasone valerate applied for three days followed by the base ointment for four days versus 1% hydrocortisone applied for seven days	174 children with mild or moderate atopic eczema	Prospective, randomised, double blind study of 18 weeks' duration	Primary outcomes were total number of scratch-free days and number of relapses. Secondary outcomes were median duration of relapses, number of undisturbed nights, disease severity, QoL measures	No differences were found between the two groups. This was consistent for all outcomes. The median number of scratch-free days was 118.0 for the mild group and 117.5 for the potent group (difference 0.5, 95% confidence interval −2.0 to 4.0, P=0.53). The median number of relapses for both	Full description of randomisation and concealment of allocation. Primary and secondary outcome measures declared up front. Intention to treat analysis carried out.	Well-reported study using CONSORT statement to report the trial[319-323]

					groups was 1.0. Both groups showed clinically important improvements in disease severity and QoL compared with baseline		

Table 18 Topical steroids versus other topical preparations in the treatment of AD

Author and date of study	Interventions and comparator	Study population and sample size	Design, description and duration	Outcome measures	Main reported results	Quality of reporting	Notes
Hiratsuka *et al* 1996[108]	Beclomethasone dipropionate three times daily versus topical sodium cromoglycate three times daily	43 children with moderate to severe atopic dermatitis	Prospective, randomised, parallel study of 2 weeks duration	Severity of inflammation, lichenification and cracking over 15 body areas. Patient diary cards for itch and sleep loss, lab' tests.	Itch and sleep disturbance estimated from graph. Sodium cromoglycate baseline score 2.3 and 2.4 reduced to 0.7 and 0.5 for itch and sleep disturbance respectively at 2 weeks and beclomethasone baseline 2.2 and 2.3 reduced to 0.9 and 0.6 for itch and sleep loss respectively at 2 weeks	Method and concealment of randomisation unclear, study described as double blind. No information of withdrawals or dropouts	Study mainly concerned with cellular and immunological changes
Korting *et al* 1995[324]	Hamamelis distallate 5.35g plus 0.64mg ketone/100g versus vehicle or 0.5% hydrocortisone	72 patients with moderate to severe atopic dermatitis	Prospective, randomised, left, right, parallel study of 2 weeks duration	Physician and patient global assessments 0-5 scale where 0=healed and 5=worse. Itch, erythema, scaling, oedema, papules, pustules, exudation, lichenification,	There was no clinical or statistical difference between hamamelis and vehicle for reduction of itching at 2 weeks. Mean itch score changed	Method and concealment of randomisation unclear, study described as double blind. 7 withdrawals/ dropouts, no ITT	Useful study with a placebo arm which provided no evidence to support efficacy of hamamelis

				excoriations, fissuring	from 2.1 to 0.8 for hydrocortisone and from 2.1 to 1.2 for hamamelis ($p<0.01$). Patient recorded efficacy was also significantly improved in hydrocortisone group when compared with hamamelis. There were no differences between hamamelis and vehicle		
Munkvad 1989[325]	Clinitar coal tar versus 1% hydrocortisone	30 patients with mild to moderate atopic eczema	Prospective, randomised, left, right, parallel study of 4 weeks duration	Infiltration, erythema, lichenification, excoriations, dryness, doctor and patient global assessments	All 5 parameters reduced significantly over the 4 week period but no significant differences between the 2 treatments	Method and concealment of randomisation unclear. No mention of blinding. No withdrawals/ dropouts	Difficult to blind due to smell of coal tar. Difficult to evaluate significance of change in scores due to small sample size and lack of data. No placebo arm
Wolf-Jürgensen 1979[326]	5% bufexamac twice daily versus 0.1% hydrocortisone or placebo twice daily	10 atopic eczema patients within a study of 72 patients with various forms of dermatoses	Prospective, randomised, parallel study of 2 weeks duration	Patient and investigator global assessment. Severity of inflammation, induration,	Change in global score was very similar for the three patients allocated to placebo, betamethasone	Method and concealment of randomisation unclear, study described as double blind. 1 withdrawal/	Impossible to interpret differences in such a small sub-sample of atopic eczema patients

				lichenification, crusts, scaling, pruritis	and bufexamac	dropout, no ITT	

Table 19 Topical steroid plus additional active agents in the treatment of AD

Author and date of study	Interventions and comparator	Study population and sample size	Design, description and duration	Outcome measures	Main reported results	Quality of reporting	Notes
Addition of antimicrobials							
Wachs & Maibach 1976[327]	Betamethasone valerate cream versus gentamicin/betamethasone valerate versus gentamicin cream three times daily	83 infected moderate to severe atopic dermatitis patients	Prospective, randomised parallel study of 22 days	Global assessment and overall severity, degree of inflammation, degree of infection, erythema, pruritis, pustules, crusting, exudation, vesiculation, lichenification	Improvement over baseline on a scale of 0-10: betamethasone/gentamicin group baseline score of 6.1 reduced to 1.0, betamethasone group 6.1 reduced to 1.8 and gentamicin group 6.6 baseline reduced to 4.2	Method and concealment of randomisation unclear, study described as double blind, 4 dropouts, no ITT	Treatment responses were very slightly larger for steroid/antibiotic combination but none statistically significant. Bacterial growth similar in all 3 groups
Hjorth *et al* 1985[328]	Betamethasone 17-valerate 0.1% versus betamethasone 17-valerate plus 2% fusidic acid	60 atopic dermatitis patients with potentially infected atopic eczema	Prospective, randomised, left, right, parallel study of 7 days duration	Bacteriological swabs. Clinical symptoms: vesicles, oedema, erythema, excoriation, crusting, lichenification, itching	Data for mean atopic dermatitis not given, only result is investigator preference: 29 no preference, 22 preferred betamethasone plus fusidic acid and 9 preferred betamethasone alone	Method and concealment of randomisation unclear, study described as double blind, no dropouts or withdrawals	Wrote to author for more data but has sadly deceased. Study provides no evidence of improved efficacy of betamethasone/fusidic- acid combination above betamethasone alone in infected

							AD
Wilkinson & Leigh 1985[329]	0.1% betamethasone plus 2% fusidic acid cream versus 0.1% betamethasone plus 0.5% neomycin cream 2 or 3 times daily	43 infected or potentially infected atopic eczema patients	Prospective, randomised, parallel study of 2 weeks duration	Severity of lesions assessed by patient and doctor as either very severe, severe, moderate, mild, minimal, or absent. Swabs taken for infection	95% patients (91% doctors) felt lesions improved after betamethasone plus fusidic acid after 2 weeks versus 100% patients (100% doctors) felt betamethasone plus neomycin. No separate data for bacteriological efficacy for atopic dermatitis	Method and concealment of randomisation unclear, study described as double blind, 9 withdrawals and dropouts but unclear which type of eczema these patients had (7 types of dermatoses reported)	Difficult to interpret in the absence of a betamethasone only arm
Meenan 1988[330]	Hydrocortisone 17-butyrate 0.1% plus 3% chlorquinaldol versus 0.1% triamcinolone acetonide plus 0.25% neomycin plus 0.025% gramicidin nystatin	40 children with eczema for 3 months to 14 years with secondary infection	Prospective, randomised parallel study of 14 days duration	Pruritis, erythema, lichenification, oozing/crusting, scaling. Skin swabs for infection. Patient and physician global score	"Both treatments produced a highly significant ($p<0.001$) linear reduction in the scores for all parameters, no significant difference between treatments." "Highly significant reduction in infection for both treatments ($p<0.001$)"	Method and concealment of randomisation unclear, study described as double blind. Withdrawals or dropouts no data given.	Both agents contained an antimicrobial/anti septic, and no steroid-only comparator
Zienicke 1993[331]	Prednicarbate	180 super-	Prospective,	Redness,	Clinical score	Method and	Duplicate

	0.25% cream versus prednicarbate 0.25% cream plus didecyldimethylammoniumchloride 0.25%	infected atopic eczema patients	randomised, parallel study of 34 days duration	swelling, papulovesicles, vesicles, pustules, bullae, papules, crusting and scaling on a score of 1-5	over baseline of 25 for both drugs reduced to 4.5 for prednicarbate and 4 for prednicarbate plus didecyl dimethylammoniumchloride. 30% patients still had *Staphylococcus aureus* at day 34 compared to 100% at start	concealment of randomisation unclear, study described as double blind. 44 withdrawals/ Dropouts, no ITT carried out	publication of Korting 1994[332]. No clinical or statistical difference between groups
Ramsay *et al* 1996[333] Study 1	Fusidic acid and 1% hydrocortisone versus 1% hydrocortisone	186 mild to moderately severe atopic dermatitis	Prospective, randomised, parallel study of 2 weeks duration	Primary: Percentage patients not failing treatment (included signs, withdrawal and various bacteriological criteria). Secondary: Erythema, scaling, oedema, itching, serous discharge, crusting, extent of lesions and overall clinical response	63.7% fucidic acid plus hydrocortisone did not fail treatment compared with 50.6% in the hydrocortisone group (p=0.11). Mean change in clinical scores not statistically significant (p=0.21)	Method and concealment of randomisation unclear, study described as double blind. 32 dropouts/ Withdrawals, no ITT	No evidence to support a clear benefit of combination over plain hydrocortisone
Ramsay *et al* 1996[333]	Fusidic acid and 1% hydrocortisone	68 patients with mild to moderately severe	Prospective, randomized, parallel study of 2	Erythema, scaling, oedema, itching, serous	36.4% fusidic acid plus hydrocortisone	Method and concealment of randomisation	Some evidence of benefit of fucidin/hydrocorti

Study 2	versus 2% fusidic acid	atopic dermatitis	weeks duration	discharge, crusting, extent of lesions and overall clinical response. Swabs taken	failed treatment and 65.6% fusidic acid failed treatment (p=0.04)	unclear, study described as double blind. 3 dropouts/withdrawals, no ITT	sone over fucidin alone
Thaci 1999[334]	Fusidic acid 2% plus 0.1% betamethasone cream versus fusidic acid 2% plus 0.1% betamethasone ointment versus ointment vehicle twice daily	59 patients with potentially infected atopic dermatitis	Prospective, randomised, parallel study of 10 days duration	Bacteriological tests, signs and symptoms on a 4-point scale, investigator assessed overall clinical response	Overall clinical response assessed by investigator as "clearance" or "marked improvement" in 92% fusidic acid/ Betamethasone cream patients, in 84% fusidic acid/ Betamethasone ointment patients, and 25% ointment vehicle patients. No statistically significant difference between the two formulations	Method and concealment of randomisation unclear, study described as double blind, no withdrawals or dropouts mentioned	Abstract only. Only results reported in text given
Addition of antifungal							
Anonymous 1967[335]	Triamcinolone acetonide 0.1% and neomycin sulphate 0.35% versus triamcinolone acetonide 0.1% and neomycin	10 infantile eczema patients within a study of 100 patients with various skin disorders	Prospective, randomised, parallel study	No change, some improvement, marked improvement, cured	Cured or marked improvement 17% for triamcinolone acetonide and neomycin sulphate compared to 100% for	Method and concealment of randomisation unclear, study described as double blind. Dropouts/withdrawals: no data	Difficult to make any conclusion in such a small subset. Length of study not given

	sulphate 0.35% plus undecylenic acid 2.5%				triamcinolone acetonide 0.1% and neomycin sulphate plus undecylenic acid	given, no ITT	
Topical steroids plus something else versus topical steroids alone							
Kaplan *et al* 1978[336]	Hydrocortisone 0.5% plus 30% caffeine versus hydrocortisone 0.5% versus betamethasone valerate 0.1%	90 atopic dermatitis patients	Prospective, randomised, parallel study of 3 weeks duration	Pruritis, erythema, scaling, lichenification, oozing, excoriation, overall global impression	Mean improvement over baseline global impression on a scale 0-5: 2.6 to 1.6 for hydrocortisone, 2.1 to 0.8 for caffeine and hydrocortisone, 2.7 to 0.6 for betamethasone	Method and concealment of randomisation unclear, study described as double blind. 7 dropouts/ Withdrawals, no ITT	Some evidence to suggest the addition of caffeine might have a small additional benefit
Chapman 1979[337]	0.1% hydrocortisone butyrate ointment versus 1% hydrocortisone alcohol with 10% urea twice daily	40 atopic eczema patients split into 2 studies. One group applied creams to dry skin, the other after wetting the skin first	Prospective, randomised, left, right parallel study of 3 weeks duration	Erythema, scaling, oedema	Mean clinical improvement dry skin 73% hydrocortisone alcohol versus 80% hydrocortisone 17-butyrate ($p>0.05$) wet skin 67% hydrocortisone alcohol versus 68% hydrocortisone 17-butyrate ($p>0.05$)	Method and concealment of randomisation unclear, study described as double blind. Dropouts/ Withdrawals; no data given.	No evidence to support efficacy of the combination treatment
Norén & Melin	Hydrocortisone	45 moderate to	Prospective,	Primary:	At end of 5 week	Method and	Useful RCT

1989[203]	versus betamethasone valerate plus hydrocortisone versus hydrocortisone plus habit reversal versus betamethasone valerate plus hydrocortisone plus habit reversal	severe atopic dermatitis patients	randomised, parallel study of 5 weeks duration	reduction in scratching, secondary: dryness, scaling, erythema, infiltration, frequency of scratching	evaluation period total skin status scores (not defined in paper) fell in all 4 groups but more so in groups which included habit reversal (data only presented in graphical form. Similar changes for other skin signs presented in graphical form	concealment of randomisation unclear, no blinding. 2 dropouts/ Withdrawals no ITT	which evaluates combinations of different treatment approaches which suggests an additional benefit of habit reversal

Table 20 Randomised controlled trials comparing different formulations of the same topical steroid in the treatment of AD

Author and date of study	Interventions and comparator	Study population and sample size	Design, description and duration	Outcome measures	Main reported results	Quality of reporting	Notes
Andersen *et al* 1988[338]	Mildison® 1% hydrocortisone versus Uniderm® 1% hydrocortisone	96 children with atopic dermatitis	Prospective, randomised, left, right parallel study of 4 weeks duration	Global severity of symptoms, global improvement of skin lesions, investigator and patient preference	Mean reduction in severity score over baseline of 1.7 for Mildison® and Uniderm® reduced to 0.7 and 0.8 respectively	Method and concealment of randomisation unclear, study described as double blind. No withdrawals or dropouts	Little efficacy difference between treatments, yet patients preferred the Mildison® preparation
Korting *et al* 1990[339]	0.039% liposomal betamethasone dipropionate versus 0.054% commercial propylene glycol gel	12 patients with atopic dermatitis	Prospective, randomised, left, right, parallel study of 2 weeks duration	Investigator assessed 10 signs and symptoms of eczema and proportion of patients with major improvement or healed and global effect on a 0-5 scale where 0=healed and 5=worse	Although data not reported in text, estimates from the figure showed that 80% evaluable patients noted healed or major improvement in liposome group compared with 60% patients in reference group at day 14	Method and concealment of randomisation unclear, study described as double blind. 2 withdrawals/ dropouts. No ITT	Small study where 10 parameters measured and data only given for some to support enhanced benefit for test substance
Malzfeldt *et al* 1989[340]	Betamethasone 17-valerate 0.0056% in liquid paraffin versus betamethasone 17-benzoate 0.00056% in	16 patients with atopic eczema	Prospective, randomised, left, right parallel study of 5-7 days duration	Investigator assessed 5 signs on a 0-3 scale (max score 15)	In low solution capacity group mean global score fell from11.9 at baseline to 3.8 at day 7 compared with 11.9 to 8.2 at baseline and day 7	Method and concealment of randomisation unclear, study described as double blind. Withdrawals or dropouts not	Study suggests that vehicle can markedly affect efficacy

	neutral oil				respectively for high solution capacity ($p<0.01$)	mentioned	
Olholm *et al* 1988[341]	Mildison® 1% hydrocortisone versus Uniderm® 1% hydrocortisone	60 atopic dermatitis patients	Prospective, randomised, left, right parallel study of 4 weeks duration	Lesions: Global severity of atopic dermatitis, investigator and patient preference of therapeutic efficacy	Physician global assessment for those aged <10 years: the proportion of those with moderate, severe, or very severe dermatitis was 94% at baseline and 14% at 4 weeks for Mildison® compared to 94% at baseline and 16% at 4 weeks for Uniderm®. For >10 years 89% baseline to 12% at 4 weeks for Mildison® and Uniderm®	Method and concealment of randomisation unclear, study described as double blind. 5 dropouts and withdrawals, no ITT	Very similar to Andersen 1988[338] study, but this time no patient preference with regards to cosmetic acceptability

Table 21a Once daily versus more frequent application of steroids: *Trials involving the same active compound*

Author and date of study	Interventions and comparator	Study population and sample size	Design, description and duration	Outcome measures	Main reported results	Quality of reporting	Notes
Sudilovsky *et al* 1981[276]	0.1% halcinonide cream once daily versus 0.1% 0.1% halcinonide cream three times daily	149 atopic eczema patients	Prospective, randomised, right, left, parallel study of 3 weeks duration	Comparative and absolute therapeutic responses: Erythema, oedema, change in size of thickness of lesions. Physician global response	Based on 116 evaluable patients at week 3 86.2% noticed good or excellent clearance in three times daily versus 85.3% in once daily group. No statistical differences	Method and concealment of randomisation unclear, study described as double blind. 33 dropouts/ withdrawals, no ITT	Table of random numbers used. Implies double blinding by use of placebo
Richelli *et al* 1990[342]	Clobetasone 17-butyrate lotion twice daily (8am and 3pm) versus twice daily (3pm and 8pm) or once daily (9pm)	30 children with atopic eczema	Prospective, randomised, right, left, parallel study of 3 weeks duration	Itching, burning, pain, erythema, oedema, exudation, blisters, bullae, scabs, scaling, lichenification, pooled into a mean score. Serum cortisol and ACTH tests	Data on severity scores only presented in graphical form. No obvious differences between 3 groups. No supporting statistics given	Method and concealment of randomisation unclear. Blinding not described. Unclear of ITT	Limited statistical detail given making it difficult to interpret
Haneke 1992[312]	Methylprednisolone aceponate ointment once daily versus twice daily	88 adults with atopic dermatitis	Prospective, randomised, left, right, parallel study of 4 weeks duration	Patient and doctor global assessments. Doctor assessed 11 signs and symptoms	No actual data for once daily versus twice daily methylprednisolone aceponate given	Method and concealment of randomisation unclear. Study described as double blind. No ITT	Results of all 3 studies impossible to disentangle
Koopmans *et al*	0.1%	150 adults and	Prospective,	Patient and doctor	78% once daily	Method and	

1995[343]	hydrocortisone 17-butyrate cream twice daily versus once daily plus vehicle once daily	children over the age of 12 suffering from atopic dermatitis	randomised, parallel study of 4 weeks duration	assessed overall severity. Clinical features assessed were erythema, induration, pruritis and excoriation	versus 93% twice daily (p=0.006) noticed considerable improvement or clearance according to patient	concealment of randomisation unclear. Study described as double blind. No ITT but only one dropout	
Bleehen *et al* 1995[344]	Fluticasone propionate 0.05% cream once daily versus twice daily	270 moderate to severe atopic dermatitis patients	Prospective, randomised, parallel study of 4 weeks duration	Patient diary cards for itch, rash and sleep disturbance. Physician assessed six signs and global assessment	Patient diary cards revealed improvement in rash, itch and sleep loss for both treatment groups within first week. 80% in once daily and 85% in twice daily groups defined as clinical success on ITT analysis (p=0.35)	Method and concealment of randomisation unclear. Probably investigator blinded but unclear. ITT carried out	

