

Eczema

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ABSTRACT

INTRODUCTION: Eczema, as defined by the World Allergy Organization (WAO) revised nomenclature in 2003, affects 15% to 20% of school children and 2% to 5% of adults worldwide. About 50% of people with eczema demonstrate atopy, with specific immunoglobulin E responses to allergens. **METHODS AND OUTCOMES:** We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of topical medical treatments, and dietary interventions in adults and children with established eczema? What are the effects of breastfeeding, reducing allergens, or dietary interventions for primary prevention of eczema in predisposed infants? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). **RESULTS:** We found 54 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. **CONCLUSIONS:** In this systematic review we present information relating to the effectiveness and safety of the following interventions: breastfeeding, controlling house dust mites, corticosteroids, dietary exclusion of eggs or cow's milk, elementary diets, emollients, essential fatty oils, few-foods diet, multivitamins, pimecrolimus, probiotics, pyridoxine, reducing maternal dietary allergens, tacrolimus, vitamin E, and zinc supplements.

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What are the primary preventive effects of dietary interventions in infants?	30

INTERVENTIONS

TOPICAL MEDICAL TREATMENTS		 Likely to be ineffective or harmful
 Beneficial		Essential fatty acids (evening primrose oil, blackcurrant seed oil, fish oil) 29
Corticosteroids	6	
Pimecrolimus	13	
Tacrolimus	19	
 Likely to be beneficial		PRIMARY PREVENTION IN INFANTS
Emollients*	4	 Unknown effectiveness
		Prolonged breastfeeding by mother straight after birth 29
DIETARY INTERVENTIONS IN ADULTS		REDUCING ALLERGENS
 Unknown effectiveness		 Unknown effectiveness
Vitamin E and multivitamins	25	Control of house dust mite 30
DIETARY INTERVENTIONS IN CHILDREN		DIETARY INTERVENTIONS IN INFANTS
 Unknown effectiveness		 Likely to be beneficial
Egg and cow's milk exclusion diet	26	Early introduction of probiotics (in last trimester and/or shortly after birth) 31
Few-foods diet	28	 Unknown effectiveness
Elemental diet	28	Maternal dietary restriction during pregnancy and lactation 30
Zinc supplementation	28	
Pyridoxine (Vitamin B6)	29	
 Unlikely to be beneficial		Footnote
Probiotics	27	*Based on consensus

Key points

- Eczema, as defined by the World Allergy Organization (WAO) revised nomenclature in 2003, affects 15% to 20% of school children worldwide and 2% to 5% of adults. Only about 50% of people with eczema demonstrate allergic sensitisation.

Remission occurs in two-thirds of children by the age of 15 years, but relapses may occur later.

- **Emollients** are generally considered to be effective for treating the symptoms of eczema. However, the few small short-term RCTs that have been done so far do not confirm this. Sufficiently powered long-term RCTs are needed to clarify the role of emollients in the treatment of eczema.
- **Corticosteroids** improve clearance of lesions and decrease relapse rates compared with placebo in adults and children with eczema, although we don't know which is the most effective corticosteroid or the most effective dosing regimen.

Topical corticosteroids seem to have few adverse effects when used intermittently, but if they are of potent or very potent strength, they may cause burning, skin thinning, and telangiectasia, especially in children.

- The calcineurin inhibitors **pimecrolimus** and **tacrolimus** improve clearance of lesions compared with placebo and may have a role in people in whom corticosteroids are contraindicated. They also seem suitable for topical use in body areas where the skin is particularly thin, such as the face.
- CAUTION: An association has been suggested between pimecrolimus and tacrolimus and skin cancer in animal models. Although this association has not been confirmed in humans, calcineurin inhibitors should be used only when other treatments have failed.
- We don't know whether **vitamin E or multivitamins** reduce symptoms in adults with eczema or whether **pyridoxine, zinc** supplementation, **exclusion** diets, or **elemental** diets are effective in children with eczema, as there are insufficient good-quality studies.

Probiotics do not seem to reduce symptoms in children with established eczema.

Essential fatty acids, such as evening primrose oil, blackcurrant seed oil, or fish oil, do not seem to reduce symptoms in people with eczema.

- We don't know whether **control of house dust mites** or **maternal dietary restriction** can prevent the development of eczema in children.

Observational data suggest that exclusive **breastfeeding** for at least 3 months does not reduce eczema risk and there is no evidence to suggest that exclusive breastfeeding alleviates eczema symptoms, unless a child is allergic to cow's milk protein.

Introduction of **probiotics** in the last trimester of pregnancy and during breastfeeding may reduce the risk of eczema in the baby, although it remains unclear whether both antenatal and postnatal supplementation together yields the strongest protective effect. It is equally unclear which strains of probiotics are most effective.