Table 21b Once daily versus more frequent application of steroids: *Trials involving different active compounds*

Author and date of study	Interventions and comparator	Study population and sample size	Design, description and duration	Outcome measures	Main Reported Results	Quality of Reporting	Notes
Hoybye *et al* 1991[345]	mometasone furoate cream once daily versus hydrocortisone 17-butyrate cream twice daily	96 adult atopic eczema patients	Prospective, randomised, parallel study of 6 weeks duration	Patient VAS (visual analogue scale) for severity of eczema, 0-3 score for doctor assessed erythema, infiltration and pruritis, global evaluation scores of 1-6	A comparison of the evaluations made by patients on a VAS after 6 weeks showed no difference in efficacy between the two treatments (p=0.30)	Method and concealment of randomisation unclear, study described as single blind. Ten dropouts/ withdrawals, no ITT	Difficult to blind a once daily treatment with a twice daily treatment. Posology of treatments not given
Vernon *et al* 1991[346]	mometasone furoate 0.1% cream versus hydrocortisone 1.0% cream once daily	48 children with moderate to severe atopic dermatitis	Prospective, randomised, parallel study of 6 weeks duration	Doctor assessed erythema, lichenification, skin surface disruption (crusting, scaling), excoriation, and pruritis on a 0-3 scale, % body surface area and global evaluation	For the 12 evaluable patients mean percent improvement in total sign/symptom score was 95% for mometasone versus 75% for hydrocortisone (p=0.01). The group with more than 25% body surface area involvement showed a wider difference in favour of	Method of randomisation unclear, study described as single blind with an 'unblinded investigator' evaluations were carried out by a 'blinded' investigator. 36 patients experienced clearing of eczema prior to end of study so were withdrawn, no ITT carried out	Efficacy advantage of mometasone (classified as potent in UK) not surprising when compared against a very mild product

					mometasone (92% versus 62%; p=0.01)		
Rafanelli *et al* 1993[347]	Mometasone furoate 0.1% cream once daily versus clobetasone 0.05% cream twice daily	60 children with atopic dermatitis	Prospective, randomised, parallel study of 3 weeks duration	Parent assessed efficacy of treatment on a 4-point scale (excellent to poor). Investigator assessed erythema, induration and pruritis, global percent improvement	Total sign/symptom score improvement over baseline, 7.8 to 1.1 ($p<0.01$) for mometasone versus 7.2 to 2.4 for clobetasone (not statistically significant)	Method of randomisation unclear, study described as third party blind. No withdrawals or dropouts	Uncertain what type of clobetasone was tested. This is important since the propionate is very potent whereas butyrate is moderately potent
Marchesi *et al* 1994[348]	Mometasone furoate ointment 0.1% once daily versus betamethasone dipropionate ointment 0.05% twice daily	60 adult patients with atopic eczema of at least moderate severity	Prospective, randomised, parallel study of 3 weeks duration	Investigator assessed erythema, induration and pruritis on a 0-3 scale, global evaluation % improvement	100% of mometasone and betamethasone patients had cleared or experienced good improvement by week 3. No baseline values given	Method of randomisation unclear, study described as third-party blind evaluator. No withdrawals or dropouts	Pity there was no comparison against once daily betamethasone
Reidhav & Svensson 1996[349]	Betamethasone valerate 0.1% cream once daily versus mometasone furoate 0.1% cream once daily	30 patients with atopic dermatitis aged 15 to 66 years	Prospective, randomised, left, right, parallel study of 4 weeks duration	Patient assessed pruritis and smarting pain on 0-3 scale, evaluator assessed erythema, scaling, lichenification, excoriation, papules, and	No significant differences were found for any of the symptoms scored following 4 weeks treatment with betamethasone valerate or	Method and concealment of randomisation unclear, study described as double blind, 10 dropouts/ withdrawals, no ITT carried out	No actual efficacy data reported, only patient preference data given

				vesicles on a 0-3 scale (max. score 18)	mometasone furoate		
Traulsen 1997[350] Study 1	hydrocortisone buteprate cream 0.1% once daily versus betamethasone valerate 0.1% cream once daily	86 atopic dermatitis patients 12+ years	Prospective, randomised, left, right parallel study of 2 weeks duration	Erythema, infiltration, lichenification, scaling, vesiculation, papules, excoriations and pruritis on a 0-4 scale, patient assessed efficacy and investigator global assessment	The sum of scores of 8 symptoms showed a mean reduction from 4.1 to 2.3 after 2 weeks treatment. There were no significant differences between the two treatments	Method and concealment of randomisation unclear, study described as double blind, 3 withdrawals/ dropouts, no ITT carried out	No differences between treatments but effect sizes similar to studies of twice daily usage
Traulsen 1997[350] Study 2	hydrocortisone buteprate ointment 0.1% once daily versus betamethasone valerate 0.1% ointment once daily	82 atopic dermatitis patients 12+ years	Prospective, randomised, left, right parallel study of 2 weeks duration	Erythema, infiltration, lichenification, scaling, vesiculation, papules, excoriations and pruritis on a 0-4 scale, patient assessed efficacy and investigator global assessment	The mean sum of scores of 5 symptoms (erythema, scaling, vesicles, papules, pruritis) decreased from baseline 8.3 to 1.6 after 2 weeks for hydrocortisone buteprate versus 8.3 to 1.4 for betamethasone valerate. A statistically significant difference was found in favour of betamethasone	Method and concealment of randomisation unclear, study described as double blind, 4 withdrawals/ dropouts, no ITT carried out	
Amerio *et al*	Mometasone	97 atopic	Prospective,	erythema,	83.1%	Method and	A study reported

1998[351]	furoate 0.1% once daily versus betamethasone valerate twice daily	dermatitis patients	randomised, parallel study of 15 days duration	oedema, exudate, scaling, excoriation, lichenification (objective symptoms) and pruritis and burning (subjective symptoms)	mometasone furoate patients and 89.2% betamethasone valerate patients experienced a reduction in signs and symptoms, not statistically significant	concealment of randomisation unclear from abstract, study described as double blind, unclear from abstract if any withdrawals or dropouts	in Italian, all information abstracted from the English abstract only. Pity there was no once daily betamethasone
Wolkerstorfer *et al* 1998[352]	Fluticasone propionate 0.05% cream once daily versus clobetasone butyrate 0.05% cream twice daily	22 children with atopic dermatitis	Prospective, randomised, parallel study of 4 weeks duration	SCORAD[141] composite scale of extent and intensity of 8 signs	At week 4, three fluticasone patients and 1 clobetasone patient were clinically healed (SCORAD <9)	Method and concealment of randomisation unclear, study described as double blind. Only one dropout, no ITT analysis carried out	Small sample over a short period of time

Table 22 Topical steroids in the prevention of relapse in AD

Author and date of study	Interventions and comparator	Study population and sample size	Design, description and duration	Outcome measures	Main reported results	Quality of reporting	Notes
Van Der Meer 1999[353]	Fluticasone propionate 0.005%(g/g) versus placebo	54 patients with moderate to severe atopic dermatitis patients identified from a larger set of 112 on the basis of enhanced steroid responses	Prospective, randomised, parallel study of 16 weeks duration	Risk of relapse and time to relapse. Clinical assessment SCORAD: Erythema, oedema/ papulation, oozing/crusts, excoriations, lichenification, dryness, pruritis and sleep loss. Skin thickness on biopsy specimens	68% of patients in the placebo group and 39% in the fluticasone group withdrew because of recurrence and relapse. Risk of relapse was 2.6 times greater in active group (95% CI 1.2-5.7). No significant changes were detected in either treatment group in serum cortisol levels or in skin thickness measurements	Method and concealment of randomisation unclear, study described as double blind. 17 withdrawals/ dropouts, no ITT. Only data up to first relapse analysed.	Good to see a longer-term study evaluating relapse as well as short-term efficacy. Difficult to say how much of the benefit in preventing relapse was due to treating old healed sites as opposed to treatment of new sites

Table 23 Trials that specifically set out to examine adverse effects of topical corticosteroids in AD

Author and date of study	Intervention and comparator	Study population and sample size	Design, description and duration	Outcome measures	Main reported results	Quality of reporting	Notes
Trials which specifically set out to examine side effects							
Lucky *et al* 1997[354]	0.05% desonide ointment versus 2.5% hydrocortisone ointment twice daily	20 children with AD	Prospective, randomised, parallel study of 4 weeks duration	hypothalamic pituitary adrenal (HPA) axis (Cortisol levels)	-1.6 and -1.3% change in cortisol levels over baseline at 28 days for desonide and hydrocortisone groups respectively	Method and concealment of randomisation unclear, study described as open label, 5 dropouts, no ITT	No evidence of HPA suppression in either group. Short term study
Sanabria-Silva *et al* 1991[355] Spanish translation	Hydrocortisone 1% versus betamethasone dipropionate 0.05% versus cold cream 'placebo'	45 children with atopic dermatitis	Prospective, randomised, open study of 4 weeks duration with 10 days suspended treatment	"Rebound phenomenon" reactivation of lesions with greater intensity than their pre-treatment state a few (<10) days after suspending the treatment with topical steroids, which had controlled them. The extensiveness of lesions according to 3 signs. Photographs taken before and after treatment.	Sudden suspension of topical steroids was followed by relapse in every case but in no case was there rebound. There was no statistical difference between the frequency of relapse in the 3 groups ($p<0.055$)	Method and concealment of randomisation unclear, open study, no blinding. No mention of withdrawals and dropouts	Although rebound is often referred to, there was no evidence of such a phenomenon in this study

Kuokkanen & Sillantaka 1987[356]	Alclometasone dipropionate 0.05% versus hydrocortisone 1.0% twice daily	37 children with eczema	Prospective, randomised, left, right, parallel study of 3 weeks duration	Cutaneous atrophy: skin thinning, shininess, striae and fine blood vessels (telangiectasia) as assessed under magnification.	Signs of cutaneous atrophy were not observed at any test site either at beginning or at 3 week evaluation period. Efficacy similar in both groups with 88% improvement signs and symptoms in alclometasone treated sites versus 86% hydrocortisone treated sites	Method and concealment of randomisation unclear, study described as double blind. 3 withdrawals/drop outs, no ITT	No evidence of skin thinning, although study duration very short

Table 24 Oral steroids in the treatment of AD

Author and date of study	Intervention and comparator	Study population and sample size	Design, description and duration	Outcome measures	Main reported results	Quality of reporting	Notes
Dickey 1976[357]	betamethasone sodium phosphate 4.0mg/ml injection versus dexamethasone sodium phosphate 4.0mg/ml injection once daily	22 patients with moderate to severe atopic dermatitis	Prospective, randomised, parallel study of 24 hours duration	Inflammation, vesiculation, pruritis, exudation, excoriations, overall evaluation	Overall evaluation on a 4 point rating scale: baseline 3.44 for betamethasone reduced to 2.89 and 3.62 for dexamethasone reduced to 2.69	Method and concealment of randomisation unclear, study described as double blind. Withdrawals and dropouts not mentioned	Although a placebo group might have been ethically difficult, patient-based views on treatment response would have been useful
Heddle *et al* 1984[358]	oral plus nasal beclomethasone dipropionate four times daily versus placebo	27 children with moderate to severe atopic eczema	Prospective, randomised, crossover study of 4 weeks duration	Patient assessed itch and sleep loss (VAS). Doctor assessed redness, vesiculation, crusting, excoriation, lichenification	Parental score for itch and antihistamine use were significantly lower on beclomethasone than placebo, but, use of topical steroids and sleep loss did not show any significant change. Other significant changes especially surface damage	Method and concealment of randomisation unclear, study described as double blind. 1 withdrawal, no ITT	Crossover study with significant treatment order interactions. Large treatment effects
La Rosa *et al* 1995[359]	Systemic flunisolide 640-1200µg twice daily versus placebo	20 children with severe atopic dermatitis	Prospective, randomised, crossover study of 2 weeks duration	pruritis, erythema/oedema, excoriation, papulation/erosion/scaling,	improvement over baseline for total clinical severity score: group A 75 reduced to 34 and	Method and concealment of randomisation unclear, study described as	Big treatment effects

				lichenification	group B 74 reduced to 29	double blind. Withdrawals/drop outs not mentioned	

CHAPTER 4

CONCLUSIONS

From the data abstraction of the included studies in Chapter 3, the following conclusions have been drawn:

4.1 ANTIHISTAMINES AND MAST CELL STABILISERS

4.1.1 Antihistamines

- RCT evidence does not suggest sedating oral antihistamines have a useful benefit in atopic eczema
- RCT evidence is limited and conflicting for the use of oral non-sedating antihistamines in the treatment of AD
- From a treatment recommendation perspective, the current RCT evidence does not support the use of antihistamines in atopic eczema

4.1.2 Doxepin - topical cream

- Two RCTs suggest that topical doxepin might produce some additional relief of itching compared to vehicle alone in first 48 hours of treatment
- None of the studies of topical doxepin have demonstrated a clinically useful benefit on eczema severity
- Drowsiness may occur with topical doxepin use
- Longer-term independent RCTs of topical doxepin are required

4.1.3 Ketotifen

- RCT evidence does not demonstrate any benefit of ketotifen in the treatment of AD

4.1.4 Nedocromil sodium

- RCT evidence does not support the use of nedocromil sodium in the treatment of AD

4.1.5 Sodium cromoglycate

- RCT evidence does not support the use of oral sodium cromoglycate (SCG) in the treatment of atopic eczema
- The results of the trials of topical di-sodium cromoglycate (DSCG) are conflicting, hence a conclusion regarding efficacy cannot be drawn
- Most of the DSCG studies that reported positive results are from the same study laboratory and need to repeated elsewhere

4.1.6 Tiacrilast

- From one RCT there is no evidence to support the benefit of topical tiacrilast in the treatment of atopic eczema

4.2 ANTIMICROBIALS AND ANTISEPTICS

- RCT evidence does not suggest that oral antibiotics are of any benefit in clinically uninfected AD
- There is some RCT evidence that a short course of cefadroxil is of benefit in clinically infected AD
- There is some evidence from a short-term study that topical mupirocin may improve AD activity as well as reduce bacterial counts, though there is concern regarding the emergence of resistant strains with such an approach
- There is no evidence that antiseptics are of benefit in AD when applied directly to the skin or in the bath
- One small short-term study in Japan suggested that spraying an acidic solution on babies with AD might result in an improvement in disease activity
- A study of head and neck AD failed to show any benefit of antifungal creams and shampoos directed against the yeast *Pitrosporum ovale*

4.3 COMPLEMENTARY MEDICINE

4.3.1 Aromatherapy

- One small study of massage with and without essential oils plus counselling has suggested benefits of counselling and tactile contact but no benefit from addition of essential oils

4.3.2 Bioresonance

- RCT evidence does not support the use of bioresonance in the treatment of AD

4.3.3 Chinese herbs

- Two studies of Chinese herbal treatment conducted in children and adults by the same research team found significant benefits compared with placebo
- Two further RCTs conducted by independent groups failed to demonstrate any clear clinical benefit
- Further larger and long term RCTs of Chinese herbal treatment seem worthwhile

4.3.4 Hypnotherapy and biofeedback

- One unblinded study of hypnotherapy and biofeedback suggests a benefit in terms of surface damage and lichenification but not erythema

4.3.5 Massage therapy

- One small study of massage therapy in addition to standard care in children has suggested benefit in terms of reduced anxiety and better coping skills

4.4 DIETARY INTERVENTIONS

4.4.1 Dietary manipulation

- There is little evidence to support an egg and milk-free diet in AD patients
- There is no evidence to support the use of an elemental or few-foods diet in AD
- There is some evidence that the addition of a probiotic such as *Lactobacillus* may be beneficial for AD in those already on a cow's milk whey hydrolysate diet, however, with the absence of a control group on no special diet it is difficult to determine a real benefit
- There is some evidence to support the use of an egg-free diet in infants with suspected egg allergy who have positive specific IgE to eggs in their blood

4.4.2 Essential fatty acid supplementation

Borage oil

- RCT evidence does not support the use of borage oil in the treatment of AD

Fish oil

- RCT evidence does not support the use of fish oil in the treatment of AD

Evening primrose oil

- RCT evidence does not support the use of evening primrose oil in the treatment of AD

4.4.3 Vitamin and mineral supplementation

Pyridoxine

- RCT evidence does not support the use of pyridoxine in the management of children with AD

Selenium and vitamin E

- RCT evidence does not support the use of selenium and vitamin E in the treatment of AD

Vitamin E and vitamin B_2

- RCT evidence does not show that vitamin E and vitamin B_2 are of any benefit in the treatment of AD

Zinc

- RCT evidence does not suggest that zinc is of any benefit in the treatment of AD

4.5 MISCELLANEOUS INTERVENTIONS

4.5.1 Nitrazepam

- RCT evidence does not support the use of nitrazepam at night to reduce scratching in patients with AD

4.5.2 Papaverine

- RCT evidence does not support the use of papaverine in the treatment of AD

4.5.3 Ranitidine

- From one RCT of ranitidine versus placebo in the treatment of AD there is evidence of benefit of ranitidine over placebo, however, due to the size and length of this study the evidence is limited

4.5.4 Salbutamol

- RCT evidence does not support the use of oral or topical salbutamol in the treatment of AD

4.5.5 Suplatast tosilate

- There is evidence that suplatast tosilate can prevent 'rebound phenomenon' from topical steroid use in AD. However, the size of the study and the lack of vehicle-only group brings this evidence into question. A study is required that is larger and compares the active drug to placebo only

4.5.6 Theophylline

- RCT evidence does not support the use of theophylline in the treatment of AD

4.6 NON-PHARMACOLOGICAL TREATMENTS

4.6.1 Detergents with and without enzymes

- RCT evidence does not support the use of enzyme-free washing powder over enzyme washing powder in those affected by AD

4.6.2 Cotton clothing

- RCT evidence does not support the sole use of cotton clothing for people with AD. It appears to be smooth fibres that are better tolerated, whether synthetic or natural

4.6.3 House dust mite hyposensitisation

- RCT evidence does not support the use of house dust mite hyposensitisation in the treatment of AD

4.6.4 House dust mite reduction

- There is some evidence to support the use of house dust mite reduction in the home for the treatment of AD. However, more research is required to establish the most clinically useful method of reduction, the clinical relevance of such a benefit, and its sustainability

4.6.5 Patient education

- There is some RCT evidence that educating the parents of children does benefit children that are affected by eczema and is a useful adjunct to conventional treatment

4.6.6 Psychological approaches

- There is RCT evidence to support the use of behaviour therapy such as habit reversal as an adjunct to conventional treatment in AD

4.6.7 Salt baths

- RCT evidence does not support the use of salt baths in the treatment of eczema, more studies are needed before a conclusion can be drawn

4.6.8 UV light

- There is some RCT evidence that UVB (broad and narrow band) is useful in the treatment of AD
- There is some RCT evidence that high dose UVA is superior to UVB/UVA in the treatment of AD
- There is some RCT evidence that narrow band UVB (TL01) is more efficacious in the treatment of AD than ordinary, i.e. not high dose, UVA
- There is more RCT evidence in support of high-dose UVA for acute AD flares than topical corticosteroids
- More research is needed to assess the cost-benefit ratio in terms of the development of skin cancer from exposure to UV light

4.7 OTHER TOPICAL TREATMENTS

4.7.1 Ascomycins

- There is some evidence that ascomycins are effective in the treatment of mild to moderate AD

4.7.2 Emollients

- There is limited RCT evidence to support the use of emollients in the treatment of AD. However, an important point to make here is that lack of RCT evidence does not equal lack of efficacy. Emollients are a good example because they are fundamental in the treatment of eczema, the efficacy of which has been proven by other types of research. Nevertheless, good quality RCTs over long periods of time are needed to support the importance of their use in the treatment of AD