DEFINITION

As defined by the World Allergy Organization (WAO) revised nomenclature in 2003, eczema (also known as atopic dermatitis) ^[1] is a chronic, relapsing, and itchy inflammatory skin condition. In the acute stage, eczematous lesions are characterised by poorly defined erythema with surface change (oedema, vesicles, and weeping). In the chronic stage, lesions are marked by skin thickening (lichenification). Although lesions can occur anywhere on the body, infants often have eczematous lesions on their cheeks and outer limbs before they develop eczema in the typical flexural areas such as behind the knees and in the folds of the elbow and neck. About 50% of people suffering from eczema also become sensitised to environmental allergens, such as house dust mite, and may then be classified as having atopic eczema under the revised WAO nomenclature. ^[2] **Diagnosis:** There is no definitive diagnostic "gold standard" for diagnosing eczema. However, a UK Working Party developed a minimum list of validated diagnostic criteria for eczema using the Hanifin and Rajka list of clinical features as building blocks (see table 1, p 36). ^[3] The criteria were shown to have a sensitivity of 85% and a specificity of 96% in children when compared with a dermatologist's diagnosis. ^[3] Although there are a large number of eczema severity scores for eczema in the public domain, only the SCORing Atopic Dermatitis (SCORAD) index, the Eczema Area Severity Index (EASI), the Patient Oriented Eczema Measure (POEM), and the Six Area, Six Sign Atopic Dermatitis severity index (SASSAD) have been shown to have adequate validity and reliability (see table 2 for full details, p 37). **Population:** For the purposes of this review, we included all adults and children defined as having established eczema. Where adults or children are considered separately, this is highlighted in the text. We also included studies assessing primary prevention of eczema using specific interventions: prolonged breastfeeding, maternal dietary restriction, house dust mite restriction, and early introduction of probiotics.

INCIDENCE/
PREVALENCE

In Europe, eczema affects 15% to 20% of school age children at some stage, and 2% to 5% of adults. ^[4] ^[5] ^[6] Global prevalence data for the symptoms of eczema were collected as part of the International Study of Asthma and Allergies in Childhood (ISAAC). The results suggest that

eczema is not only a problem in industrialised countries, but also in urban areas of developing nations.^[7] One UK-based population study showed that 2% of children under the age of 5 years have severe disease and 84% have mild disease.^[8] Affected adults more frequently have chronic and severe eczema and are also at an increased risk of developing allergic contact dermatitis.^[9]

AETIOLOGY/ RISK FACTORS	Although eczema has become increasingly common over past decades, the causes are not well understood and are probably a combination of genetic and environmental factors. ^[10] Eczema risk is increased in first degree relatives, and the discovery of the filaggrin gene strongly suggests that an impaired skin barrier is fundamentally involved in eczema development. However, genetics alone cannot explain the raise in the prevalence of eczema over past decades and also cannot explain why eczema often clears spontaneously. Migrant studies have found that children acquire the background population risk of their new home country. ^[11] There is also some evidence to suggest that eczema is associated with factors linked to a "Western" lifestyle, as the disease tends to be more common in industrialised countries and urban centres of developing nations. ^[12] ^[13] Eczema is also more common in people of higher socioeconomic class. ^[14] Several individual environmental influences have been studied. For instance, broad-spectrum antibiotics during pregnancy and in early life seem to increase eczema risk, ^[15] and it has been speculated that this may be because of alterations in the infant's gut microflora. The influence of specific bacterial and viral pathogens both <i>in utero</i> and postnatally on disease development remains uncertain, but studies on day-care attendance during infancy, endotoxin exposure, consumption of unpasteurised cow's milk, and dog exposure in early life ^[16] point towards a protective effect from non-pathogenic microbial exposure. There is also the suggestion that helminth parasites can partially protect against allergic sensitisation and eczema. ^[17] At the same time, bacterial skin infection, for instance with <i>Staphylococcus aureus</i> , is known to worsen eczema. Allergic sensitisation, for instance to house dust mite, is also associated with higher eczema risk, but seems a secondary phenomenon rather than a primary cause. With the heightened interest in skin barrier dysfunction, one of the key future research areas is the interaction between skin barrier gene mutation carriage and environmental factors, such as house dust mite sensitisation, water hardness, and washing practices, which could all contribute to an impaired skin barrier and therefore eczema phenotype. ^[2] ^[18]
PROGNOSIS	Remission occurs by the age of 15 years in 60% to 70% of cases, although a large number of people re-present with hand eczema later on in life. ^[19] While no treatments are currently known to alter the natural history of eczema, several interventions can help to control symptoms and prevent flares.
AIMS OF INTERVENTION	To prevent eczema in predisposed infants and children; to minimise the impact of established eczema on quality of life in children and adults, with minimal adverse effects of treatment.
OUTCOMES	<i>For questions on treatment:</i> Symptom severity (itching, sleep disturbance) and signs (erythema, oozing/crusting, lichenification, cracking, oedema, excoriation, dryness); reduction in surface area affected (sometimes described in this review as clearance); relapse rates (sometimes described in this review as maintenance), includes need for corticosteroids as rescue medication for flares; quality of life of adults and children with eczema and of parents of children with eczema; area of skin involvement; adverse effects of treatments. Trials use a large number of eczema scoring systems, including composite quantitative scales such as Scoring Atopic Dermatitis (SCORAD), Eczema Area Severity Index (EASI), the Patient-Oriented Eczema Measure (POEM), and the Six Area, Six Sign Atopic Dermatitis severity scale (SASSAD) (see table 2 for full details, p 37). These scales vary in the degree that they have been validated, and many more completely non-validated scales are in use. ^[20] <i>For question on prevention:</i> Development of eczema, adverse effects of treatment.
METHODS	<i>Clinical Evidence</i> search and appraisal May 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to May 2009, Embase 1980 to May 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 1 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, open or blinded, and containing >20 individuals of whom >80% were followed up. There were high discontinuation rates in many of the RCTs; we have included these RCTs if they performed an intention-to-treat analysis following up all participants and provided data on withdrawal rates. There was no minimum length of follow-up required to include studies. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design

criteria for inclusion as we did for benefits. We also did a search for retrospective or prospective cohort studies of 20 people or more assessing adverse effects of tacrolimus and pimecrolimus. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 39). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of topical medical treatments in adults and children with established eczema?

OPTION EMOLLIENTS (ALONE OR PLUS TOPICAL CORTICOSTEROIDS)

Symptom severity

Compared with placebo We don't know whether emollients are more effective at reducing skin dryness, erythema, lichenification, pruritus, or local symptoms ([very low-quality evidence](#)).

Emollients plus corticosteroids compared with corticosteroids alone We don't know whether emollients plus corticosteroids are more effective at improving disease severity scores and pruritus ([very low-quality evidence](#)).

Different emollients compared with each other We don't know which emollient is more effective in reducing skin dryness ([very low-quality evidence](#)).

Compared with corticosteroids Emollients may be more effective than mild corticosteroids (hydrocortisone cream 0.05%) in relieving pruritus, erythema, and desquamation ([very low-quality evidence](#)).

Compared with emollients plus corticosteroids Emollients alone may be less effective at improving symptom severity scores ([low-quality evidence](#)).

Relapse rates

Compared with corticosteroids Emollients may be less effective than potent corticosteroids (fluticasone propionate 0.05%) used intermittently twice weekly in reducing relapse rates at 16 weeks ([low-quality evidence](#)).

Compared with emollients plus corticosteroids Emollients alone seem less effective at improving relapse rates ([moderate-quality evidence](#)).

Quality of life

Emollients plus corticosteroids compared with corticosteroids alone We don't know whether emollients plus corticosteroids are more effective at improving quality of life in children with eczema or in their parents ([low-quality evidence](#)).

Note

Emollients are generally considered to be effective for treating the symptoms of eczema. They have been associated with transient burning, although most RCTs identified did not report on adverse events of emollients.

For GRADE evaluation of interventions for eczema, [see table, p 39](#).

Benefits:

Emollient versus placebo:

We found one systematic review (search date 1999, 2 RCTs) ^[21] and 4 subsequent RCTs. ^{[22] [23] [24] [25]}

Symptom severity

The first RCT identified by the review (80 adults and children with eczema) found that urea cream 10% improved skin redness, hydration, and induration compared with a vehicle (significance not assessed). ^[21]

The second RCT identified by the review (46 children with eczema) found that ammonium lactate 6% significantly reduced lichenification at day 15, and erythema at day 30 compared with the cream base alone. ^[21]

The first subsequent RCT (109 adults [mean age 34 years] with eczema) found no significant difference between glycerine and placebo in a skin dryness severity score at 30 days (results presented graphically; $P = 0.42$).^[22]

The second subsequent RCT (197 adults [mean age 35 years] with eczema) found no significant difference between glycerine cream and placebo in skin dryness severity score at 30 days (proportion of people with improvement: 85% with glycerin v 63% with placebo; $P = 0.56$).^[23]

The third subsequent RCT (72 adults [mean age 46 years] with moderate eczema) was a three-arm trial comparing an emollient (Kamillosan cream), mild corticosteroids (hydrocortisone cream 0.5%), and vehicle.^[24] It found that Kamillosan cream marginally improved skin pruritus, erythema, and desquamation compared with placebo, but significance was not assessed.

The fourth subsequent RCT (24 people with eczema aged 15–49 years; all participants had mild to moderate local severity of eczema on both forearms) compared emollient (cream with glycerol 20%) and placebo cream (no glycerol) twice daily for 4 weeks.^[25] Each participant was randomised to receive either emollient or placebo to one forearm, and the alternative medication to the other forearm. The RCT found no significant difference between emollient and placebo in local severity (as measured by the SCORing Atopic Dermatitis index [SCORAD] at the forearms only; scale 0–18, with higher score indicating worse symptoms) at 4 weeks (absolute results displayed graphically; reported as not significant; P values between groups not reported).