4.7.3 Lithium succinate ointment

- The RCT evidence to date does not support the use of this drug in the treatment of AD

4.7.4 Tacrolimus ointment

- There is good quality RCT evidence to support the use of tacrolimus ointment in the treatment of moderate to severe AD

4.7.5 Topical coal tar

- RCT evidence does not support the use of coal tar in the treatment of AD. However, this is based on one small RCT of poor quality, therefore, more research is required before conclusions can be drawn

4.8 SYSTEMIC IMMUNOMODULATORY AGENTS

4.8.1 Allergen-antibody complexes of house dust mite

- There is some RCT evidence from one small RCT that allergen-antibody complexes of house dust mite are useful in the treatment of AD

4.8.2 Cyclosporin

- The RCT evidence does not support the use of topical cyclosporin for AD. However, the RCT evidence for oral cyclosporin is good but must be weighed against the serious side effects associated with the long-term use of this drug

4.8.3 Levamisole

- There is some RCT evidence for levamisole in the treatment of AD but it is not enough to justify its use

4.8.4 Platelet-activating factor antagonist

- Based on one small study there is no evidence to support the use of PAF antagonist in treating AD

4.8.5 Interferon-gamma

- This does appear to be beneficial in treating AD but it induces flu-like symptoms which may deter clinicians and patients from using it

4.8.6 Thymic extracts

- RCT evidence suggests some benefit from thymic extracts, such as thymostimulin, thymomodulin and thymopentin for treating AD. However, thymopentin is delivered via injection which may limit its use

4.8.7 Immunoglobulin

- There is evidence from one RCT that immunoglobulin is effective in the treatment of AD based on a poor quality study, therefore, good quality RCTs are needed before a conclusion can be drawn

4.8.8 Transfer factor

- From one small Cuban RCT there was no evidence of efficacy of transfer factor for its use in AD

4.9 TOPICAL CORTICOSTEROIDS AND ORAL STEROIDS

- There is RCT evidence to support the use of topical corticosteroids in the treatment of AD bearing the following in mind:
- The vehicle used may have an impact upon the topical corticosteroid's efficacy
- The evidence does not offer any guidance as to the best topical corticosteroid to use for the different severities of eczema that can be presented
- There is no evidence to support the use of antibiotic/corticosteroid combination over corticosteroid alone
- The RCT evidence does not resolve the issue of how often to use a topical corticosteroid, i.e., once or twice daily
- Even though nearly 200 RCTs assessing topical corticosteroids were located, there are some important questions that remain unanswered, such as 'How does dilution of topical corticosteroids affect their stability and efficacy?' 'What are the economic implications for the NHS of the plethora of topical corticosteroids available that haven't been compared to one another and vary in price so much?' and 'Does patient preference have a role to play in the efficacy of topical corticosteroids?'
- In terms of oral steroids there is some RCT evidence for their efficacy in atopic eczema, however, the evidence is based on short-term data only and longer term studies are needed to take into account the chronicity of the disease and the safety of long-term use

CHAPTER 5

DISCUSSION

This research summarises the randomised controlled trials that are in the public domain that address treatments for atopic dermatitis. We can deduce from this research that there are lots of trials covering many interventions, but gaps are evident. The trials that exist do not necessarily answer questions that are clinically important to doctors and patients, for example:

- Does regular use of emollients reduce disease relapse?
- How effective are wet-wraps, with and without emollients or topical steroids?

This could be because there is a lack of independent trials with the vast majority sponsored by the pharmaceutical industry, thereby addressing the research priorities set by this industry.

To provide a summary of this systematic review, which is itself a summary of all RCTs of AD, is difficult due to the heterogeneity of the included trials. Nevertheless, the results suggest the following:

- There is evidence of a benefit in the treatment of AD with psychological approaches, UV light, ascomycin derivatives, topical tacrolimus, oral cyclosporin A and topical corticosteroids
- There is conflicting evidence of a benefit in the treatment of AD with topical disodium cromoglycate
- There is limited evidence of a benefit in the treatment of AD with non-sedatory antihistamines, topical doxepin, the oral antibiotic Cefadroxil on clinically infected AD, the topical antibacterial Mupirocin on clinically uninfected AD, topical antibacterial acid solution on infected AD, Chinese herbs, hypnotherapy and biofeedback, massage therapy, dietary manipulation, ranitidine, house dust mite reduction, patient education, emollients, allergen antibody complexes of house dust mite, levamisole, immunoglobulin, interferon-gamma and thymic extracts. It is important to note that interferon-gamma and thymic extracts showed evidence of benefit but at a cost of untreatable flu-like symptoms with interferon-gamma and administration of thymic extracts via weekly injections that can be both costly and invasive
- There is no evidence of benefit in the treatment of AD with sedatory antihistamines, ketotifen, nedocromil sodium, oral sodium cromoglycate, tiacrilast, oral antibiotics on clinically uninfected AD, topical antibacterials, topical antifungals, bioresonance, aromatherapy essential oils, borage

oil, fish oil, evening primrose oil, vitamin and mineral supplementation, nitrazepam, papaverine, salbutamol, suplatast tosilate, theophylline, enzyme-free clothes detergent, cotton clothing, house dust mite hyposensitisation, salt baths, lithium succinate, topical coal tar, topical cyclosporin and platelet-activating-factor antagonist

Table 25 summarises the above findings with the number of trials given for each intervention. This is important to note because the majority of treatments that fall into the category of 'no evidence of benefit' have only 1 trial, generally of poor quality with which to prove their worth and it could be argued that basing a clinical decision on one poor quality RCT would not be evidence based. Indeed, this could also apply to the trials that appear in the categories 'limited evidence of benefit' and 'conflicting evidence of benefit'. The category of 'evidence of benefit' differs from the other categories because trials included are either high in numbers such as topical steroids (n=83), and/or well reported and good quality such as topical tacrolimus and have a clear clinical benefit to people with AD. Whether this evidence has the potential to change clinical practice is equivocal and I refer readers to books that have produced excellent chapters on the issues, and there are many, surrounding the implementation of evidence based findings[360]. However, one or two poignant comments made in these books are worth drawing on here: Effective health care strategies can often take years to catch on, even among the experts who should be at the cutting edge of practice[361], [362], and randomised controlled trials, even if assembled into a perfect systematic review, are just one of many different types of information that can inform decisions[363].

It is important to point out that lack of evidence does not equal lack of efficacy and this research cannot be taken in isolation of treatments that have not been subjected to RCTs. Because a systematic review is designed to identify which trials exist, another strategy was required to identify treatments that have not been subjected to RCTs. Clinicians working in the field of dermatology were contacted to help identify what treatments for AD are used in current practice that do not appear on the identified-RCT list in this thesis. No RCTs could be found that assess occlusive dressings, water softening devices and stress management. These and more are listed in Table 26. This is a way of highlighting gaps in research, which could help write the future research agenda.

The intervention with the highest number of trials is topical steroids and although we can deduce from the evidence available that they are effective in the treatment of AD, there is still no clear indication of how they should be used clinically, even though they remain the mainstay of treatment for AD[35], and, where less expensive alternatives such as bandages, coal tar and salt baths fit in to the treatment regimen. Cyclosporin A has been studied extensively highlighting its ability to suppress AD in severe cases but at a cost of potential toxicity, but it hasn't been compared to alternatives such as azathioprine, topical tacrolimus or oral steroids giving the impression that cyclosporine is more effective that its alternatives when what it really shows is that there is insufficient evidence to decide between them at present and comparative trials are needed. It was surprising to find that there is very limited data on emollient therapy particularly considering one study estimated 81% of total NHS prescribing costs is spent on children with AD in the community[41].

To go back to Chapter 1 and the rationale for a review of this kind, I referred to a champion of systematic reviews who said "Systematic reviews of research evidence are invaluable scientific activities. The rationale for such reviews is well established. Health care providers, researchers, and policy makers are inundated with unmanageable amounts of information; they need systematic reviews to efficiently integrate existing information and provide data for rational decision making"[364]. To the best of my knowledge, this is the first review of its kind worldwide, which could help clinicians gain an understanding of the treatment of atopic dermatitis from an evidence based perspective, albeit the early stages of the evidence-based process, needed to make clinical decisions about treatment of AD as long as it isn't taken in isolation of the fact that lack of evidence does not equal lack of efficacy. This review could also be used as the backbone of Cochrane Collaboration question-driven systematic reviews, several of which are under way including antihistamines for atopic eczema, Chinese herbal medicine for atopic eczema, emollients for atopic eczema and psychological interventions for atopic eczema in children[365]. This, added to the identified research gaps in Table 26, could be a useful tool towards the development of treatment and research recommendations for AD in the future.

There are, of course, limitations to carrying out a systematic review of this size, which attempts to cover all treatments of a condition. Furthermore, the systematic review methodology itself may be open to its own set of biases:

- Many of the data are from the 1970s and 1980s, before the rigour of evidence based medicine and peer review that is now in place in medical journals. This is reflected in the randomisation and blinding that is inconsistent across the studies reviewed leading to potential bias[366];
- Whether these trials apply to primary care, where most AD cases are seen, is not clear as the majority were carried out in secondary care settings;
- Data that is not in the public domain and/or held on electronic databases probably exist elsewhere.

To address the last point, pharmaceutical companies were written to asking for unpublished data but there was a poor response rate with only one new trial identified via this route; electronic databases have been shown to miss a proportion of trial reports although this is improving with better 'tagging' of entries into Medline[367]. As mentioned in Chapter 2 hand searching, that is, manually searching a journal page by page, has been identified by the Cochrane Collaboration as a way of locating missed studies via electronic database searching alone[43]. This is a huge task, which is currently being co-ordinated by the Cochrane Skin Group for the whole of dermatology. There are over 200 specialist dermatology journals worldwide to hand search, which is far beyond the scope of this review. Nevertheless, as journals were hand searched by the Cochrane Skin Group results were checked and missed trials located and included. It is possible that the electronic database searches used for this review were more sensitive than searches asking specific questions due to broad search terms used (Personal communication with Betsy Anagnostelis, Librarian and Search Advisor for the Systematic Reviews Training Unit in the UK). Indeed, when the results of this study were compared to hand searching of *Clinical and Experimental Dermatology* none had been missed.

Other systematic reviews have been published[126,368,369] one of which addressed Chinese herbal medicine for the treatment of AD[370]. It reported 2 RCTs of AD, missing another 2 that have been

included in this review[371], [372]. The authors concluded that 'At present it is unclear whether Chinese herbal treatments of eczema do more good than harm'.The other systematic reviews for AD studied prevention of AD via maternal antigen avoidance during lactation[368] and maternal antigen avoidance during pregnancy[369]. Prevention of AD was not covered in this review, which focused purely on treatments.

There are non-systematic reviews for AD treatments, which tend to focus on only one treatment or intervention. These reviews are either not treatments for atopic dermatitis or are reviews of single interventions such as Assman *et al* 2000[373] and Cheer *et al* 2001[374] which review topical tacrolimus in AD, and Prakash *et al* 1998[375], which reviews the potent topical corticosteroid, mometasone, for the treatment of AD.

It appears this is the first review of its kind assessing all treatments of atopic dermatitis and is the first step in the chain of events that could lead to evidence based treatment recommendations for AD. If this research is to be put to good use it needs to be kept up-to-date and broken down into individual questions and subjected to the Cochrane review process, of which several are already under way.

Table 25 Conclusions summary

No evidence of benefit	Limited evidence of benefit	Conflicting evidence of benefit	Evidence of benefit
• Antihistamines (sedatory) (n=5)	• Antihistamines (non-sedatory) (n=14)	• Topical disodium cromoglycate (n=10)	• Psychological approaches (n=3)
• Ketotifen (n=2)	• Topical doxepin (n=4)		• Ultraviolet light (n=7)
• Nedocromil sodium (n=3)	• Oral antibiotic Cefadroxil on infected AD (n=1)		• Ascomycin derivatives (n=4)
• Sodium cromoglycate (oral) (n=10)	• Topical antibacterial Mupirocin on clinically uninfected AD (n=1)		• Topical tacrolimus ointment (n=7)
• Tiacrilast (n=1)	• Topical antibacterial acid solution (n=1)		• Cyclosporin A (oral) (n=10)
• Oral antibiotics on clinically uninfected AD (n=2)	• Chinses herbs (n=4)		• Topical corticosteroids (n=83)
• Topical antibacterials (n=4)	• Hypnotherapy and biofeedback (n=1)		
• Topcial antifungals (n=1)	• Massage therapy (n=1)		
• Bioresonance (n=1)	• Dietary manipulation (n=9)		
• Aromatherapy essential oils (n=1)	• Ranitidine (n=1)		
• Borage oil (n=5)	• House dust mite reduction (n=8)		
• Fish oil (n=4)	• Patient education (n=1)		
• Evening Primrose Oil (n=14)	• Emollients (n=5)		
• Vitamins and minerals (n=5)	• Allergen antibody complexes of house dust mite (n=2)		
• Nitrazepam (n=1)	• Levamisole (n=1)		
• Papaverine (n=2)	• Immunoglobulin (n=1)		
• Salbutamol (n=1)	• Interferon-gamma (n=2)		
• Suplatast tosilate (n=1)	• Thymic extracts (n=8)		
• Theophylline (n=1)			
• Enzyme-free clothes detergent (n=1)			
• Cotton clothing (n=3)			
• House dust mite hyposensitisation			

(n=3)

- Salt baths (n=1)
- Lithium succinate (n=1)
- Topical coal tar (n=1)
- Topical cyclosporin (n=2)
- Platelet-activating factor antagonist (n=1)
- Transfer factor (n=1)

Table 26 Treatments in use by dermatologists for which no RCTs could be found at end of year 2000

Pharmacological	**Complementary therapies**	**Miscellaneous**
Antimetabolites such as methotrexate	Acupuncture	Antibacterial clothing
Cytotoxic immunosuppressants e.g. Mycophenolate mofetil	Calendula cream	Climatotherapy
Leukotrine receptor antagonists e.g. Montelukast*		Exercise
Oral azathioprine*		Extracorporeal photopheresis
Oral prednisolone*		Hospital admission
Thalidomide		Occlusive dressings
Type IV phosphodiesterase inhibitors		Organization of care
		Stress management
		Water softening devices
		Ways of improving adequate dosage/concordance
		Impregnated bandages
		Wet-wrap bandages

*on-going trials identified for these agents

REFERENCES

1. Coca AF, Cooke RA. On the classification of the phenomena of hypersensitiveness. J Immunol 1923; 8:163-82.

2. Ring J. Atopy: condition, disease or syndrome? Ruzicka T, Ring J, Przybilla B., Editors. Handbook of atopic eczema. Berlin: Springer-Verlag, 1991: 3-7.

3. Williams HC. Inflammatory skin diseases I: atopic dermatitis. Williams HC, Strachan DP., Editors. The Challenge of Dermato-epidemiology. Boca Raton: CRC Press, 1997: 125-44.

4. Diepgen TL, Fartasch M, Hornstein OP. Evaluation and relevance of atopic basic and minor features in patients with atopic dermatitis and in the general population. Acta Derm Venereol (Stockh) 1989; 144:50-4.

5. Archer CB. The pathophysiology and clinical features of atopic dermatitis. Williams HC., Editor. Atopic dermatitis: the epidemiology, causes and prevention of atopic eczema. UK: Cambridge University Press, 2000.

6. Holden CA, Parish WE. Atopic Dermatitis. Rook AJ WDEF, Editors. Textbook of Dermatology. 6th edition. Oxford: Blackwekk Scientific Publications, 1998.

7. Hanifin JM, Rajka G. Diagnostic features of atopic eczema. Acta Derm Venereol (Stockh) 1980; 92:44-7.

8. Williams HC, Burney PG, Pembroke AC, Hay RJ. The UK Working party's diagnostic criteria for atopic dermatitis. III independent hospital validation. British Journal of Dermatology 1994; 131(3):406-16.

9. Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. Br J Dermatol 1998; 139:73-6.

10. Kay J, Gawkrodger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. Journal of the American Academy of Dermatology 1994; 30(1):35-9.

11. Williams HC. Is the prevalence of atopic dermatitis increasing? Clin Exp Dermatol 1992; 17:385-91.

12. Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G., et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood. Journal of Allergy and Clinical Immunology 1999; 103(1 (Part 1)):125-38.

13. Schultz-Larsen F, Holm NV, Henningsen K. Atopic dermatitis. A genetic-epidemiological study in a population-based twin sample. J Am Acad Dermatol 1986; 15:487-94.

14. Savin JA. Atopy and its inheritance. British Medical Journal 1993; 307:1019-20.

15. Atherton DJ. Eczema in Childhood: the facts. UK: Oxford University Press, 1994.

16. Prinz JC, and Riebber EP. Regulation of IgE Synthesis. Ruzicka T, Ring J, and Przybilla B., Eds. Handbook of Atopic Eczema. Berlin, Heidelberg: Springer Verlag, 1991: 141-53.

17. Diepgen TL, Fartasch M. Recent epidemiological and genetic studies in atopic dermatitis. Acta Derm Venereol 1993; Suppl 176:13-8.

18. Dold S, Wjst M, Von Mutius E, Reitmeir P, Stiepel E. Genetic risk for asthma, allergic rhinitis and

atopic dermatitis. Archives of Disease in Childhood 1992; 67:1018-22.

19. Waite DA, Eyles EF, Tonkin SL, O'Donnell TV. Asthma prevalence in Tokelauan children in two environments. Clinical Allergy 1980; 10:71-5.

20. Worth RM. Atopic dermatitis among Chinese infants in Honolulu and San Francisco. Hawaiian Medical Journal 1962; 22:31-6.

21. Williams HC, Pembroke AC, Forsdyke H, Boodoo G, Hay RJ, Burney PGJ. London-born black caribbean children are at increased risk of atopic dermatitis. Journal of the American Academy of Dermatology. Vol 32(2 I) (Pp 212-217), 1995.

22. Williams HC, Strachan DP, Hay RJ. Childhood eczema: disease of the advantaged? Br Med J 1994; 308:1132-5.

23. Strachan DP. Hayfever, hygiene and household size. British Medical Journal 1989; 299:1259-60.

24. McNally N, Phillips D. Social factors and atopic dermatitis. Williams HC, Editor. Atopic Dermatitis. Cambridge: Cambridge University Press, 2000: 139-47.

25. Friedmann PS. Dust mite avoidance in atopic dermatitis. Clinical and Experimental Dermatology 1999; 24:433-7.

26. Lyon WF. Ohio State Universioty Extension Fact Sheet. Entomology: House Dust Mites [Web Page]. 2002; Available at www.ohioline.osu.edu/hyg-fact/2000/2157.html. (Accessed 2 January 1918).

27. Korsgaard J. Epidemiology of house-dust mites. Allergy 1998; 53((Suppl. 48)):36-40.

28. Heyer G, Ulmer FJ, Schmitz J, Handwerker HO. Histamine induced itch and alloknesis (itchy skin) in atopic eczema patients and controls. Acta Derm Venereol Stockh 1995; 75:348-52.

29. Murphy GF. Spongiotic dermatitis. Murphy GF, Editor. Dermatopathology: A Practical Guide to Common Disorders. Philadelphia: WB Saunders Company, 1995: 49-71.

30. Leung DYM. Atopic dermatitis: immunobiology and treatment with immune modulators. Clinical Experimental Immunology 1997; 107((Suppl. 1)):25-30.