Emollients plus corticosteroids versus corticosteroids alone:

We found three RCTs comparing emollient plus corticosteroids versus corticosteroids alone.^[26]
^[27] ^[28]

Symptom severity

The first RCT (173 children aged <12 months with moderate to severe eczema, mean SCORAD score of 35) compared emollient (containing oat extracts) plus topical corticosteroids (micronised desonide 0.1% cream or desonide 0.1% cream) for inflammatory lesions versus topical corticosteroids for inflammatory lesions alone for 6 weeks.^[26] The RCT found no significant difference in disease severity (as measured by SCORAD) between emollient and no emollient at 6 weeks (mean: 15.96 with emollient v 16.45 with no emollient; $P = 0.92$). However, it was underpowered to detect a clinically important difference between groups in this outcome, as it was designed to assess the primary outcome of corticosteroids use (see comment below).

The second RCT (86 children with mild to moderate eczema aged 4–48 months) compared 5 different treatment regimens of 21 days: (A) topical corticosteroids twice daily, (B) topical corticosteroids twice daily plus emollient twice daily, (C) topical corticosteroids once daily, (D) topical corticosteroids once daily plus emollient twice daily, and (E) topical corticosteroids once every other day plus emollient twice daily.^[27] The topical corticosteroids used were desonide 0.05% and the emollient was sunflower oil oleodistillate. The RCT found that there was no significant difference among all 5 groups in the percentage change in the SCORAD score between 0 and 21 days (–63% with A v –72% with B v –58% with C v –74% with D v –75% with E; P among groups = 0.81).

In the third RCT, there was no significant difference in pruritus (as measured by a 10-point visual analogue scale, where higher score indicates worse itching) between the two groups at 2 weeks (2.24 with topical corticosteroids plus emollient v 3.2 with topical corticosteroids alone; $P = 0.08$), but at 6 weeks, topical corticosteroids plus emollient significantly reduced pruritus compared with topical corticosteroids alone (2.52 with topical corticosteroids plus emollient v 4.95 with topical corticosteroids alone; $P = 0.002$).^[28]

Quality of life

The first RCT found no significant difference in the change in quality of life in children (measured using the Infant's Dermatitis Quality of Life Index [IDQOL]) and in parents (measured using the Dermatitis Family Impact Questionnaire [DFI]) between the two groups over 42 days (percentage change in IDQOL: –43% with emollient v –48% with no emollient; $P = 0.131$; percentage change in DFI: –56% with emollient v –45% with no emollient; $P = 0.208$).^[26]

The second RCT assessed change in quality of life between 0 and 21 days in children using the IDQOL (percentage change in IDQOL; scale 0–30, with higher score indicating greater impairment on quality of life) and in parents using the DFI (percentage change in DFI; scale 0–30, with higher score indicating greater impairment on quality of life); however, it did not perform statistical analyses among groups (IDQOL: –55% with A v –75% with B v –38% with C v –67% with D v –65% with E; DFI: –60% with A v –74% with B v –56% with C v –73% with D v –88% with E; significance among groups not assessed).^[27]

The third RCT did not assess quality of life. ^[28]

Different emollients versus each other:

We found one systematic review ^[21] and two subsequent RCTs. ^[22] ^[23]

Symptom severity

The systematic review identified one RCT of poor quality (50 people, aged 18–55 years). It found no significant difference between a new urea 5% cream compared with an established licensed cream containing urea 4%. ^[21]

The first subsequent RCT (109 people with eczema) found that urea 4% plus sodium chloride 4% cream reduced skin dryness severity score to a significantly greater extent than did glycerin cream at 30 days (dry skin area and severity index; results presented graphically; $P = 0.024$). ^[22]

Emollients versus corticosteroids:

See benefits of corticosteroids, p 6 .

Emollients plus corticosteroids versus emollients alone:

See benefits of corticosteroids, p 6 .

Harms:

Emollients versus placebo:

One RCT identified by the review ^[21] found a similar proportion of people with transient burning with urea cream compared with vehicle cream (absolute numbers not reported; significance assessment not performed). ^[29] The subsequent RCTs did not report on harms. ^[22] ^[23] ^[24] ^[25]

Emollients plus corticosteroids versus corticosteroids alone:

The RCTs gave no information on adverse effects with combined treatment versus corticosteroids alone. ^[27] ^[26] ^[28]

Different emollients versus each other:

The RCTs gave no information on adverse effects. ^[21] ^[22] ^[23]

Emollients versus corticosteroids:

See harms of corticosteroids, p 6 .

Emollients plus corticosteroids versus emollients alone:

See harms of corticosteroids, p 6 .