31. Leung DYM. Atopic dermatitis: the skin as a window into the pathogenesis of chronic allergic diseases. Journal of Allergy and Clinical Immunology 1995; 96:302-19.

32. Abel EA, Farber EM. Atopic dermatitis, eczema, and ichthyosis. Scientific American Medicine 1994; 2(IV):1-9.

33. Hanifin J, Chan SC. Diagnosis and treatment of atopic dermatitis. Dermatol Ther 1996; 1:9-18.

34. Roitt I, Brostoff J MD. Immunology 4th ed. New York: Mosby, 1996.

35. McHenry P, Williams HC, Bingham EA. Managment of atopic eczema. Br Med J 1995; 310:843-7.

36. Lane AT. Efficacy and safety of topical steroids in paediatric atopic dermatitis. Journal of the European Academy of Dermatology and Venereology 1997; 8(Suppl. 1):S24-S27.

37. Anonymous. Introduction: New perspectives on emollient therapy. Journal of Dermatological Treatment 1997; 8(Suppl. 1):S1.

38. Charman C. Atopic eczema. Godlee F., Clinical EvidenceLondon: BMJ Publishing Group, 1999.

39. Hoare C, LiWanPo A, Williams H. Systematic review of treatments for atopic eczema. Heath Technology Assessment 2000; 4(37).

40. Herd RM, Tidman MJ, Prescott RJ, Hunter JAA. The Cost of Atopic Eczema. British Journal of Dermatology 1996; 135:20-3.

41. Emerson RM, Williams HC, Allen BR. What is the cost of atopic dermatitis in preschool children? British Journal of Dermatology 2001; 143:514-22.

42. Long CC, Funnell CM, Collard R, Finaly AY. What do members of the National Eczema Society really want? Clinical and Experimental Dermatology 1993; 18:516-22.

43. Delamere F., Trial Search Co-ordinator . The Cochrane Skin Group [Web Page]. October 2001; Available at http://www.nottingham.ac.uk/~muzd/dermjnls01.htm. (Accessed October 2001).

44. Clarke M, Oxman AD, editors. Cochrane Reviewers' Handbook. 4.0 edition1999.

45. Greenhalgh T. How to read a paper: the basics of evidence based medicine. London: BMJ Publishing Group, 1997.

46. Anonymous. Undertaking Systematic Reviews of Research on Effectiveness: CRD Guidelines for Those Carrying Out or Commissioning Reviews. CRD Report 4. York, UK: York Publishing Services Ltd, 1996.

47. Medline Electronic Database (1966-2000) [Web Page]. Available at http://www.bids.ac.uk/medline.

48. Embase Electronic Database (1980-2000) [Web Page]. Available at http://www.bids.ac.uk/embase.

49. Embase. Available at http://biomed.niss.ac.uk/ .

50. Cochrane Skin Group. Cochrane Skin Group Specialised Register [Web Page]. Available at http://www.nottingham.ac.uk/~muzd/.

51. Nghiem P. "Topical immunomodulators?": Introducing old friends and a new ally, tacrolimus. Journal of the American Academy of Dermatology 2001; 44 (1):111-3.

52. Thomas KS, Armstrong S, Avery A *et al.* Randomised controlled trial of short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children with mild or moderate atopic eczema. British Medical Journal 2002; 324:768-71.

53. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ 1994; 309:1286-91.

54. Godlee F (ed). Clinical Evidence: a compendium of the best available evidence for effective health care. London: BMJ Publishing Group, 1999.

55. ProCite Software. Version 4 editionResearch Information Systems, 1997.

56. Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. Controlled Clinical Trials 1995; 16:62-73.

57. Moher D, Cook DJ, Jadad AR, *et al.* Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses. Health Technol Assess 1999; 3((12)).

58. Berth-Jones J, Graham-Brown RA. Failure of terfenadine in relieving the pruritus of atopic

dermatitis [see comments]. British Journal of Dermatology 1989; 121(5):635-7.

59. Doherty V, Sylvester DG, Kennedy CT, Harvey SG, Calthrop JG, Gibson JR. Treatment of itching in atopic eczema with antihistamines with a low sedative profile. BMJ 1989; 298(6666):96.

60. Foulds IS, MacKie RM. A double-blind trial of the h2 receptor antagonist cimetidine, and the h1 receptor antagonist promethazine hydrochloride in the treatment of atopic dermatitis. Clinical Allergy 1981; 11(4):319-23.

61. Frosch PJ, Schwanitz HJ, Macher E. A double blind trial of h1 and h2 receptor antagonists in the treatment of atopic dermatitis. Archives of Dermatological Research 1984; 276(1):36-40.

62. Hamada T, Ishii M, Nakagawa K *et al.* Evaluation of the clinical effect of terfenadine in patients with atopic dermatitis. A comparison of strong corticosteroid therapy to mild topical corticosteroid combined with terfenadine administration therapy. Skin Research. 1996; Vol 38(1):97-103.

63. Hannuksela M, Kalimo K, Lammintausta K *et al.* Dose ranging study: cetirizine in the treatment of atopic dermatitis in adults. Annals of Allergy 1993; 70(2):127-33.

64. Henz BM, Metzenauer P, O'Keefe E, Zuberbier T. Differential effects of new-generation h1-receptor antagonists in pruritic dermatoses. Allergy 1998; 53(2):180-3.

65. Hjorth N. Terfenadine in the treatment of chronic idiopathic urticaria and atopic dermatitis. Cutis 1988; 42(4A):29-30.

66. Ishibashi Y, Ueda H, Niimura M *et al.* Clinical evaluation of E-0659 in atopic dermatitis in infants and children. Dose-finding multicenter study by the double-blind method. Skin Research. Vol 31(3) (Pp 458-471), 1989. 1989.

67. ISHIBASHI Yasumasa, TAMAKI Kunihiko, YOSHIDA Hikotaro *et al.* Clinical evaluation of E-0659 on atopic dermatitis. Multicenter double-blind study in comparison with ketotifen. Rinsho Hyoka (Clinical Evaluation) 1989; 17(1):77-115.

68. Klein GL, Galant SP. A comparison of the antipruritic efficacy of hydroxyzine and cyproheptadine in children with atopic dermatitis. Annals of Allergy 1980; 44(3):142-5.

69. Langeland T, Fagertun HE, Larsen S. Therapeutic effect of loratadine on pruritus in patients with atopic dermatitis. A multi-crossover-designed study. Allergy 1994; 49(1):22-6.

70. La Rosa M, Ranno C, Musarra I, Guglielmo F, Corrias A, Bellanti JA. Double-blind study of cetirizine in atopic eczema in children. Annals of Allergy 1994; 73(2):117-22.

71. Monroe EW. Relative efficacy and safety of loratadine, hydroxyzine, and placebo in chronic idiopathic urticaria and atopic dermatitis. Clinical Therapeutics 1992; 14(1):17-21.

72. Patel P, Gratton D, Eckstein G *et al.* A double-blind study of loratadine and cetirizine in atopic dermatitis. Journal of Dermatological Treatment 1997; 8(4):249-53.

73. Savin JA, Paterson WD, Adam K, Oswald I. Effects of trimeprazine and trimipramine on nocturnal scratching in patients with atopic eczema. Archives of Dermatology 1979; 115(3):313-5.

74. Savin JA, Dow R, Harlow BJ, Massey H, Yee KF. The effect of a new non-sedative h1-receptor antagonist (In2974) on the itching and scratching of patients with atopic eczema. Clinical & Experimental Dermatology 1986; 11(6):600-2.

75. Simons R Estelle F , Simons KJ, Becker AB, Haydey RP. Pharmacokinetics and antipruritic

effects of hydroxyzine in children with atopic dermatitis. Journal of Pediatrics 1984; 104(1):123-7.

76. Wahlgren CF, Hagermark O, Bergstrom R. The antipruritic effect of a sedative and a non-sedative antihistamine in atopic dermatitis. British Journal of Dermatology 1990; 122(4):545-51.

77. Zuluaga de Cadena A, Ochoa de V. A, Donado JH, Mejia JI, Chamah H. M, Montoya de Restrepo F. Estudio comparativo del efecto de la hidroxicina la terfenadina y el astemizol en ninos con dermatitis atopica: Hospital General de Medellin-Centro de Especialistas C.E.S. 1986-1988 / Comparative study of the effect of the hidroxicina the terfenadina and the astemizol in children with atopic demratitis: Hospital General de Medellin-Centro de Especialistas C.E.S. 1986-1988. CES-Med 1989; 3:7-13.

78. Drake LA, Fallon JD, Sober A. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. The doxepin study group. Journal of the American Academy of Dermatology 1994; 31(4):613-6.

79. Breneman DL, Dunlap FE, Monroe EW, Schupbach CW, Shmunes E, Phillips SB. Doxepin cream relieves eczema-associated pruritus within 15 minutes and is not accompanied by a risk of rebound upon discontinuation. Journal of Dermatological Treatment. Vol 8(3) (Pp 161-168), 1997. 1997.

80. Berberian BJ, Breneman DL, Drake LA *et al.* The addition of topical doxepin to corticosteroid therapy: an improved treatment regimen for atopic dermatitis. International Journal of Dermatology 1999; 38(2):145-8.

81. Drake LA, Cohen L, Gillies R *et al.* Pharmacokinetics of doxepin in subjects with pruritic atopic dermatitis. Journal of the American Academy of Dermatology 1999; 41(2 I):209-14.

82. Schmutzler W. Antihistamines. Ruzicka T, Ring J, Przybilla B, Eds. Handbook of Atopic Eczema. London: Springer-Verlag, 1991: 396-406.

83. Falk ES. Ketotifen in the treatment of atopic dermatitis. Results of a double blind study. Rivista Europea Per Le Scienze Mediche e Farmacologiche 1993; 15(2):63-6.

84. White MP, MacDonald TH, Garg RA. Ketotifen in the young asthmatic--a double-blind placebo-controlled trial. Journal of International Medical Research 1988; 16(2):107-13.

85. Kemmett D and Barneston RST. Topical nedocromil sodium: a double blind placebo controlled study in atopic dermatitis. British Journal of Dermatology 1987; 123(Suppl. 37):60.

86. Van Bever HP, Stevens WJ. Nedocromil sodium cream in the treatment of atopic dermatitis [letter]. European Journal of Pediatrics 1989; 149(1):74.

87. Benton EC, McFarlane HA, Barnetson RS. Trial of nedocromil sodium in atopic eczema. British Journal of Dermatology 1990; 122(6):817-20.

88. Businco L, Cantani A. Mast cell blockers and atopic eczema. Ruzicka T, Ring J, Przybilla B, Eds. Handbook of atopic eczema. London: Springer-Verlag, 1991.

89. Ventura A, De Seta L, Martelossi S *et al.* Soy allergy and dscg in atopic eczema: "much ado about nothing"?. Pediatria Medica e Chirurgica 1996; 18(3):283-8.

90. Kimata H, Igarashi M. Topical cromolyn (disodium cromoglycate) solution in the treatment of young children with atopic dermatitis [see comments]. Clinical & Experimental Allergy 1990; 20(3):281-3.

91. Larsen FS, Jacobsen KU. Atopic dermatitis and systemic treatment with a new chromone

compound (FPL 57787): a double blind clinical trial. Acta-Derm-Venereol-Suppl-Stockh 1980; Suppl. 92:128-9.

92. Haider-SA. Treatment of atopic eczema in children: clinical trial of 10% sodium cromoglycate ointment. Br-Med-J 1977; 1:1570-2.

93. Graham P, Hall-Smith SP, Harris JM, Price ML. A study of hypoallergenic diets and oral sodium cromoglycate in the management of atopic eczema. British Journal of Dermatology 1984; 110(4):457-67.

94. Moore C, Ehlayel MS, Junprasert J, Sorensen RU. Topical sodium cromoglycate in the treatment of moderate-to-severe atopic dermatitis. Annals of Allergy, Asthma, & Immunology 1998; 81(5 Pt 1):452-8.

95. Thirumoorthy T, Greaves MW. Disodium cromoglycate ointment in atopic eczema [letter]. British Medical Journal 1978; 2(6135):500-1.

96. Croner S, Fagerlund E, Kjellmann NIM, Leijon I. Sodium cromoglycate ointment in atopic eczema during childhood. Opuscula Medica. Vol 26(2)(Pp 49-50), 1981 1981.

97. Kimata H, Hiratsuka S. Effect of topical cromoglycate solution on atopic dermatitis: combined treatment of sodium cromoglycate solution with the oral anti-allergic medication, oxatomide. European Journal of Pediatrics 1994; 153(2):66-71.

98. Ariyanayagam M, Barlow TJ, Graham P, Hall-Smith SP, Harris JM. Topical sodium cromoglycate in the management of atopic eczema--a controlled trial. British Journal of Dermatology 1985; 112(3):343-8.

99. Atherton DJ, Soothill JF, Elvidge J. A controlled trial of oral sodium cromoglycate in atopic eczema. British Journal of Dermatology 1982; 106(6):681-5.

100. Kavli G, Larsen PO. Double-blind crossover trial comparing systemic chromosome-carboxylic acid with placebo in patients with atopic dermatitis. Allergy 1981; 36(8):597-600.

101. Businco-L, Benincori-N, Nini-G, Businco-E, Cantani-A, De-Angelis-M. Double-blind crossover trial with oral sodium cromoglycate in children with atopic dermatitis due to food allergy. Ann-Allergy 1986; 57:433-8.

102. Larsen PO, Larsen FS. Clinical trial of a new chromone compound for systemic treatment of atopic dermatitis. Acta Dermato-Venereologica 1979; 59(3):270-1.

103. Burks AW, Sampson HA. Double-blind placebo-controlled trial of oral cromolyn in children with atopic dermatitis and documented food hypersensitivity. Journal of Allergy & Clinical Immunology 1988; 81(2):417-23.

104. Birkeland SA, Larsen PO, Larsen FS. Subpopulations of lymphocytes and lymphocyte transformation tests in atopic dermatitis: evaluation of a systemic treatment with a new chromone compound and comparison with a normal group. Journal of Investigative Dermatology 1981; 76(5):367-70.

105. Kjellman NI, Gustafsson IM. Topical sodium cromoglycate in atopic dermatitis. A disappointing but informative trial. Allergy 1986; 41(6):423-8.

106. Lindskov R, Knudsen L. Oral disodium cromoglycate treatment of atopic dermatitis. Allergy 1983; 38(3):161-5.

107. Pike MG, Atherton DJ. Failure of a new topical sodium cromoglycate formulation to improve atopic dermatitis [letter]. European Journal of Pediatrics 1988; 148(2):170.

108. Hiratsuka S, Yoshida A, Ishioka C, Kimata H. Enhancement of in vitro spontaneous ige production by topical steroids in patients with atopic dermatitis. Journal of Allergy & Clinical Immunology 1996; 98(1):107-13.

109. Czarnetzki BM, Brechtel B, Braun-Falco O *et al.* Topical tiacrilast, a potent mast cell degranulation inhibitor, does not improve adult atopic eczema. Dermatology 1993; 187(2):112-4.

110. Hobbs FDR. Managing *Staphylococcus Aureus* in Eczema. UK: Round Table Series, 1999; 61.

111. Hoare C. Infection and Eczema. Exchange 2001; 102(September):34-5.

112. Salo OP, Gordin A, Brandt H, Antikainen R. Efficacy and tolerability of erythromycin acistrate and erythromycin stearate in acute skin infections of patients with atopic eczema. Journal of Antimicrobial Chemotherapy. 1988; 21 suppl D(101-6).

113. Weinberg E, Fourie B, Allmann B, Toerien A. The use of cefadroxil in superinfected atopic dermatitis. CURR THER RES CLIN EXP 1992; 52(5):671-6.

114. Ewing CI, Ashcroft C, Gibbs AC, Jones GA, Connor PJ, David TJ. Flucloxacillin in the treatment of atopic dermatitis. British Journal of Dermatology 1998; 138(6):1022-9.

115. Lever R, Hadley K, Downey D, Mackie R. Staphylococcal colonization in atopic dermatitis and the effect of topical mupirocin therapy. British Journal of Dermatology 1988; 119(2):189-98.

116. Stalder JF, Fleury M, Sourisse M *et al.* Comparative effects of two topical antiseptics (chlorhexidine vs kmn04) on bacterial skin flora in atopic dermatitis. Acta Dermato-Venereologica. 1992; Suppl Issue 176:132-4.

117. Sasai-Takedatsu M, Kojima T, Yamamoto A *et al.* Reduction of staphylococcus aureus in atopic skin lesions with acid electrolytic water--a new therapeutic strategy for atopic dermatitis. Allergy 1997; 52(10):1012-6.

118. Harper J. Double-blind comparison of an antiseptic oil-based bath additive (Oilatum Plus) with regular Oilatum (Oilatum Emollient) for the treatment of atopic eczema. Lever R and Levy J, Editors. The Bacteriology of Eczema. UK: The Royal Society of Medicine Press Limited, 1995.

119. Holland KT BRaCW. A comparison of the effect of treatment of atopic eczema with and without antimicrobial compounds. Lever R and Levy J , Editors. The Bacteriology of Eczema. UK: The Royal Society of Medicine Press Limited, 1995.

120. Hizawa T, Sano H, Endo K, Fukuzumi T, Kataoka Y, Aoki T. Is povidone-iodine effective to the lesions of atopic dermatitis? Skin Research 1998; 40(SUPPL. 20):134-9.

121. Broberg A, Faergemann J. Topical antimycotic treatment of atopic dermatitis in the head/neck area. A double-blind randomised study. Acta Dermato-Venereologica 1995; 75(1):46-9.

122. Zollman C, Vickers A. ABS of complementary medicine: what is complementary medicine? British Medical Journal 1999; 319:693-6.

123. Anderson C. Lis Balchin M. The effect of aromatherapy on childhood atopic eczema (presented at the 5th Annual Symposium on Complementary Healthcare, 10-12 December 1998, Exeter). FACT: Focus on Alternative and Complementary Therapies 1998; 3:189.

124. Schoni MH, Nikolaizik WH, Schoni-Affolter F. Efficacy trial of bioresonance in children with atopic dermatitis. International Archives of Allergy & Immunology 1997; 112(3):238-46.

125. Xu X-J, Banerjee P, Rustin MHA, Poulter LW. Modulation by Chinese herbal therapy of immune mechanisma in the skin of patients with atopic eczema. British Journal of Dermatology 1997; 136:54-9.

126. Armstrong NC, Ernst E. The treatment of eczema with Chinese herbs: a systematic review of randomised clinical trials. British Journal Clinical Pharmacology 1999; 48:262-4.

127. Sheehan MP, Atherton DJ. A controlled trial of traditional chinese medicinal plants in widespread non-exudative atopic eczema. British Journal of Dermatology 1992; 126(2):179-84.

128. Sheehan MP, Rustin MH, Atherton DJ *et al.* Efficacy of traditional chinese herbal therapy in adult atopic dermatitis [published erratum appears in lancet 1992 jul 18;340(8812):188] [see comments]. Lancet 1992; 340(8810):13-7.

129. Sheehan MP, Rustin MH, Atherton DJ *et al.* Efficacy of traditional chinese herbal therapy in adult atopic dermatitis [published erratum appears in lancet 1992 jul 18;340(8812):188] [see comments]. Lancet 1992; 340(8810):13-7.

130. Fung AY, Look PC, Chong LY, But PP, Wong E. A controlled trial of traditional Chinese herbal medicine in Chinese patients with recalcitrant atopic dermatitis. International Journal of Dermatology 1999; 38(5):387-92.