Comment:

All the trials identified by the systematic review were of poor methodological quality. ^[21] The RCTs analysed in the systematic review included a mixed population of adults and children, and it is likely that the results can be generalised to both groups. ^[21] One RCT assessed corticosteroid use when corticosteroids were combined with emollients compared with use of corticosteroids alone. ^[26] The RCT found that the amount of high-potency corticosteroids used (measured in grams) was significantly lower with emollients than with no emollient over 21 and 42 days (21 days: 4.86 g with emollient v 8.87 g with no emollient; $P = 0.02$; 42 days: 8.56 g with emollient v 14.70 g with no emollient; $P = 0.02$). The RCT found no significant difference between emollient and no emollient in the amount of moderate-potency corticosteroids used over 21 and 42 days (21 days: 4.66 g with emollient v 4.91 g with no emollient; $P = 0.80$; 42 days: 7.43 g with emollient v 8.03 g with no emollient; $P = 0.72$).

Clinical guide:

Emollients are almost universally recommended as first-line treatment for eczema in adults and children. ^[3] Our own clinical experience is in accordance with this recommendation. However, this review highlights that there are only a few small RCTs that have investigated the efficacy of emollients in eczema over a rather short period of time. These RCTs failed to show significant benefits of short-term emollient therapy. Therefore, sufficiently powered long-term RCTs are needed to clarify the role of emollients in the treatment of eczema and to provide evidence-based clinical recommendations. Emollients vary and long-term use is probably governed appropriately by patient preference. Examples include white soft paraffin/liquid paraffin in a 50:50 mixture, agents that retain water in the skin such as lactic acid or urea, and aqueous cream. In general, the more oily the preparation, the better and longer lasting the emollient effect. However, adults, and adolescents in particular, often find the most greasy preparations too messy for routine use, especially on the hands and face. Many people prefer to use different emollients for the face and body.

OPTION

CORTICOSTEROIDS (ALONE OR USED CONCURRENTLY WITH EMOLLIENTS)

Symptom severity

Compared with placebo Corticosteroids (moderate, potent, and very potent) may be more effective in clearing eczema, and in improving disease severity and pruritus ([low-quality evidence](#)).

Different frequencies of corticosteroid application versus each other Twice daily application of corticosteroids may be no more effective than once-daily application in people with acute flares (low-quality evidence).

Different formulations of corticosteroid compared with each other The potent corticosteroid clobetasol propionate may be equally effective in lotion and emollient formulations at improving symptom severity and pruritus (low-quality evidence).

Different corticosteroids compared with each other We don't know which corticosteroids are more effective at improving disease severity and pruritus (low-quality evidence).

Corticosteroids plus emollients compared with emollients alone Corticosteroids plus emollients may be more effective at improving symptom severity scores (low-quality evidence).

Compared with emollients Mild corticosteroids (hydrocortisone 0.05% cream) may be less effective in relieving pruritus, erythema, and desquamation ([very low-quality evidence](#)).

Compared with pimecrolimus 1.0% Corticosteroids may be more effective at improving clearance at 1 week, and at improving pruritus at 1 or 3 weeks (low-quality evidence).

Compared with pimecrolimus 1.0% plus corticosteroids We don't know whether vehicle plus corticosteroids is more effective at improving global symptoms, or at increasing the proportion of target sites clear or almost clear of eczema at 15 days (very low-quality evidence).

Corticosteroids given topically for flares in people receiving vehicle compared with pimecrolimus 1.0% Vehicle plus topical corticosteroids for flares seems less effective at improving clearance at 1 week, but we don't know if it is more effective at 24 weeks ([moderate-quality evidence](#)).

Compared with tacrolimus 0.03% and 0.1% Corticosteroids (mild) seem to be less effective at improving disease severity, but we don't know whether clobetasone butyrate (moderate), hydrocortisone butyrate (potent), and methylprednisolone aceponate (potent) are more effective than tacrolimus 0.03% and 0.1% (moderate-quality evidence).

Compared with tacrolimus 0.03% plus corticosteroids We don't know whether corticosteroids (moderate) are more effective than tacrolimus 0.03% plus corticosteroids (moderate) at improving disease severity scores (low-quality evidence).

Corticosteroids plus tacrolimus compared with tacrolimus alone Corticosteroids (moderate and potent) plus tacrolimus may be more effective at improving disease severity (very low-quality evidence).

Relapse rates

Corticosteroids plus emollients compared with emollients alone Corticosteroids plus emollients seem more effective at improving relapse rates (moderate-quality evidence).

Compared with emollients Potent corticosteroids (fluticasone propionate 0.05%) used intermittently twice weekly may be more effective in reducing relapse rates at 16 weeks (low-quality evidence).

Different corticosteroids compared with each other Potent corticosteroids may be more effective at reducing relapse rates compared with mild corticosteroids (low-quality evidence).