131. Latchman Y, Banerjee P, Poulter LW, Rustin M, Brostoff J. Association of immunological changes with clinical efficacy in atopic eczema patients treated with traditional chinese herbal therapy (zemaphyte). International Archives of Allergy & Immunology 1996; 109(3):243-9.

132. Sheehan MP, Atherton DJ. One year follow-up of children treated with Chinese medicinal herbs for atopic eczema. British Journal of Dermatology 1994; 130:488-93.

133. Sokel B, Kent CA, Lansdown R, Atherton D, Glover M, Knibbs J. A comparison of hypnotherapy and biofeedback in the treatment of childhood atopic eczema. Contemp Hypnosis 1993; 10(3).

134. David TJ, Patel L, Ewing CI, Stanton RHJ. Dietary factors in established atopic dermatitis. Williams HC, Editor. Atopic Dermatitis. UK: Cambridge University Press, 2000: 193-201.

135. Atherton DJ, Sewell M, Soothill JF, Wells RS, Chilvers CE. A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. Lancet 1978; 1(8061):401-3.

136. Munkvad M, Danielsen L, Hoj L *et al.* Antigen-free diet in adult patients with atopic dermatitis. A double-blind controlled study. Acta Dermato-Venereologica 1984; 64(6):524-8.

137. Cant AJ, Bailes JA, Marsden RA, Hewitt D. Effect of maternal dietary exclusion on breast fed infants with eczema: two controlled studies. British Medical Journal Clinical Research Ed. 1986; 293(6541):231-3.

138. Neild VS, Marsden RA, Bailes JA, Bland JM. Egg and milk exclusion diets in atopic eczema. British Journal of Dermatology 1986; 114(1):117-23.

139. Mabin DC, Sykes AE, David TJ. Controlled trial of a few foods diet in severe atopic dermatitis. Archives of Disease in Childhood 1995; 73(3):202-7.

140. Isolauri EMD, Sutas YMD, Makinen-Kiljunen SMSc, Oja Simo S MD, Isosomppi RMSc, Turjanmaa KMD. Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy. Journal of Pediatrics 1995; 127(4):550-7.

141. Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology 1997; 195:10-9.

142. Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. Journal of Allergy & Clinical Immunology 1997; 99(2):179-85.

143. Lever R, MacDonald C, Waugh P, Aitchison T. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. Pediatric Allergy & Immunology 1998; 9(1):13-9.

144. Ferreira MJ, Fiadeiro T, Silva M, Soares AP. Electrical conductance: A controversial parameter in the evaluation of emollients in atopic dermatitis. Skin Research & Technology. Vol 4(3) (Pp 138-141), 1998 1998.

145. Ferreira MJ, Fiadeiro T, Silva M, Soares AP. Topical gamma-linolenic acid therapy in atopic dermatitis. A clinical and biometric evaluation. Allergo Journal. Vol 7(4) (Pp 213-216), 1998 1998.

146. Henz BM et al. Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema. British Journal of Dermatology 1999; 140:685-8.

147. Costa C, Rilliet A, Nicolet M, Saurat JH. Scoring atopic dermatitis: the simpler the better? Acta Dermato Venereologica (Stockh) 1989; 69:41-5.

148. Borrek S. Hildebrandt A. Forster J. Gamma-linolenic-acid-rich borage seed oil capsules in children with atopic dermatitis. A placebo-controlled double-blind study. Klinische Padiatrie 1997; 209(3):100-4.

149. Buslau M, Thaci D. Atopic dermatitis: Borage oil for systemic therapy. Zeitschrift Fur Dermatologie. 1996; 182(3):131-2+134-136.

150. Bahmer FA. ADASI Score: Atopic Dermatitis Area and Severity Index. Acta Dermato Venereology (Stockh) 1992; Suppl. 176:32-3.

151. Valsecchi R, Di Landro A, Pansera B, Reseghetti A. Gammalinolenic acid in the treatment of atopic dermatitis [1]. Journal of the European Academy of Dermatology & Venereology. 1996; Vol 7(1):77-9.

152. Bahmer FA, Schafer J. [Treatment of atopic dermatitis with borage seed oil (glandol)--a time series analytic study]. [German]. Kinderarztliche Praxis 1992; 60(7):199-202.

153. Gimenez-Arnau A, Barranco C, Alberola M *et al.* Effects of linoleic acid supplements on atopic dermatitis. Advances in Experimental Medicine & Biology. 1997; 433:285-9.

154. Berkow SG. A method of estimating the extensiveness of lesions (burns and scalds) based on surface area proportions. Archives of Surgery 1924; 8:138-48.

155. Rajka G, Langeland T. Grading of the severity of atopic dermatitis. Acta Dermato Venereologica 1989; Suppl. 144:13-4.

156. Soyland E, Funk J, Rajka G *et al.* Dietary supplementation with very long-chain n-3 fatty acids in patients with atopic dermatitis. A double-blind, multicentre study. British Journal of Dermatology 1994; 130(6):757-64.

157. Bjorneboe A, Soyland E, Bjorneboe GE, Rajka G, Drevon CA. Effect of n-3 fatty acid supplement to patients with atopic dermatitis. Journal of Internal Medicine. Supplement 1989; 225(731):233-6.

158. Bjorneboe A, Soyland E, Bjorneboe G-EA, Rajka G, Drevon CA. Effect of dietary supplementation with eicosapentaenoic acid in the treatment of atopic dermatitis. British Journal of Dermatology. Vol 117(4) (Pp 463-469), 1987. 1987.

159. Hederos CA, Berg A. Epogam evening primrose oil treatment in atopic dermatitis and asthma. Archives of Disease in Childhood 1996; 75(6):494-7.

160. Biagi PL, Bordoni A, Hrelia S *et al.* The effect of gamma-linolenic acid on clinical status, red cell fatty acid composition and membrane microviscosity in infants with atopic dermatitis. Drugs Under Experimental & Clinical Research 1994; 20(2):77-84.

161. Humphreys F, Symons JA, Brown HK, Duff GW, Hunter JAA. The effects of gamolenic acid on adult atopic eczema and premenstrual exacerbation of eczema. European Journal of Dermatology. Vol 4(8) (Pp 598-603), 1994. 1994.

162. Berth-Jones J, Graham-Brown R A C. Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. Lancet 1993; 341(8860):1557-60.

163. Berth-Jones J, Graham-Brown RAC. Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. Lancet 1993; 341:1557-60.

164. Bordoni A, Biagi PL, Masi M *et al.* Evening primrose oil (efamol) in the treatment of children with atopic eczema. Drugs Under Experimental & Clinical Research 1987; 14(4):291-7.

165. Schalin-Karrila M, Mattila L, Jansen CT, Uotila P. Evening primrose oil in the treatment of atopic eczema: effect on clinical status, plasma phospholipid fatty acids and circulating blood prostaglandins. British Journal of Dermatology 1987; 117(1):11-9.

166. Bamford JT, Gibson RW, Renier CM. Atopic eczema unresponsive to evening primrose oil (linoleic and gamma-linolenic acids). Journal of the American Academy of Dermatology 1985; 13(6):959-65.

167. Wright S. Atopic dermatitis and essential fatty acids: a biochemical basis for atopy? Acta Derm Venereol (Stockh) 1985; Suppl. 114:143-5.

168. Wright S, Burton JL. Oral evening-primrose-seed oil improves atopic eczema. Lancet 1982; 2(8308):1120-2.

169. Lovell CR, Burton JL, Horrobin DF. Treatment of atopic eczema with evening primrose oil [letter]. Lancet 1981; 1(8214):278.

170. Gehring W, Bopp R, Rippke F, Gloor M. Effect of topically applied evening primrose oil on epidermal barrier function in atopic dermatitis as a function of vehicle. Arzneimittel-Forschung 1999; 49(7):635-42.

171. Anstey A, Quigley M, Wilkinson JD. Topical evening primrose oil as treatment for atopic eczema. Journal of Dermatological Treatment. Vol 1(4) (Pp 199-201), 1990. 1990.

172. Mabin DC, Hollis S, Lockwood J, David TJ. Pyridoxine in atopic dermatitis. British Journal of Dermatology 1995; 133(5):764-7.

173. Fairris GM, Perkins PJ, Lloyd B, Hinks L, Clayton BE. The effect on atopic dermatitis of supplementation with selenium and vitamin e. Acta Dermato-Venereologica 1989; 69(4):359-62.

174. Hakakawa R, Ogino Y. Effects of combination therapy with vitamins e and b2 on skin diseases. Doudle blind controlled clinical trial. Skin Research. Vol 31(6) (Pp 856-881), 1989. 1991.

175. Ewing CI, Gibbs AC, Ashcroft C, David TJ. Failure of oral zinc supplementation in atopic eczema. European Journal of Clinical Nutrition 1991; 45(10):507-10.

176. Ebata T, Izumi H, Aizawa H, Kamide R, Niimura M. Effects of nitrazepam on nocturnal scratching in adults with atopic dermatitis: a double-blind placebo-controlled crossover study. British Journal of Dermatology 1998; 138(4):631-4.

177. Ebata T, Izumi H, Aizawa H, Kamide R, Niimura M. Effects of nitrazepam on nocturnal scratching in adults with atopic dermatitis: a double-blind placebo-controlled crossover study. British Journal of Dermatology 1998; 138(4):631-4.

178. Berth-Jones J, Graham-Brown RA. Failure of papaverine to reduce pruritus in atopic dermatitis: a double-blind, placebo-controlled cross-over study. British Journal of Dermatology 1990; 122(4):553-7.

179. Shupack J, Stiller M, Meola T Jr, Orbuch P. Papaverine hydrochloride in the treatment of atopic dermatitis: a double-blind, placebo-controlled crossover clinical trial to reassess safety and efficacy. Dermatologica 1991; 183(1):21-4.

180. Veien NK, Kaaber K, Larsen PO, Nielsen AO, Thestrup-Pedersen K. Ranitidine treatment of hand eczema in patients with atopic dermatitis: a double-blind, placebo-controlled trial. Journal of the American Academy of Dermatology 1995; 32(6):1056-7.

181. Archer CB, MacDonald DM. Treatment of atopic dermatitis with salbutamol. Clinical & Experimental Dermatology 1987; 12(5):323-5.

182. Kimata H. Selective enhancement of production of IgE, IgG4, and Th2-cell cytokine during the rebound phenomenon in atopic dermatitis and prevention by suplatast tosilate. Annals of Allergy 1999; 82(3):293-5.

183. Ruzicka T. Effect of theophylline in atopic dermatitis: a double-blind cross-over study. Archives of Dermatological Research 1980; 269(1):109-10.

184. Rothe MJ, Grant-Kels JM. Diagnostic criteria for atopic dermatitis. Lancet 1996; 348:1391-2.

185. Andersen PH, Bindslev-Jensen C, Mosbech H, Zachariae H, Andersen KE. Skin symptoms in patients with atopic dermatitis using enzyme-containing detergents. A placebo-controlled study. Acta Dermato-Venereologica 1998; 78(1):60-2.

186. Diepgen TL, Stabler A, Hornstein OP. Irritation from textiles in atopic eczema and controls. Textile intolerance in Atopic Eczema: a controlled clinical study. Zeitschrift Fur Hautkrankheiten. 1990; 65(10):907-10.

187. Diepgen TL SBTAHO. A study of skin irritations by textiles under standardized sweating conditions in patients with atopic eczema. Melliand English 1995; 12:268.

188. Seymour JL, Keswick BH, Hanifin JM, Jordan WP, Milligan MC. Clinical effects of diaper types on the skin of normal infants and infants with atopic dermatitis. Journal of the American Academy of Dermatology 1987; 17(6):988-97.

189. Glover MT, Atherton DJ. A double-blind controlled trial of hyposensitization to dermatophagoides pteronyssinus in children with atopic eczema. Clinical & Experimental Allergy 1992; 22(4):440-6.

190. Galli E, Chini L, Nardi S *et al.* Use of a specific oral hyposensitization therapy to dermatophagoides pteronyssinus in children with atopic dermatitis. Allergologia Et Immunopathologia 1994; 22(1):18-22.

191. Wen T, Wang E, Shen S *et al.* Allergenic potency of smu-df extract in comparison with vus-df extract; and diagnosis and immunotherapy for atopic dermatitis and rhinitis with smu-df extract in china. Arbeiten Aus Dem Paul Ehrlich Institut - Bundesamt Fur Sera Und Impfstoffe - Zu Frankfurt Am 1992; (85):217-27.

192. Friedmann PS TBB. Mite Elimination - clinical effect on eczema. Allergy 1998; 53 ((Suppl. 48)):97-100.

193. Colloff MJ, Lever RS, McSharry C. A controlled trial of house dust mite eradication using natamycin in homes of patients with atopic dermatitis: effect on clinical status and mite populations [see comments]. British Journal of Dermatology 1989; 121(2):199-208.

194. Tan BB, Weald Dawn, Strickland Ian, Friedmann PS. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. Lancet 1996; 347(8993):15-8.

195. Endo K, Fukuzumi T, Adachi J *et al.* [Effect of vacuum cleaning of room floors and bed clothes of patients on house dust mites counts and clinical scores of atopic dermatitis. A double blind control trial]. [Japanese]. Arerugi - Japanese Journal of Allergology 1997; 46(10):1013-24.

196. Nishioka K, Yasueda H, Saito H. Preventive effect of bedding encasement with microfine fibers on mite sensitization. Journal of Allergy & Clinical Immunology 1998; 101(1 Pt 1):28-32.

197. Mitchell T, Paige D, Spowart K. Eczema and Your Child: A Parent's Guide. London: Class publishing, 1998.

198. Broberg A, Kalimo K, Lindblad B, Swanbeck G. Parental education in the treatment of childhood atopic eczema. Acta Dermato-Venereologica 1990; 70(6):495-9.

199. Papadoulos L, Bor R. Psychological Approaches to Dermatology. UK: The British Psychological Society, 1999.

200. Bridgett C, Noren P, Staughton R. Atopic Skin Disease: a manual for practitioners. UK: Wrightson Biomedical, 1996.

201. Hoare C. Psychological aspects of atopic eczema. Journal of Community Nursing 2001; 15(7):38-40.

202. Melin L, Frederiksen T, Noren P, Swebilius BG. Behavioural treatment of scratching in patients with atopic dermatitis. British Journal of Dermatology 1986; 115(4):467-74.

203. Noren P, Melin L. The effect of combined topical steroids and habit-reversal treatment in patients with atopic dermatitis. British Journal of Dermatology 1989; 121(3):359-66.

204. Ehlers A, Stangier U, Gieler U. Treatment of atopic dermatitis: a comparison of psychological and dermatological approaches to relapse prevention. Journal of Consulting & Clinical Psychology 1995; 63(4):624-35.

205. Gibbons S. Living with Psoriasis. UK: Harper Collins, 1992.

206. Adachi J, Sumitsuzi H, Endo K, Fukuzumi T, Aoki T. [Evaluation of the effect of short-term application of deep sea water on atopic dermatitis]. [Japanese]. Arerugi - Japanese Journal of Allergology 1998; 47(1):57-60.

207. Morison WL. Ultraviolet radiation therapy of atopic eczema. Ruzicka T, Ring J, Przybilla B., Editors. Handbook of Atopic Eczema. London: Springer-Verlag, 1991: 452-7.

208. Ruzicka T, Ring J, Przybilla B. Therapy of atopic eczema: synopsis. Ruzicka T, Ring J, Przybilla B., Editors. Handbook of Atopic Eczema. London: Springer-Verlag, 1991: 466-70.

209. Diffey BL. Human exposure to ultraviolet light. Semin Dermatol 1990; 9(1):2-10.

210. Sheehan-Dare RA, Goodfield MJ, Rowell NR. Topical psoralen photochemotherapy (PUVA) and superficial radiotherapy in the treatment of chronic hand eczema. British Journal of Dermatology 1989; 121:65-9.

211. Der-Petrossian M, Seeber A, Honigsmann H, Tanew A. Half-side comparison study on the efficacy of 8-methoxypsoralen bath- PUVA versus narrow-band ultraviolet B phototherapy in patients with severe chronic atopic dermatitis. British Journal of Dermatology 2000; 142(1):39-43.

212. Reynolds NJ FVGJDBaFP. Effectiveness of narrow-band UVB (TL01) compared to UVA in adult atopic eczema: a randomised controlled trial. British Journal of Dermatology 1999; 141 (suppl 55):20.

213. Krutmann J, Diepgen TL, Luger TA *et al.* High-dose uva1 therapy for atopic dermatitis: results of a multicenter trial. Journal of the American Academy of Dermatology 1998; 38(4):589-93.

214. Jekler J. Phototherapy of atopic dermatitis with ultraviolet radiation. Acta Dermato-Venereologica. Supplementum. 1992; 171:1-37.

215. Krutmann J, Czech W, Diepgen T, Niedner R, Kapp A, Schopf E. High-dose uva1 therapy in the treatment of patients with atopic dermatitis. Journal of the American Academy of Dermatology 1992; 26(2 Pt 1):225-30.

216. Jekler J, Larko O. Uva solarium versus uvb phototherapy of atopic dermatitis: a paired-comparison study. British Journal of Dermatology 1991; 125(6):569-72.

217. Jekler J, Larko O. Uvb phototherapy of atopic dermatitis. British Journal of Dermatology 1988; 119(6):697-705.

218. Van Leent EJ, Graber M, Thurston M, Wagenaar A, Spuls PI, Bos JD. Effectiveness of the ascomycin macrolactam SDZ ASM 981 in the topical treatment of atopic dermatitis. Archives of Dermatology 1998; 134(7):805-9.

219. Eichenfield LF, Lucky AW, Boguniewicz M *et al.* Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. Journal of the American Academy 2002; 46(4):495-504.

220. Luger T, Van Leent EJM, Graeber M *et al.* SDZ ASM 981: an emerging safe and effective treatment for atopic dermatitis. British Journal of Dermatology 2001; 144:788-94.

221. Van Leent EJM, Graber M, Thurston M, Wagenaar A, Spuls PI, and Bos JD. Effectiveness of the ascomycin macrolactam SDZ ASM 981 in the topical treatment of atopic dermatitis. Archives of Dermatology 1998; 134:805-9.

222. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Experimental Dermatology 2001; 10:11-8.

223. Cork MJ. Complete Emollient Therapy. The National Association of Fundholding Practices year book. London: Scorpio, 1998.

224. Kantor I, Milbauer J, Posner M, Weinstock IM, Simon A, Thormahlen S. Efficacy and safety of emollients as adjunctive agents in topical corticosteroid therapy for atopic dermatitis. TODAY'S THER. TRENDS 1993; 11:157-66.

225. Hanifin JM, Hebert AA, Mays SR *et al.* Effects of a low-potency corticosteroid lotion plus a

moisturizing regimen in the treatment of atopic dermatitis. Current Therapeutic Research, Clinical & Experimental. Vol 59(4) (Pp 227-233), 1998. 1998.

226. Wilhelm KP, Scholermann A. Efficacy and tolerability of a topical preparation containing 10% urea in patients with atopic dermatitis. Aktuelle Dermatologie. 1998; Vol 24(1-2):26-30.

227. Andersson AC, Lindberg M, Loden M. The effect of two urea-containing creams on dry, eczematous skin in atopic patients. I. Expert, patient and instrumental evaluation. Journal of Dermatological Treatment 1999; 10(3):165-9.

228. Larregue M, Devaux J, Audebert C, Gelmetti DR. A double-blind controlled study on the efficacy and tolerability of 6% ammonium lactate cream in children with atopic dermatitis. Nouvelles Dermatologiques. Vol 15(10) (Pp 720-721), 1996. 1996.

229. Anonymous. British National Formulary 42. London: BMA, 2001.

230. Anstey A, Wilkinson JD. Lithium succinate ointment in the treatment of atopic eczema[1]. Journal of Dermatological Treatment. 1991; 2(1):37-8.

231. Ruzicka T, Assmann T, Homey B. Tacrolimus: the drug for the turn of the millennium? Archives of Dermatology 1999; 135:574-80.

232. Cheer SM, Plosker GL. Tacrolimus ointment: a review of its therapeutic potential as a topical therapy in atopic dermatitis. American Journal of Clinical Dermatology 2001; 2(6):389-406.

233. Hanifin JM, Ling MR, Langley R, Breneman D, Rafal E, and the Tacrolimus Ointment Study Group. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: Part I, Efficacy. Journal of the American Academy of Dermatology 2001; 44(1):S28-S38.

234. Paller A, Eichenfield LF, Leung DYM, Stewart D, Appell M, and the Tacrolimus Ointment Study Group. A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. The Journal of the American Academy of Dermatology 2001; 44(1):S47-S57.

235. Reitamo S, Van Leent EJM, Ho V *et al.* Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. The Journal of Allergy and Clinical Immunology 2002; 109(3):539-46.

236. Reitamo S, Rustin M, Ruzicka T *et al.* Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. The Journal of Allergy and Clinical Immunology 2002; 109(3):547-55.

237. Boguniewicz M, Fielder VC, Raimer S, Lawrence ID, Leung DYM, Hanifin JM. The Journal of Allergy and Clinical Immunology 1998; 102(4 (1)):637-44.

238. Ruzicka T, Bieber T, Schopf E *et al.* A short-term trial of tacrolimus ointment for atopic dermatitis. The New England Journal of Medicine 1997; 337:816-21.

239. Niordson AM, Stahl D. Treatment of psoriasis with clinitar cream. A controlled clinical trial. British Journal of Clinical Practice 1985; 39(2):67-8.

240. van Schooten FJ, Moonen EJC, Rhijnsburger E, van Agen, Thijssen HHW, Kleinjans JCS. Dermal updake of polycyclic aromatic hydrocarbons after hairwash with coal-tar shampoo. Lancet 1994; 344:1504-5.

241. Leroy BP, Boden G, Jacquemin MG, Lachapelle JM, Saint-Remy JMR. Allergen-antibody complexes in the treatment of atopic dermatitis: preliminary results of a double-blind placebo-controlled study. Acta Dermato-Venereologica. 1992; Supplementum. Issue

176:129-31.

242. Leroy BP, Boden G, Lachapelle JM, Jacquemin MG, Saint-Remy JM. A novel therapy for atopic dermatitis with allergen-antibody complexes: a double-blind, placebo-controlled study. Journal of the American Academy of Dermatology 1993; 28(2 Pt 1):232-9.

243. De Rie MA, Meinardi MM, Bos JD. Lack of efficacy of topical cyclosporin a in atopic dermatitis and allergic contact dermatitis. Acta Dermato-Venereologica 1991; 71(5):452-4.

244. De Prost Y, Bodemer C, Teillac D. Randomised double-blind placebo-controlled trial of local cyclosporin in atopic dermatitis. Acta Dermato-Venereologica. Supplementum. Vol 69(144) (Pp 136-138), 1989. 1989; 69(144):136-8.

245. Harper JI, Ahmed I, Barclay G *et al.* Cyclosporin for severe childhood atopic dermatitis: Short course versus continuous therapy. British Journal of Dermatology 2000; 142(1):52-8.

246. Berth-Jones FA. Six area, six sign, atopic dermatitis (SASSAD) severity score: a simple system for monitoring disease activity in atopic dermatitis. British Journal of Dermatology 1996; 135(Suppl. 48):25-30.

247. Cordero Miranda MA, Flores Sandoval G, Orea Solano M, Estrada Parra S, Serrano Miranda E. [Safety and efficacy of treatment for severe atopic dermatitis with cyclosporin A and transfer factor]. [Spanish]. Revista Alergia Mexico 1999; 46(2):49-57.

248. Zurbriggen B, Wuthrich B, Cachelin AB, Wili PB, Kagi MK. Comparison of two formulations of cyclosporin A in the treatment of severe atopic dermatitis. Aa double-blind, single-centre, cross-over pilot study. Dermatology 1999; 198(1):56-60.

249. Sowden JM, Berth-Jones J, Ross JS *et al.* Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis [see comments]. Lancet 1991; 338(8760):137-40.

250. Zonneveld-IM, De-Rie-MA, Beljaards-RC *et al.* The long-term safety and efficacy of cyclosporin in severe refractory atopic dermatitis: a comparison of two dosage regimens. Br-J-Dermatol 1996; 15-20.

251. Munro CS, Levell NJ, Shuster S, Friedmann PS. Maintenance treatment with cyclosporin in atopic eczema. British Journal of Dermatology 1994; 130(3):376-80.

252. van Joost T, Heule F, Korstanje M, van den Broek MJ, Stenveld HJ, van Vloten WA. Cyclosporin in atopic dermatitis: a multicentre placebo-controlled study. British Journal of Dermatology 1994; 130(5):634-40.

253. Salek MS, Finlay AY, Luscombe DK *et al.* Cyclosporin greatly improves the quality of life of adults with severe atopic dermatitis. A randomized, double-blind, placebo-controlled trial. British Journal of Dermatology 1993; 129(4):422-30.

254. Finlay AY, Khan GK, Luscombe DK, *et al.* Validation of sickness impact profile and psoriasis disability index in psoriasis. British Journal of Dermatology 1990; 123:751-6.

255. Allen BR. A multicentre double blind placebo controlled crossover to assess the efficacy and safety of cyclosporin A in adult patients with severe refractory atopic dermatitis. Wolff K (Ed) Cyclosporin A and the Skin: Proceedings, Satellite Symposium to the 2nd Congress of the European Academy of Dermatology and Venereology, Athens Greece, 12 October 1991 (International Congress and Symposium Series, No. 192) London: Royal Society of Medicine Services Ltd. 1992, P. 29-37 1991.

256. Wahlgren CF, Scheynius A, Hagermark O. Antipruritic effect of oral cyclosporin a in atopic

dermatitis. Acta Dermato-Venereologica 1990; 70(4):323-9.

257. White CR, Hanifin JM. Levamisole therapy in atopic dermatitis: randomized double-blind evaluation. Archives of Dermatology 1978; 114(9):1314-5.

258. Abeck D, Andersson T, Grosshans E *et al.* Topical application of a platelet-activating factor (paf) antagonist in atopic dermatitis. Acta Dermato-Venereologica 1997; 77(6):449-51.

259. Hanifin JM, Schneider LC, Leung DY *et al.* Recombinant interferon gamma therapy for atopic dermatitis. Journal of the American Academy of Dermatology 1993; 28(2 Pt 1):189-97.

260. Jang I, Yang J, Lee H *et al.* Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. Journal of the American Academy of Dermatology 2000; 42(6):1033-40.

261. Fiocchi A, Grasso U, Rottoli A *et al.* A double blind clinical trial on the effectiveness of a thymic derivative (thymomodulin) in the treatment of children with atopic dermatitis. International Journal of Immunotherapy. 1987; Vol 3((4)):279-84.

262. Cavagni G, Piscopo E, Rigoli E, Iuliano P, Bertolini P, Cazzola P. "Food allergy in children: an attempt to improve the effects of the elimination diet with an immunomodulating agent (thymomodulin). A double-blind clinical trial". Immunopharmacology & Immunotoxicology 1989; 11(1):131-42.

263. Staughton RCD, Byrom NA, Nagvekar NM, et al. A double-blind cross-over trial of thymostimulin in atopic eczema. British Journal of Dermatology. Vol 109(Suppl.), 1983. 1983; 38.

264. Harper JI, Mason UA, White TR, Staughton RC, Hobbs JR. A double-blind placebo-controlled study of thymostimulin (tp-1) for the treatment of atopic eczema. British Journal of Dermatology 1991; 125(4):368-72.

265. Kang K, Cooper KD, Hanifin JM. Thymopoietin pentapeptide (tp-5) improves clinical parameters and lymphocyte subpopulations in atopic dermatitis. Journal of the American Academy of Dermatology 1983; 8(3):372-7.

266. Leung DY, Hirsch RL, Schneider L *et al.* Thymopentin therapy reduces the clinical severity of atopic dermatitis. Journal of Allergy & Clinical Immunology 1990; 85(5):927-33.

267. Stiller MJ, Shupack JL, Kenny C, Jondreau L, Cohen DE, Soter NA. A double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of thymopentin as an adjunctive treatment in atopic dermatitis. Journal of the American Academy of Dermatology 1994; 30(4):597-602.

268. Hsieh KH, Shaio MF, Liao TN. Thymopentin treatment in severe atopic dermatitis--clinical and immunological evaluations. Archives of Disease in Childhood 1992; 67(9):1095-102.

269. Pons-Guiraud-A. [Value of Allerglobulin in the treatment of atopic dermatitis in children and young adults. A double-blind randomized study]. Rev-Med-Interne 1986; 7(5):537-42.

270. Valdes Sanchez AF, Fernandez Ortega C, Gomez Echeverria AH, Gillama NieblaE. , Lastra Alfonso G, Lopez Saura P. [Atopic dermatitis. Treatment with transfer factor. A controlled clinical trial]. [Spanish]. Revista Alergia 1991; 38(6):158-62.

271. Yohn JJ, Weston WL. Topical glucocorticoids. Weston WL., Editor. Current Problems in Dermatology. Vol. 11. 1990: Year Book Medical Publishers, 34-63.

272. Brock W, Cullen SI. Triamcinolone acetonide in flexible collodion for dermatologic therapy.

Archives of Dermatology 1967; 96(2):193-4.

273. Gehring W, Gloor M. Treatment of the atopic dermatitis with a water-in-oil emulsion with or without the addition of hydrocortisone - Results of a controlled double-blind randomized study using clinical evaluation and bioengineering methods. H+G Zeitschrift Fur Hautkrankheiten. 1996; 71:554-60.

274. Vanderploeg-DE. Betamethasone dipropionate ointment in the treatment of psoriasis and atopic dermatitis: a double-blind study. South-Med-J 1976; 69:862-3.

275. Roth HL, Brown EP. Hydrocortisone valerate. Double-blind comparison with two other topical steroids. Cutis 1978; 21(5):695-8.

276. Sudilovsky A, Muir JG, Bocobo FC. A comparison of single and multiple applications of halcinonide cream. International Journal of Dermatology 1981; 20(9):609-13.

277. Lupton ES, Abbrecht MM, Brandon ML. Short-term topical corticosteroid therapy (halcinonide ointment) in the management of atopic dermatitis. Cutis 1982; 30(5):671-5.

278. Sefton J, Loder JS, Kyriakopoulos AA. Clinical evaluation of hydrocortisone valerate 0.2% Ointment. Clinical Therapeutics 1984; 6(3):282-93.

279. Wahlgren CF, Hagermark O, Bergstrom R, Hedin B. Evaluation of a new method of assessing pruritus and antipruritic drugs. Skin Pharmacology 1988; 1(1):3-13.

280. Stalder JF, Fleury M, Sourisse M, Rostin M, Pheline F, Litoux P. Local steroid therapy and bacterial skin flora in atopic dermatitis. British Journal of Dermatology 1994; 131(4):536-40.

281. Lebwohl M. Efficacy and safety of fluticasone propionate ointment, 0.005%, In the treatment of eczema. Cutis 1996; 57(2 Suppl):62-8.

282. Sears HW, Bailer JW, Yeadon A. Efficacy and safety of hydrocortisone buteprate 0.1% Cream in patients with atopic dermatitis. Clinical Therapeutics 1997; 19(4):710-9.

283. Maloney JM, Morman MR, Stewart DM, Tharp MD, Brown JJ, Rajagopalan R. Clobetasol propionate emollient 0.05% In the treatment of atopic dermatitis. International Journal of Dermatology 1998; 37(2):142-4.

284. Binder R, McCleary J. Comparison of fluocinonide in a double-blind study with betamethasone valerate. Current Therapeutic Research, Clinical & Experimental 1972; 14(1):35-8.

285. Almeyda J, Fry L. Controlled trial of the treatment of atopic eczema with a urea-hydrocortisone preparation versus betamethasone 17-valerat. British Journal of Dermatology 1973; 88(5):493-5.

286. Leibsohn E, Bagatell FK. Halcinonide in the treatment of corticosteroid responsive dermatoses. British Journal of Dermatology 1974; 90(4):435-40.

287. Almeyda J, Burt BW. Double blind controlled study of treatment of atopic eczema with a preparation of hydrocortisone in a new drug delivery system versus betamethasone 17-valerate. British Journal of Dermatology 1974; 91(5):579-83.

288. Lundell ER, Koch E. Uber ein im Doppelblind-Versuch gepruftes neues corticosteroid. Zeitschrift Fur Allgemeinmedizin 1974; 50:463-6.

289. Bjornberg A, Hellgren L. [Comparison between 2 steroid dosage forms in psoriasis and eczema]. [German]. Zeitschrift Fur Hautkrankheiten. Suppl 2:13-5, 1975. 1975; Suppl 2.

290. Bleeker J. Double-blind comparison between two new topical corticosteroids, halcinonide 0.1% And clobetasol propionate cream 0.05%. Current Medical Research & Opinion 1975; 3(4):225-8.

291. Morley N, Fry L, Walker S. Clinical evaluation of clobetasone butyrate in the treatment of children with atopic eczema, and its effect on plasma corticosteroid levels. Current Medical Research & Opinion 1976; 4(3):223-8.

292. Savin RC. Betamethasone dipropionate in psoriasis and atopic dermatitis. Connecticut Medicine 1976; 40(1):5-7.

293. Yasuda T. Clinical experiences with hydrocortisone 17-butyrate. Deramtologica 1976; 152(Suppl. 1):221-9.

294. Mali JW. An evaluation of betamethasone dipropionate (diprosone) versus locacorten 0.02% Cream. Dermatologica 1976; 153(3):177-8.

295. Bluefarb SM, Howard FM, Leibsohn E, Schlagel CA, Wexler L. Diflorasone diacetate: vasoconstrictor activity and clinical efficacy of a new topical corticosteroid. Journal of International Medical Research 1976; 4(6):454-61.

296. el-Hefnawi H, el-Shiemy S, Paris R, Tadros SS. Double-blind paired comparison clinical trial of halcinonide and hydrocortisone. Cutis 1978; 22(1):97-9.

297. Fisher M, Kelly AP. Multicenter trial of fluocinonide in an emollient cream base. International Journal of Dermatology 1979; 18(8):660-4.

298. Ramelet AA, Mauracher E. Treatment of resistant steroid-responsive dermatoses: a comparison of Diprolene and Neriforte. Clinical Trials Journal 1982; 19:298-307.

299. Sefton J, Kyriakopoulos AA. Comparative efficacy of hydrocortisone valerate 0.2 Percent ointment in the treatment of atopic dermatitis. Cutis 1983; 32(1):89-91.

300. Lassus A. Clinical comparison of alclometasone dipropionate cream 0.05% With hydrocortisone butyrate cream 0.1% In the treatment of atopic dermatitis in children. Journal of International Medical Research 1983; 11(5):315-9.

301. Bagatell FK, Barkoff JR, Cohen HJ, et al. A multicenter comparison of alclometasone dipropionate cream 0.05% And hydrocortisone cream 1.0% In the treatment of atopic dermatitis. Current Therapeutic Research, Clinical & Experimental. Vol 33(1)(Pp 46-52), 1983. 1983.

302. Van DelRey ML, Geller M, Azulay RD. Estudo duplo-cego sobre a eficacia e a seguranca do creme de alcometasoma no tratamento de dermatite atopica. / Double-blind study on the efficacy and safety of alclomethasone cream in the treatment of atopic dermatitis. An.-Bras.-Dermatol 1983; 58:177-80.

303. Harder F, Rufli T. [Therapy of eczema. Once daily use of diflorasone diacetate in comparison to thrice daily use of betamethasone-17-valerate]. [German]. Schweizerische Rundschau Fur Medizin Praxis 1983; 72(39):1240-2.

304. Konzelmann M, Harms M. [Diflorasone diacetate cream compared to betamethasone dipropionate cream in the treatment of eczemas]. [German]. Schweizerische Rundschau Fur Medizin Praxis 1983; 72(20):709-11.

305. Duke EE, Maddin S, Aggerwal A. Alclometasone dipropionate in atopic dermatitis: a clinical study. Current Therapeutic Research, Clinical & Experimental. Vol 33(5)(Pp 769-774), 1983. 1983.

306. Lassus A. Alclometasone dipropionate cream 0.05% Versus clobetasone butyrate cream 0.05%. A controlled clinical comparison in the treatment of atopic dermatitis in children. International Journal of Dermatology 1984; 23(8):565-6.

307. Veien NK, Hattel T, Justesen O, Norholm A, Verjans HL. Hydrocortisone 17-butyrate (locoid) 0.1% Cream versus hydrocortisone (uniderm) 1% cream in the treatment of children suffering from atopic dermatitis. Journal of International Medical Research 1984; 12(5):310-3.

308. Nolting S. [Treatment with topical corticosteroids in severe or resistant dermatoses]. [German]. Dermatosen in Beruf Und Umwelt 1985; Occupational & Environmental Dermatoses. 33(4):140-4.

309. Rajka G, Verjans HL. Hydrocortisone 17-butyrate (locoid) 0.1% Fatty cream versus desonide (apolar) 0.1% Ointment in the treatment of patients suffering from atopic dermatitis. Journal of International Medical Research 1986; 14(2):85-90.

310. Majerus JP, Reiffers-Mettelock J. Sicorten: a synthetic corticosteroid for topical treatment of common dermatoses. Journal of International Medical Research 1986; 14(1):46-9.

311. Ulrich R, Andresen I. Double-blind comparative trial involving 0.5% Halomethasone (sicorten(tm)) cream versus 0.25% Prednicarbate cream in patients with acute episodes of atopic dermatiti. Fortschritte Der Medizin. Vol 109(36) (Pp 49-50+53-54), 1991. 1991; VOL 109 (36):49-50+53-54(EMBASE) OR 741-4(MEDLINE).

312. Haneke E. The treatment of atopic dermatitis with methylprednisolone aceponate (mpa), a new topical corticosteroid. Journal of Dermatological Treatment. Vol 3(SUPPL. 2) (Pp 13-15), 1992. 1992.

313. Rampini E. Methylprenisolone aceponate (mpa) - use and clinical experience in children. Journal of Dermatological Treatment. Vol 3(SUPPL. 2) (Pp 27-29), 1992. 1992.

314. Ottevanger V, Hoybye S, Balk-Moller S, De Cunha Bang F, Veien NK. Continuous and intermittent treatment of atopic dermatitis in adults with momethasone furoate (elocon(tm)) vs. Hydrocortisone 17-butyrate (locoid tm.). Acta Dermato-Venereologica. 1992; Suppl 176:139.

315. Gelmetti C, Grimalt R, Del Campo G, Caputo R. Tolerability and efficacy of topical budesonide in the treatment of atopic dermatitis in pediatric age. Giornale Italiano Di Dermatologia e Venereologia. Vol 129(3) (Pp XIII-XVII), 1994. 1994.

316. Jorizzo J, Levy M, Lucky A *et al.* Multicenter trial for long-term safety and efficacy comparison of 0.05% Desonide and 1% hydrocortisone ointments in the treatment of atopic dermatitis in pediatric patients. Journal of the American Academy of Dermatology 1995; 33(1):74-7.

317. Camacho F, Garcia Bravo B, Diaz Perez JL *et al.* A comparative intraindividual double blind assay between prednicarbate and fluocortolone in the management of atopic dermatitis. Actas Dermo-Sifiliograficas. Vol 87(1-2) (Pp 59-63), 1996. 1996.