Corticosteroids given topically for flares in people receiving vehicle compared with pimecrolimus 1.0% Topical corticosteroids plus vehicle for flares may be less effective at reducing the number of flares, and reducing the number of days of corticosteroids use at 6 to 12 months (low-quality evidence).

Quality of life

Compared with emollients plus corticosteroids We don't know how corticosteroids alone and emollients plus corticosteroids compare for improving quality of life in children with eczema or in their parents (low-quality evidence).

Note

Corticosteroids are associated with skin burning sensations.

For GRADE evaluation of interventions for eczema, [see table, p 39](#).

Benefits:

Corticosteroids versus placebo:

We found one systematic review (search date 1999) ^[21] and three subsequent RCTs ^[30] ^[31] ^[32] comparing corticosteroids versus placebo. The systematic review ^[21] identified 11 RCTs in children

and adults but did not include a meta-analysis for clinical outcomes of interest because of poor quality of reporting and scant methodological details. The RCTs were found to be of poor methodological quality (see comment), and they are not considered further here. We have used the designations of corticosteroid preparation as mild, moderate, potent, and very potent as defined in the *British National Formulary* ^[33] or *Martindale*. ^[34]

Symptom severity

The first subsequent RCT (94 children aged 2–12 years with active atopic eczema, involving at least 20% of the body surface) found that, compared with peanut oil vehicle, the moderate corticosteroid fluocinolone acetonide 0.01% in peanut oil significantly increased the proportion of people with >75% clearance at 1 week (>75% clearance at 1 week: 26% with fluocinolone acetonide v 2% with peanut oil; $P < 0.001$; absolute numbers not reported). ^[30] It also found that, compared with peanut oil, fluocinolone acetonide 0.01% in peanut oil significantly increased the proportion of people with >50% clearance at 1 week (63% with fluocinolone acetonide v 14% with peanut oil; $P < 0.001$; absolute numbers not reported).

The second subsequent RCT (284 children aged 3 months to <18 years with stable mild to moderate eczema) compared the potent corticosteroid hydrocortisone butyrate 0.1% twice daily with vehicle cream twice daily for up to 4 weeks; treatment was discontinued at day 22 if a child achieved total clearing of eczema. ^[31] The RCT found that hydrocortisone butyrate 0.1% significantly increased the proportion of people with clear or almost clear eczema compared with vehicle at 29 days (68/139 [49%] with hydrocortisone butyrate 0.1% v 35/145 [24%] with vehicle; $P < 0.001$). It found that hydrocortisone butyrate 0.1% significantly improved the percentage change in disease severity (as measured by the Eczema Area Severity Index [EASI]; symptom severity score 0–72, where higher score indicates more severe eczema) compared with vehicle between baseline and 29 days (75% with hydrocortisone butyrate 0.1% v 38% with vehicle; $P < 0.001$). It also found that the potent corticosteroid hydrocortisone butyrate 0.1% significantly improved the change in self-reported pruritus (as measured by a 4-point scale; 0–3, where higher score indicates worse itching) compared with vehicle between baseline and 29 days (–1.4 with hydrocortisone butyrate 0.1% v –0.7 with vehicle; $P < 0.001$). ^[31]

The third subsequent three-armed RCT (229 people with moderate to severe stable eczema; aged 12–84 years) compared three interventions: the very potent corticosteroid clobetasol propionate 0.05% in lotion formulation twice daily (96 people), clobetasol propionate 0.05% in emollient cream formulation twice daily (100 people), and lotion vehicle twice daily (33 people) for 2 weeks. ^[32] The RCT found that clobetasol propionate 0.05% lotion significantly improved the proportion of people who achieved "success" (0, 0.5, or 1 on the Global Severity Scale; scale 0–4, where higher score indicates more severe disease) compared with vehicle at 2 weeks (73% with clobetasol propionate 0.05% lotion v 74% with clobetasol propionate 0.05% emollient v 36% with vehicle; $P = 0.001$ for clobetasol propionate lotion v vehicle; P value not reported for clobetasol propionate emollient v vehicle; absolute results not reported). It also found that the very potent corticosteroid clobetasol propionate 0.05% lotion significantly improved the proportion of people with no pruritus compared with vehicle at 2 weeks (58% with clobetasol propionate 0.05% lotion v 15% with vehicle; $P = 0.001$; absolute results not reported). ^[32] At 4 weeks (2 weeks after treatment cessation), the proportion of people with no pruritus was highest in the clobetasol propionate 0.05% lotion group, although significance was not assessed (51% with clobetasol propionate 0.05% lotion v 36% with clobetasol propionate 0.05% emollient v 19% with vehicle; significance among groups not assessed; absolute results not reported).