318. Lebwohl M, Lane A, Savin R *et al.* A comparison of once-daily application of mometasone furoate 0.1% cream compared with twice-daily hydrocortisone valerate 0.2% cream in pediatric atopic dermatitis patients who failed to respond to hydrocortisone. International Journal of Dermatology 1999; 38(8):604-6.

319. Cox N, Williams HC. Can you COPE with CONSORT? Br J Dermatol 2000; 142:1-7.

320. Begg C, Cho M, Eastwood S *et al.* Improving the quality of reporting of randomized controlled trials: The CONSORT Statement. JAMA 1996; 276(8):637-9.

321. Rennie D. How to report randomized controlled trials: The CONSORT Statement. JAMA 1996; 276:649.

322. Moher D. CONSORT: An evolving tool to help improve the quality of reports of randomized controlled trials. JAMA 1998; 279:1489-91.

323. Meinert CL. Beyond CONSORT: Need for improved reporting standards for clinical trials. JAMA 1998; 279:1487-9.

324. Korting HC, Schafer-Korting M, Klovekorn W, Klovekorn G, Martin C, Laux P. Comparative efficacy of hamamelis distillate and hydrocortisone cream in atopic eczema. European Journal of Clinical Pharmacology 1995; 48(6):461-5.

325. Munkvad M. A comparative trial of clinitar versus hydrocortisone cream in the treatment of atopic eczema. British Journal of Dermatology 1989; 121(6):763-6.

326. Wolf-Jurgensen-P. Efficacy of bufexamac cream versus betamethasone valerate cream in contact dermatitis: a double-blind trial. Curr-Med-Res-Opin 1979; 5:779-84.

327. Wachs GN, Maibach HI. Co-operative double-blind trial of an antibiotic/corticoid combination in impetiginized atopic dermatitis. British Journal of Dermatology 1976; 95(3):323-8.

328. Hjorth N, Schmidt H, Thomsen K. Fusidic acid plus betamethasone in infected or potentially infected eczema. Pharmatherapeutica 1985; 4(2):126-31.

329. Wilkinson RD, Leigh DA. Comparative efficacy of betamethasone and either fusidic acid or neomycin in infected or potentially infected eczema. Current Therapeutic Research 1985; 38:177-82.

330. Meenan FO. A double-blind comparative study to compare the efficacy of locoid c with tri-adcortyl in children with infected eczema. British Journal of Clinical Practice 1988; 42(5):200-2.

331. Zienicke H. Topical glucocorticoids and anti-infectives: a rational combination?. Current Problems in Dermatology. 21:186-91, 1993. 1993.

332. Korting HC, Zienicke H, Braun-Falco O *et al.* Modern topical glucocorticoids and anti-infectives for superinfected atopic eczema: do prednicarbate and didecyldimethylammoniumchloride form a rational combination? [Published erratum appears in infection 1995 jan-feb;23(1):67]. [Review] [22 refs]. Infection 1994; 22(6):390-4.

333. Ramsay CA, Savoie JM, Gilbert M, Gidon M, Kidson P. The treatment of atopic dermatitis with topical fusidic acid and hydrocortisone acetate. Journal of the European Academy of Dermatology & Venereology. Vol 7(SUPPL. I) (Pp S15-S22), 1996. 1996.

334. Thaci D KJaKR. Fusidic acid/betamethasone 17-valerate in potentially infected atopic dermatitis. Journal of the European Academy of Dermatology and Venereology 1999; 12(Supplement 2):S163.

335. Anonymous. Treatment of eczemas and infected eczemas. British Journal of Clinical Practice 1967; 21(10):505-7.

336. Kaplan RJ, Daman L, Rosenberg EW, Feigenbaum S. Topical use of caffeine with hydrocortisone in the treatment of atopic dermatitis. Archives of Dermatology 1978; 114(1):60-2.

337. Chapman RS. Treatment of atopic dermatitis. Practitioner 1979; 223(1337):713-6.

338. Andersen BL, Andersen KE, Nielsen R, Stahl D, Niordson A, Roders GA. Treatment of dry atopic dermatitis in children. A double-blind comparison between mildison lipocream(tm) (1% hydrocortisone) and uniderm(tm) (1% hydrocortisone) ointment. CLIN TRIALS J, Vol 25(4) (Pp 278-284), 1988. 1988.

339. Korting HC, Zienicke H, Schafer-Korting M, Braun-Falco O. Liposome encapsulation improves efficacy of betamethasone dipropionate in atopic eczema but not in psoriasis vulgaris. European Journal of Clinical Pharmacology 1990; 39(4):349-51.

340. Malzfeldt E, Lehmann P, Goerz G, Lippold BC. Influence of drug solubility in the vehicle on clinical efficacy of ointments. Archives of Dermatological Research. Vol 281(3) (Pp 193-197), 1989. 1989.

341. Olholm Larsen P, Brandrup F, Roders GA. Report on a double-blind, left-right study comparing the clinical efficacy of mildison (hydrocortisone 1%) lipocream(tm) with uniderm(tm) (hydrocortisone 1%) cream in the treatment of children with atopic dermatitis. Current Therapeutic Research, Clinical & Experimental. Vol 44(3) (Pp 421-425), 1988. 1988.

342. Richelli C, Piacentini GL, Sette L, Bonizzato MC, Andreoli A, Boner AL. Clinical efficacy and tolerability of clobetasone 17-butyrate 0.5% Lotion in children with atopic dermatitis. Current Therapeutic Research, Clinical & Experimental. Vol 47(3) (Pp 413-417), 1990. 1990.

343. Koopmans B, Lasthein Andersen B, Mork NJ, Austad J, Suhonen RE. Multicentre randomized doulble-blind study of locoid lipocream fatty cream twice daily versus locoid lipocream once daily and locobase once daily. Journal of Dermatological Treatment. Vol 6(2) (Pp 103-106), 1995. 1995.

344. Bleehen SS, Chu AC, Hamann I, Holden C, Hunter JA, Marks R. Fluticasone propionate 0.05% Cream in the treatment of atopic eczema: a multicentre study comparing once-daily treatment and once-daily vehicle cream application versus twice-daily treatment. British Journal of Dermatology 1995; 133(4):592-7.

345. Hoybye S, Balk Moller S, De Cunha Bang F, Ottevanger V, Veien NK. Continuous and intermittent treatment of atopic dermatitis in adults with mometasone furoate versus hydrocortisone 17-butyrate. Current Therapeutic Research, Clinical & Experimental. Vol 50(1) (Pp 67-72), 1991. 1991.

346. Vernon HJ, Lane AT, Weston W. Comparison of mometasone furoate 0.1% Cream and hydrocortisone 1.0% Cream in the treatment of childhood atopic dermatitis. Journal of the American Academy of Dermatology 1991; 24(4):603-7.

347. Rafanelli A, Rafanelli S, Stanganelli I, Marchesi E. Mometasone furoate in the treatment of atopic dermatitis in children. Journal of the European Academy of Dermatology & Venereology. Vol 2(3) (Pp 225-230), 1993. 1993.

348. Marchesi E, Rozzoni M, Pini P, Cainelli T. Comparative study of mometasone furoate and betamethasone dipropionate in the treatment of atopic dermatitis. Giornale Italiano Di Dermatologia e Venereologia. Vol 129(1-2) (Pp IX-XII), 1994. 1994.

349. Reidhav I, Svensson A. Betamethasone valerate versus mometasone furoate cream once daily in atopic dermatitis. Journal of Dermatological Treatment. 1996; 7:87-8.

350. Traulsen J. Hydrocortisone buteprate versus betamethasone valerate for once-daily treatment of atopic dermatitis. Journal of Dermatological Treatment. Vol 8(2) (Pp 109-114), 1997. 1997.

351. Amerio PL, Biggio P, Bossi G *et al.* Mometasone furoate 0.1% once a day in allergic contact dermatitis and in atopic dermatitis: Controlled study versus betamethasone valerate.

Dermatologic Clinics 1998; 18(4):255-60.

352. Wolkerstorfer A, Strobos MA, Glazenburg EJ, Mulder PGH, Oranje AP. Fluticasone propionate 0.05% cream once daily versus clobetasone butyrate 0.05% cream twice daily in children with atopic dermatitis. Journal of the American Academy of Dermatology. Vol 39(2 I) (Pp 226-231), 1998 1998.

353. Van Der Meer JB GEea. The management of moderate to severe atopic dermatitis in adults with topical fluticasone propionate. British Journal of Dermatology 1999; 140:1114-21.

354. Lucky AW, Grote GD, Williams JL *et al.* Effect of desonide ointment, 0.05%, On the hypothalamic-pituitary-adrenal axis of children with atopic dermatitis. Cutis 1997; 59(3):151-3.

355. Sanabria-Silva E, Laterza AM, Tamayo L, Ruiz-Maldonado R. Evaluation of rebound phenomenon in children with atopic dermatitis tretaed with topical corticosteroids. Dermatologia Revista Mexicana. Vol 35(2) (Pp 84-89), 1991. 1991.

356. Kuokkanen K, Sillantaka I. Alclometasone dipropionate 0.05% Vs hydrocortisone 1.0%: Potential to induce cutaneous atrophy in children. Clinical Therapeutics 1987; 9(2):223-31.

357. Dickey RF. Parenteral short-term corticosteroid therapy in moderate to severe dermatoses. A comparative multiclinic study. Cutis 1976; 17(1):179-83.

358. Heddle RJ, Soothill JF, Bulpitt CJ, Atherton DJ. Combined oral and nasal beclomethasone diproprionate in children with atopic eczema: a randomised controlled trial. British Medical Journal Clinical Research Ed. 1984; 289(6446):651-4.

359. La Rosa M, Musarra I, Ranno C *et al.* A randomized, double-blind, placebo-controlled crossover trial of systemic flunisolide in the treatment of children with severe atopic dermatitis. Current Therapeutic Research, Clinical & Experimental. Vol 56(7) (Pp 720-726), 1995. 1995.

360. Greenhalgh T. How to read a paper: the basics of evidence based medicine. London: BMJ Publishing Group, 1997.

361. Halliday HL. Overview of clinical trials comparing natural and synthetic surfactants. Biol Neonate 1995; 67(Suppl 1):32-47.

362. Haines A, Donald A. Looking forward: getting research findings into practice: making better use of research findings. British Medical Journal 1998; 317:72-5.

363. Jadad A. Randomised Controlled Trials. London: BMJ Publishing Group, 1998.

364. Mulrow CD. Rationale for systematic reviews. BMJ 1994; 309:597-9.

365. Leonard T. Review Group Co-ordinator. Cochrane Skin Group 2002; tina.leonard@nottingham.ac.uk.

366. Spence D. Interpreting the evidence. British Medical Journal 2002; 325(7364):587.

367. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. Chalmers I, Altman DG., Editors. Systematic Reviews. London: BMJ Publishing Group, 1995: 17-36.

368. Kramer MS. Maternal antigen avoidance during lactation for preventing atopic disease in infants of women at high risk (Cochrane Review). The Cochrane Library. Oxford: Update Software, 1999.

369. Kramer MS. Maternal antigen avoidance during pregnancy for preventing atopic disease in infants of women at high risk (Cochrane Review). The Cochrane Library. Issue 4 edition. Oxford: Update Software for the Cochrane Collaboration, 1999.

370. Armstrong NC, Ernst E. The treatment of eczema with Chinese herbs: a systematic review of randomised clinical trials. Br J Clin Pharm 1999; 48:262-4.

371. Fung AY, Look PC, Chong LY, But PP, Wong E. A controlled trial of traditional Chinese herbal medicine in Chinese patients with recalcitrant atopic dermatitis. International Journal of Dermatology 1999; 38(5):387-92.

372. Latchman Y, Banerjee P, Poulter LW, Rustin M, Brostoff J. Association of immunological changes with clinical efficacy in atopic eczema patients treated with traditional chinese herbal therapy (zemaphyte). International Archives of Allergy & Immunology 1996; 109(3):243-9.

373. Assmann T, Homey B, Ruzicka T. Applications of tacrolimus for the treatment of skin disorders. Immunopharmacology 2000; 47:203-13.

374. Cheer SM, Plosker GL. Tacrolimus ointment: a review of its therapeutic potential as a topical therapy in atopic dermatitis. American Journal of Clinical Dermatology 2001; 2(6):389-406.

375. Prakash A, Benfield P. Topical mometasone: a review of its pharmacological properties and therapeutic use in the treatment of dermatological disorders. Drugs 1998; 55(1):145-63.

APPENDIX 1

Excluded trials of topical steroids

Author	Date	Interventions	Reason for Exclusion
Topical steroid versus 'placebo' vehicle			
Cullen	1973	Betamethasone benzoate gel 0.025% versus placebo gel	Atopic dermatitis not separated from other dermatoses in results
Rosenthal	1980	Clocortolone pivalate 0.1% cream versus placebo cream base	Atopic dermatitis not separated from other dermatoses in results
Gartner	1984	Diproderm cream 0.05% versus placebo vehicle	Atopic dermatitis not separated from other dermatoses in results
Guzzo	1991	Halobetasol propionate 0.05% ointment versus vehicle	Atopic dermatitis not separated from other dermatoses in results
Lebwohl	1996	Fluticasone propionate 0.005% ointment versus vehicle	Unclear if 'eczema' is atopic dermatitis in this study, especially as most of the subjects were adult – author has been written to for clarification
Schachner	1996	Hydrocortisone 17-butyrate ointment versus vehicle	No randomisation mentioned
Heuck	1997	Topical bedesonide versus base	The atopic dermatitis patients (study one) were part of an open case series. The two remaining randomised controlled trials in this study were all on asthma patients
Topical steroid versus another topical steroid			

Zimmerman	1967	Betamethasone 17-valerate 0.05% ointment compared against fluocinolone acetonide 0.025%	First study was a case series, and it is unclear if randomisation occurred in second study
Grater	1967	Flumethasone versus 0.1% triamcinolone versus 1% hydrocortisone	Atopic dermatitis not separated from other dermatoses in results
Rosenberg	1971	0.05% fluocinonide versus 0.1% betamethasone valerate	Atopic dermatitis not separated from other dermatoses in results
Bluefarb	1972	Desonide cream 0.05% versus betamethasone valerate cream 0.1%	Atopic dermatitis not separated from other dermatoses in results
Meenan	1972	Flucinonide 0.05% versus betamethasone 17 valerate cream 0.1%	Atopic dermatitis not separated from other dermatoses in results
Borelli	1973	Clocortolone (C168) versus fluocinolone	'eczema' group not specified sufficiently
McCuiston	1973	Fluocinonide 0.01% and 0.05% versus betamethasone valerate	Not clear if randomised, outcome measures not described at all
Polano	1973	Hydrocortisone butyrate 0.1% versus triamcinolone acetonide 0.1% versus hydrocortisone acetate 1%	Atopic dermatitis not separated from other dermatoses in results
Stewart	1973	Desonide versus triamcinolone acetonide versus betamethasone 17-valerate	Atopic dermatitis not separated from other dermatoses in results
Nordwell	1974	Betamethasone 17, 21-dipropionate 0.05% cream versus fluocortolone caproate 0.25% plus fluocortolone pivalate 0.25% cream	Atopic dermatitis not separated from other dermatoses in results
Sparkes	1974	Clobetasol propionate 0.05% versus betamethasone 17-valerate ointment and cream versus fluclorolone acetonide ointment and cream and fluocinonide	Atopic dermatitis not separated from other dermatoses in results
Laurberg	1975	1% hydrocortisone in a stabilized 10% urea cream versus betamethasone 17-valerate 0.1% cream	Atopic dermatitis results mixed up with patients with 'atopic winter feet'
Lundell	1975	Desoximetasone 0.25% versus fluocinolone acetonide 0.025% cream	Nature of 'endogenous eczema' unclear. Inadequate description to classify as atopic dermatitis
Ludvigsen	1975	Calmuril-hydrocortisone 1% cream versus triamcinolone acetonide 0.1% cream	Unclear if randomised. No study results given!

Meyer-Rohn	1975	Desoximetason 0.25% versus betamethasone-valerate 0.1%	Atopic dermatitis not separated from other dermatoses in results
Sudilovsky	1975	Halcinonide cream 0.1% versus fluocinonide 0.05% cream	Disease definition, i.e. 'eczematous dermatoses which would normally be treated with topical steroids' not acceptable as a term synonymous with atopic eczema
Parish	1976	Betamethasone benzoate 0.025% gel versus betamethasone valerate 0.1% cream	Cannot be sure that study subjects with 'eczematous dermatoses' had atopic eczema
Thormann	1976	Hydrocortisone 17-butyrate versus betamethasone 17-valerate	Results of 5 different skin disorders mixed up and only one patient with atopic eczema
Roessel	1977	Triamcinolone acetonide benzoyl-ß-amino-isobutyrate versus betamethasone dipropionate	Atopic dermatitis not separated from other dermatoses in results
Khan	1978	1% hydrocortisone plus 10% urea versus 0.05% fluocinonide	Dry eczematous dermatoses in adults mixed up with atopic dermatitis
Lassus	1979	Clobetasone butyrate 0.05% cream versus hydrocortisone butyrate 0.1% cream	Atopic dermatitis not separated from other dermatoses in results
Helander	1982	Hydrocortisone 17-butyrate 0.1% cream versus betamethasone 17-valerate 0.1% cream	Atopic dermatitis not separated from other dermatoses in results
Hersle	1982	Diflorasone diacetate 0.05% versus betamethasone valerate	Atopic dermatitis not separated from other dermatoses in results
Turnbull	1982	Locoid versus Betnovate lotion	Study of seborrhoeic and atopic dermatitis of the scalp with results not separated
Gip	1983	Hydrocortisone 17-butyrate 0.1% cream versus betamethasone 17-valerate 0.1% cream	Atopic dermatitis not separated from other dermatoses in results
Schmidt	1984	D-homosteroids domoprednate 0.1% ointment versus 0.1% betamethasone valerate ointment	Atopic dermatitis not separated from other dermatoses in results
Gip	1987	Hydrocortisone 17-butyrate 0.1% cream versus betamethasone 17-valerate 0.1% cream	Atopic dermatitis not separated from other dermatoses in results
Schmidt	1987	Domoprednate 0.1% ointment versus hydrocortisone butyrate ointment	Atopic dermatitis not separated from other dermatoses in results

Handa	1988	Alclometasone dipropionate 0.05% ointment versus 1% hydrocortisone ointment	Atopic dermatitis not separated from other dermatoses in results
Panja	1988	Alclometasone dipropionate 0.05% cream versus 1% hydrocortisone cream	Atopic dermatitis not separated from other dermatoses in results
Celleno	1990	Alclometasone dipropionate 0.1% versus 0.1% hydrocortisone 17-butyrate	Atopic dermatitis not separated from other dermatoses in results
Viglioglia	1990	Mometasone furoate 0.1% cream once daily versus betamethasone valerate 0.1% cream twice daily	Atopic dermatitis not separated from other dermatoses in results
Brunner	1991	Halobetasol propionate 0.05% ointment versus 0.1% diflucortolone valerate ointment	Atopic dermatitis results mixed up with patients with lichen simplex
Datz	1991	Halobetasol propionate ointment 0.05% versus clobetasol 17-propionate ointment 0.05%	Atopic dermatitis results mixed up with lichen simplex
Rajka	1993	Mometasone furoate 0.1% fatty cream versus betamethasone valerate 0.1% cream	Atopic dermatitis not separated from other dermatoses in results
Schäfer-Korting	1993	Prednicarbate 0.025% -0.25% versus hydrocortisone aceponate versus hydrocortisone butyrate 0.1% versus betamethasone 17-valerate 0.1% versus hydrocortisone 1% versus 2 drug-free vehicles	Conducted in healthy volunteers not atopic eczema subjects
Blum	1994	Betamethasone dipropionate 0.05% in propylene glycol versus clobetasol propionate 0l05% ointment	Atopic dermatitis not separated from other dermatoses in results
Delescluse	1996	Fluticasone propionate ointment 0.005% versus betamethasone 17, 21-dipropionate ointment 0.05%	Atopic dermatitis not separated from other dermatoses in results
Juhlin	1996	Fluticasone propionate 0.05% cream versus hydrocortisone 17-butyrate 0.1% cream	Atopic dermatitis results not separated from patients with other eczemas of a known cause
Meffert	1999	Topical methylprednisolone aceponate versus amcinonide, betamethasone valerate, hydrocortisone butyrate and vehicle	Whole range of 'acute eczemas' not separated in results
Topical steroid versus another topical			
Bjornberg	1967	Crotamiton versus Crotamiton/hydrocortisone combo	Atopic eczema not specified/separated