Different frequencies of corticosteroid application versus each other:

We found one systematic review (search date 2003), which identified 7 RCTs. ^[35] The systematic review did not perform a meta-analysis because of heterogeneity of trials. ^[35] With the exception of one RCT, the quality of the reporting and of the methods used in these RCTs was generally poor, and therefore 6 of the 7 RCTs are not reported further.

Symptom severity

The RCT identified by the review (376 people aged 12–65 years with moderate/severe eczema recruited during an acute flare) compared 4 interventions: fluticasone propionate 0.05% cream (potent) once or twice daily versus fluticasone propionate 0.005% ointment (potent) once or twice daily for a 4-week stabilisation phase followed by a 16-week maintenance phase. ^[35] The proportion of people in remission at the end of the first 4 weeks was not significantly different across the 4 treatment groups (absent or mild rash on a 3-item severity score, where 0 = absent, 1 = mild, 2 = moderate, and 3 = severe; remission with fluticasone propionate at 4 weeks: 76/95 [80%] with cream once daily v 76/91 [84%] with cream twice daily v 77/100 [77%] ointment once daily v 64/90 [71%] ointment twice daily; $P = 0.55$ for fluticasone propionate 0.05% cream once v twice daily and $P = 0.25$ for fluticasone propionate 0.005% ointment once v twice daily). ^[35]

Different formulations of corticosteroid versus each other:

We found one three-arm RCT (229 people with moderate to severe stable eczema; aged 12–84 years) comparing three interventions: the very potent corticosteroid clobetasol propionate 0.05% lotion twice daily (96 people), clobetasol propionate 0.05% emollient cream twice daily (100 people), and vehicle lotion twice daily (33 people) for 2 weeks. ^[32]

Symptom severity

The RCT found that there was no significant difference between the very potent corticosteroid clobetasol propionate 0.05% lotion and the very potent corticosteroid clobetasol propionate 0.05% emollient in the proportion of people who achieved "success" (0, 0.5, or 1 on the Global Severity Scale; scale 0–4, where higher score indicates more severe disease) at 2 weeks (73% with clobetasol propionate 0.05% lotion v 74% with clobetasol propionate 0.05% emollient; reported as not significant; P value and absolute results not reported). ^[32]

The RCT found that at 4 weeks (2 weeks after treatment cessation), the proportion of people with no pruritus was highest in people receiving the very potent corticosteroid clobetasol propionate 0.05% in lotion formulation, although significance was not assessed (51% with clobetasol propionate 0.05% lotion v 36% with clobetasol propionate 0.05% emollient v 19% with vehicle; significance among groups not assessed; absolute results not reported). ^[32]

Different corticosteroids versus each other:

We found two RCTs comparing different types of corticosteroids. ^{[36] [37]}

Symptom severity

The first RCT (265 children aged 2–14 years with severe eczema) involved two studies of identical design; one comparing fluticasone propionate 0.05% cream (potent) versus hydrocortisone 1% cream (mild) and the other comparing fluticasone propionate 0.05% cream versus hydrocortisone butyrate 0.1% cream (potent). ^[36] Treatments were applied daily for 2 to 4 weeks until eczema was stabilised and thereafter intermittently "as required" (up to twice daily) to affected areas at the first sign of a relapse. It found that, compared with either hydrocortisone 1% cream or hydrocortisone butyrate 0.1% cream, fluticasone propionate 0.05% significantly improved disease severity (total severity score) over 12 weeks (mean severity score in acute phase [0–30, higher is worse]: 7.06 [62 people] with fluticasone propionate 0.05% v 9.45 [65 people] with hydrocortisone 1% cream; P < 0.001; 6.34 [56 people] with fluticasone propionate 0.05% v 7.59 [52 people] with hydrocortisone butyrate 0.1%; P = 0.04).

The second RCT (174 children aged 1–15 years with mild or moderate eczema defined by the Hanifin and Rajka scale) compared betamethasone valerate 0.1% (potent) for 3 days followed by the base ointment for 4 days versus hydrocortisone 1% (mild) applied for 7 days. It found that both groups showed similar, clinically important (>20% improvement on the [Six Area, Six Sign Atopic Dermatitis severity scale](#) [SASSAD]) improvements in disease severity compared with baseline (55% with hydrocortisone v 56% with betamethasone; absolute numbers not reported; P = 1.00). It also found no significant difference between betamethasone valerate 0.1% and hydrocortisone 1% in the number of scratch-free days (118 days with hydrocortisone 1% v 117.5 days with betamethasone valerate 0.1%; P = 0.53). ^[37]

Relapse rates

The first RCT found that, compared with either the mild corticosteroid hydrocortisone 1% cream or the potent corticosteroid hydrocortisone butyrate 0.1% cream, the potent corticosteroid fluticasone propionate 0.05% significantly reduced relapse rates over 12 weeks (mean atopic dermatitis score in maintenance phase: 5.10 [53 people] with fluticasone propionate 0.05% v 6.98 [54 people] with hydrocortisone 1% cream; P = 0.006; 3.95 [49 people] with fluticasone propionate 0.05% v 5.33 [37 people] with hydrocortisone butyrate 0.1%; P = 0.04). ^[36]