Christiansen	1977	Bufexamac versus 0.1% triamcinolone acetonide, 1% hydrocortisone cream and placebo	Atopic dermatitis results not separated from other dermatoses
Topical steroid plus additional active agents			
Bjornberg	1966	Topical flumethasone plus vioform versus hydrocortisone with 5, 7Dichlor-8-hydroxy-2-methylquinolin 3%	Besnier's prurigo included, results not separated
Sasagawa	1970	Betamethasone valerate plus gentamicin sulphate versus betamethasone	Atopic dermatitis not separated from other dermatoses in results
Weitgasser	1972	Topical dexamethasone versus topical nandrolone plus chlorhexadine	Rag bag of dermatoses (atopic dermatitis not among them) and results not separated
Aertgeerts	1973	Topical dexamethasone versus topical nandrolone plus chlorhexdine	Various dermatoses lumped together
Carpenter	1973	Vioform-hydrocortisone cream versus components alone and base cream vehicle	Atopic dermatitis not separated from other dermatoses in results
Aertgeerts	1976	Dexamethasone plus chlorhexidine versus flumethasone – pivalate 0.02% plus iodochlorohydroxy-quinolone	Atopic dermatitis not separated from other dermatoses in results
Cunliffe	1976	Fluclorolone acetonite 0.025% in FAPG versus betamethasone 17-valerate plus 0.5% neomycin	Atopic dermatitis not separated from other dermatoses in results
Strategos	1986	Fusidic acid/betamethasone combination versus gentamicin – betamethasone combination	Only 5 patients with atopic eczema all present in only one treatment arm
Weitgasser	1993	Halometasone/triclosan cream versus betamethasone dipropionate/getamicin sulphate cream	Atopic dermatitis not separated from other dermatoses in results
Poyner	1996	Fusidic acid/hydrocortisone cream versus miconazole/hydrocortisone cream	Unclear if patients with 'clinically infected eczema' had atopic eczema. Author contacted for clarification
Comparison of different formulations of the same topical steroids			
Pilgaard	1980	Hydroderm versus hydrokortison DAK	Atopic dermatitis not separated from other dermatoses in results

Once daily versus more frequent application of topical steroids			
Tharp	1996	Fluticasone propionate 0.05% once versus twice daily	Eczema unspecified
Fredricksson	1980	Halcinonide cream 0.1% once daily versus same cream three times daily	Psoriasis and atopic dermatitis results mixed up
Schmid	1981	Topical fluocinoloneacetonid 0.025% once daily, twice daily or interval therapy	Not clearly atopic dermatitis patients
English	1989	Betamethasone Dipropionate once versus twice daily	Atopic dermatitis not separated from other dermatoses in results
Topical steroids in the prevention of relapse			
Vickers	1976	Maintenance on low-potency topical steroids switching to high-potency for short periods versus use of high-potency steroid throughout treatment versus high-potency steroid regularly once daily using a low-potency steroid for the second application	Not a randomised controlled trial although a clear intention to conduct one. Subsequent RCT never published
Moller	1983	Clobetasol propionate versus flupredniden acetate	Atopic dermatitis not separated from other dermatoses in results

Excluded trials of "eczema" for other reasons

Author	Date	Intervention	Reason for Exclusion
Smith	1961	Trimeprazine versus methdilazine	Atopic eczema data not separated in results
Brown	1971	Psychiatric treatment	Only one case of atopic eczema
Chan-Yeung	1971	Disodium cromoglygate	Asthma study
Anonymous	1973	Carbamide in hyperkeratosis	Atopic eczema results not separated
D'Souza	1973	House dust mites	People had asthma or hay fever
Baraf	1976	Antihistamines: cyproheptadine versus hydroxyzine	Atopic eczema results not separated from other dermatoses
Baertschi	1976	Antibiotic prophylaxis	'Eczema' only mentioned as side-effect
Friedman	1978	Monoamione oxidase inhibitors	Unclear if any of the neurodermatitis patients had atopic eczema
Buch-Rasmussen	1979	Hydrocortisone alcoholic solutions	Study of external otitis
Newbold	1980	Emollients	Atopic eczema results not given separately
Anonymous	1981	5% butyl flufenamate versus bufexamac	Atopic dermatitis not separated from other dermatoses in results
Bazex	1982	Terfenadine versus clemastine	Atopic eczema results not separated from other dermatoses in results

Cooper	1983	Thymopoietin pentapeptide	No clinical outcomes measured or reported
Archer	1984	Adrenoreceptor agonists	Not a therapeutic trial
Fairris	1984	Superficial X-Ray therapy (of the feet)	Unclear if patients had atopic eczema
Fairris	1985	Superficial X-Ray therapy (of the hands)	Unclear if patients had atopic eczema
Meyrick-Thomas	1985	Ranitidine	Healthy atopic volunteers
Svensson	1985	Diagnostic tool based on clinical criteria	Diagnostic study "subjects randomly collected"
Bernstein	1986	Doxepin hydrochloride	Abstract only
Niimura	1988	Oral acyclovir	Study of eczema herpeticum
Roberts	1988	PAF antagonist versus placebo	Not atopic eczema patients
Warren	1988	The importance of bradykinin and histamine in the skin response to antigen	Not atopic eczema patients, not a therapeutic trial
Burr	1989	Risk factors for atopic eczema	Not an RCT of an intervention for atopic eczema, instead, an observational study of risk factors for atopic eczema within another breast-feeding RCT.
Ebden	1989	Evening primrose oil	Asthma not atopic eczema
Monroe	1989	Nalmefene opiate antagonist versus placebo	Atopic eczema results not presented separately
Sheehan-Dare	1989	PUVA versus superficial radiotherapy	Not clear atopic dermatitis

Brandrup	1990	Occlusive dressing	'Eczema' only mentioned as side-effect
Markey	1990	Platelet activating factor	Atopic subjects without evidence of atopic eczema
Michel	1990	Cetirizine	Pollen sensitive patients unspecified
Heyer	1991	Substance P and topical mustard oil	Not a therapeutic trial
Peter	1991	Ketaconazole	Study of seborrhoeic dermatitis
Schafer	1991 (a)	Evening primrose oil	No clinical outcomes
Schafer	1991 (b)	Phospholipid fatty acid composition and LTB_4 release of neutrophils	No clinical outcomes
Kerscher	1992	Topical steroids	Healthy volunteers
Korting	1992	Prednicarbate cream	Healthy volunteers
Nierop	1992	Auranofin	Study of asthma only
Olsen	1992	Systemic steroids with 2% minoxidil	Study of alopecia areata with eczema mentioned as side-effect
Couser	1993	Surfactant	Unspecified eczema as outcome measure
Lutsky	1993	Loratadine syrup versus terfenadine suspension	Atopic eczema results not given separately
Rombo	1993	Malaria prophylaxis	'Eczema' mentioned as side-effect
Zepelin	1993	Omega-3 fatty acid	Psoriasis patients

Lee	1994	Surfactant mixtures	Healthy volunteers
Lovegrove	1994	Milk free diet versus normal diet	No separate data on atopic eczema
Nakagawa	1994	Tacrolimus ointment 0.03, 0.1 and 0.3%	Randomisation not described, 3 actives compared in hand and neck area, unblinded
Soyland	1994	n-3 omega fatty acid supplementation	Atopic eczema severity outcome data not given
Syed	1994	Podophyllotoxin cream	Study of molluscum
Tegner	1994	Skin blanching by hydrogen peroxide	Side effect study of skin blanching of hydrogen peroxide
Zimmermann	1994	Balneophototherapy with daily 15% synthetic Dead Sea Salt bath and selective ultraviolet phototherapy versus balneophototherapy with daily 3% NaCl salt bath and selective ultraviolet phototherapy	Atopic dermatitis not separated from other dermatoses in results
Roquet	1995	Loratadine	Atopic subjects not necessarily having eczema
Simon	1995	Ioxaglate versus Iopamidol	Not a study of atopic eczema outcomes. A study to see if allergic reactions are commoner in 1 type of contrast medium in patients with atopic disease.
Simon	1995	Gamma Interferon	No clinical outcomes
Snyman	1995	Betahistine	Simply "atopic volunteers" not necessarily atopic *eczema*
Verwimp	1995	Whey-protein hydrolysate based formulas	Unclear if atopic eczema patients
Wahlgren	1995	Interleukin-2	Laboratory experiment with no clinical outcomes, not a therapeutic trial
Anonymous	1997	Cetirizine versus placebo	No atopic eczema outcomes

Kalpakliogu	1997	Heparin	Asthma study
Heyer	1997	Opiate and H1 antagonist effects	Healthy volunteers
Kekki	1997	Skin-prick and patch-test reactivity	Diagnostics
Lippert	1997	Antigen-induced cytokine release	Not a clinical trial of a therapeutic agent. Only cytokines measured.
Pigatto	1997	Colloidal grain suspensions	Not a therapeutic trial
Rukwied	1997	Cetirizine versus placebo	Experimentally-induced flare responses
Sabroe	1997	Doxepin versus terfenadine	No atopic eczema outcomes
Ishibashi	1997	FK506 versus placebo	Unclear if randomized
Frossard	1998	Cetirizine	Healthy volunteers
Hill	1998	Betamethasone plus clioquinol cream versus betamethasone plus fusidic acid cream	Hand eczema
Hanifin	1998	Tacrolimus ointment versus vehicle	Does-escalation study
Iyaku	1998	Tacrolimus ointment (FK506)	Unclear if randomized
Kang	1998	Tacrolimus versus vehicle	Dose-escalation study (abstract only)
Lippert	1998	Certirizine	Laboratory experiment with no clinical outcomes
Reitamo	1998	Tacrolimus ointment versus betamethasone-valerate versus vehicle	Collagen synthesis study

Sorensen	1998	Intravenous immunoglobulin	Study of multiple sclerosis with eczema mentioned as side effect
Syed	1998	Imiquimod 1%	Study of molluscum
Warnecke	1998	Ichthyol oil	Healthy volunteers
Weisshaar	1998	Topical capsaicin versus placebo	Effect of capsaicin on experimentally induced whealing from histamine icthyosis
Darsow	1999	Aeroallergen sensitization	Diagnostics
Goh	1999	Mometasone furoate cream versus clobetasol propionate cream	Unspecified chromic limb eczema
Grundmann-Kollmann	1999	PUVA bath versus PUVA cream	Atopic eczema results not separated
Ortonne	1999	SDZ ASM 981 versus topical steroids and vehicle	Healthy volunteers
Rudofsky	1999	Intravenous prostaglandin	Study of venous ulcers with eczema mentioned as side-effect
Simons	1999	Cetirizine 0.25mg/kg twice daily versus placebo	Safety study
Drake	2001	Tacrolimus ointment versus vehicle	QoL study based on earlier RCTs already included in section 3.8.4. Trial details not given
Soter	2001	Tacrolimus ointment versus vehicle	Safety study
Queille-Roussel	2001	SDZ ASM 981 versus medium and potent topical steroids versus vehicle	Skin atrophy study – no efficacy data

Trials excluded at an early stage because eczema was unspecified

Author	Date	Interventions	Reason for Exclusion
(1) Topical Steroids			
Leo Pharmaceuticals unpublished data on file	-	Fucicort® versus Betnovate®	Unspecified hand eczema
Stahle	1965	Fluocinolone versus tumenol prednisolone	Description of 'patches of eczema' unclear
Stahle	1965	Full versus half strength betamethasone 17-valerate	Description of 'patches of eczema' unclear
Munro	1967	Betamethasone 17-valerate versus fluocortolone caproate ointment	'Eczema' unspecified
Anonymous	1969	Flurandrenolone with clioquinol in 2 different strengths	Unclear if 'eczema' included atopic eczema
Lloyd	1969	Fluocinolone acetonide 0.025% versus flucinolone containing neomycin	Nature of inflammatory dermatitis unclear
Portnoy	1969	1% hydrocortisone versus 0.2% fluocortolone	'Eczema' unspecified
Ashurst	1970	Beclomethasone dipropionate versus betamethasone 17-valerate	'Conditions responsive to topical applications of steroids' – unclear if this included atopic eczema
Ashurst	1972	Hydrocortisone 17-butyrate versus fluocinolone acetonide versus hydrocortisone butyrate with chlorquinaldol	Inadequate description of 'eczema'
Hall-Smith	1972	Betamethasone valerate versus betamethasone benzoate	Description of 'steroid-responsive dermatoses' insufficient
Harman	1972	Fluclorolone acetonide versus betamethasone 17-valerate	Various types of 'dermatitis' unclear

Neering	1972	Betamethasone 17-valerate versus triamcinolone acetanide under occlusive dressing	'Eczema' unspecified
Sarkany	1972	Fluocinonide versus betamethasone valerate	Type of 'eczema' unclear
Alexander	1973	Hydrocortisone 17-butyrate versus betamethasone valerate 0.1%	Nature of 'eczema' unclear
Craps	1973	Clocortolone pivalate versus controls in 17 double-blind trials	Non-specific 'eczema'
Cullen	1973	Betamethasone benzoate versus placebo gel	'Eczematous dermatoses' not separated
Marks	1973	Betamethasone 17-valerate 0.1% versus formocortal 0.025%	'Eczema of the hands' unclear
Wilson	1973	Betamethasone 17-valerate ointment lanolin-free versus original formulation versus fluclorolone acetonide ointment	Type of eczema unclear
Garretts	1975	Fluprednylidene acetate cream versus base	Inflammatory skin disease unspecified
Ronn	1976	Betamethasone versus fluocinonide	'Eczema' unspecified
Munro	1977	Betamethasone valerate ointment versus fluocinonide FAPG	'Eczema' unspecified
Palmerio	1977	Halopredone acetate versus betamethasone valerate	Nature of 'eczema' unclear
Dotti	1978	Dexamethasone 17-valerate versus 0.1% betamethasone versus 1% hydrocortisone acetate	Nature of 'eczematous lesions' unclear
Afzelius	1979	Betamethasone dipropionate 0.05% versus fluocinolone acetonide 0.025%	Unclear if atopic eczema included
Doherty	1979	Diflucortolone valerate 0.3% oily cream versus clobetasone propionate 0.05% cream	'Chronic severe eczema' too non-specific
Rosenberg	1979	Amcinonide versus betamethasone valerate	'Eczematous dermatitis' unclear

Vollum	1979	Betamethasone valerate versus halcinonide	Nature of eczema lesions unclear
Allenby	1981	Clobetasone butyrate 0.05% versus hydrocortisone butyrate 0.1%	Unclear if atopic eczema
Anonymous	1981	Hydrocortisone 17-butyrate versus betamethasone 17-valerate creams	Unspecified uninfected eczema
Guenther	1981	Amcinonide cream 0.1% versus halcinonide cream 0.1%	Nature of 'eczematous dermatitis' unclear
Bickers	1984	Amcinonide versus halcinonide	Nature of 'sub acute eczematous dermatitis' unclear
Johansson	1984	Diflorasone diacetate versus betamethasone valerate	Nature of 'eczematous dermatitis' unclear
August	1985	Diflucortolone versus betamethasone cream	Unspecified symmetrical eczema
Jegasothy	1985	Clobetasol propionate versus fluocinonide cream	Nature of 'chronic eczema' unclear
Jaffé	1986	Hydrocortisone plus potassium hydroxyquinoline versus 1% hydrocortisone plus 2% miconazole cream	Nature of 'infected eczema' unclear
Barry	1987	Desonide 0.05% and 0.1% cream	'Non-infected hand eczemas' unclear
Williamson	1987	Hydrocortisone/urea cream versus betamethasone valerate cream	Nature of 'dry eczema' unclear
Lutsky	1993	Loratadine syrup versus Terfenadine suspension	Atopic dermatitis not separated from other dermatoses in results
Gip	1994	Betamethasone 17-valerate 0.1% lipocream versus betamethasone 17-valerate 0.1% cream	Nature of 'dry chronic dermatitis' unclear
Kejda	1994	1% hydrocortisone cream versus Locoid 0.1%	Nature of 'chronic eczema' unclear
Nakagawa	1994	Tacrolimus ointment 0.03, 0.1 and 0.3%	Randomisation not described, unblinded open study

Tharp	1996	Fluticasone once daily versus twice daily	Unspecified eczema
Jorizzo	1997	Clobetasol propionate 0.05% versus emollient vehicle	'Eczema' unspecified
(2) Radiation			
King	1984	Superficial radiotherapy versus simulated therapy	Nature of 'palmar' eczema unclear
Cartwright	1987	Grenz versus placebo	Nature of 'bilateral hand eczema' unclear if atopic eczema
(3) Cromoglycate			
Dannaeus	1977	Sodium cromoglycate versus placebo	Unspecified eczema
Pacor	1992	Disodium chromoglycate versus oxatomide	Nature of eczema unspecified
(4) Antihistamines			
Hellier	1963	Trimeprazine versus amylobarbitone	Unspecified eczema
Laugier	1978	Mequitazine versus placebo	Unspecified 'dermatological conditions'
(5) Miscellaneous			
de Gregorio	1970	Topical bendazac versus placebo versus 3% hydrocortisone acetate	Nature of 'eczematous eruptions' unclear
Fredrikksson	1975	Urea creams	Nature of eczematous dermatitis of hands unclear
Zimmermann	1981	Intravenous demetindenmaleat compared with clemastine	Nature of 'allergic dermatoses' unclear

Fairris	1984	Superficial X-ray therapy	Nature of unspecified constitutional eczema of the hands unclear
Veien	1985	Oral challenge with balsam of Peru versus placebo	Various types of 'dermatitis' unclear
Lauharanta	1991	Emulsion cleansing versus washing with soap	Nature of 'hand eczema' unclear
Drake	1995	5% doxepin cream versus vehicle cream	Description of study subjects suggests that 'eczematous dermatitis' did not include atopic dermatitis

APPENDIX 2

Courses attended by Colette Hoare/Chambers 1998-2002

Course	Date	Hours
British Epidermo-Epidemiology Society: evidence based dermatology	Jan 2000	7
University of Nottingham: Data analysis with Excel	June 2000	6
Cochrane Collaboration Protocol workshop	Jan 2000	7
Cochrane Collaboration RevMan workshop	June 2000	7
Systematic Reviews Training Unit: Getting on with your systematic review	June 1999	28
University of Nottingham MSc Public Health Module: Basic Statistics	Sept to Dec 1999	48
University of Nottingham: Basic HTML	Feb 1999	6
University of Nottingham: Advanced HTML	May 1999	6
Total hours	**1998 to 2002**	**115**