The second RCT found that the median number of relapses for both groups was one. ^[37]

Corticosteroids plus emollients versus emollients alone:

We found two RCTs comparing corticosteroids plus emollient versus emollient alone. ^{[38] [39]}

Symptom severity

The first RCT (91 people with atopic dermatitis, mean age 27 years) compared corticosteroids plus a lipid mixture (ceramide-3 and patented nanoparticles) versus the lipid mixture alone. ^[38] It found that adding topical [corticosteroids](#) (selected for each participant on the basis of clinical severity of symptoms) to a lipid mixture significantly improved erythema (P = 0.04) and overall severity of disease (P = 0.007) at week 4 compared with a lipid mixture alone (outcomes measured using a visual 4-point rating scale; absolute results presented graphically). ^[38]

The RCT also found that adding topical corticosteroids to a lipid mixture (ceramide-3 and patented nanoparticles) significantly improved pruritus at week 8 ($P = 0.018$) compared with the lipid mixture alone (measured using a visual 4-point rating scale; absolute results presented graphically).^[38]

The second RCT (221 people aged 12 years or older with a history of moderate to severe eczema for at least 2 years and with a severe or very severe acute flare) compared two weekly regimens: methylprednisolone aceponate 0.1% (potent) once daily plus emollient once daily for two consecutive days, followed by emollient twice daily for 5 days for up to 16 weeks, versus emollient alone twice daily for up to 16 weeks.^[39] Before being randomised, all participants had been treated for their acute flare using open-label methylprednisolone aceponate 0.1% and open-label emollient for a maximum of 4 weeks; only those people whose flare was stabilised were randomised. The RCT found that disease severity (as measured by EASI) worsened in both groups, but that topical corticosteroids plus emollient had significantly lower deterioration compared with emollient alone at 16 weeks (mean increase of 0.50 with topical corticosteroids plus emollient v mean increase of 2.97 with emollient alone; $P < 0.001$).^[39]

Relapse rates

The second RCT found that topical corticosteroids plus emollient significantly increased the proportion of people who did not have a relapse compared with emollient alone by 16 weeks (87% with topical corticosteroids plus emollient v 66% with emollient alone; $P < 0.0001$; HR 3.5, 95% CI 1.9 to 6.4; absolute results not reported).^[39]

Corticosteroids versus emollients:

We found one RCT comparing mild corticosteroids versus emollients,^[24] and one systematic review (search date 2003, 1 RCT)^[35] and one additional RCT^[40] comparing potent corticosteroids versus emollients.

Symptom severity

The RCT (72 adults, mean age 45.5 years with moderate eczema) that compared mild corticosteroids versus emollients was a three-arm trial comparing hydrocortisone 0.5% cream, Kamillosan cream, and vehicle cream in a left–right side comparison design. The results should be interpreted with caution as the study design comparing Kamillosan versus either alternative treatment means that there was considerably more data available for Kamillosan (results available for 69 people for Kamillosan, 36 for hydrocortisone, and 33 for vehicle cream); this may have biased the results in favour of Kamillosan. The RCT found that hydrocortisone 0.5% was less effective than Kamillosan cream for improving pruritus, erythema, and desquamation (significance assessment not performed).^[24]

Relapse rates

The RCT identified by the systematic review^[35] (295 adults, aged 12–65 years, with moderate eczema who had been previously stabilised using fluticasone propionate 0.05% cream or 0.005% ointment once or twice daily) found that participants applying fluticasone propionate 0.05% cream or 0.005% ointment twice weekly were less likely to experience a disease flare within 16 weeks than were participants allocated to emollient (fluticasone propionate 0.05% cream v emollient: RR 5.8, 95% CI 3.1 to 10.8; $P < 0.001$; results presented graphically; fluticasone propionate 0.005% ointment v emollient: RR 1.9, 95% CI 1.2 to 3.2; $P = 0.010$; results presented graphically). Participants using fluticasone propionate were advised to apply cream to both known "healed" sites and any newly occurring sites of eczema and improvement in scoring of eczema was measured overall. Therefore, it is uncertain whether improvements in eczema score were because of prevention of relapse or improvement in newly occurring sites of eczema.

The additional RCT (231 children and 117 adults, aged 3 months to 65 years, with moderate to severe eczema who had previously responded to fluticasone propionate 0.05% cream twice daily for up to 4 weeks) also observed a significantly lower relapse rate in children applying fluticasone propionate 0.05% cream twice weekly plus emollients compared with children receiving vehicle plus emollients for 16 weeks (relapse rate: 58/229 [25%] with fluticasone v 79/119 [66%] with emollient; OR 7.7, 95% CI 4.6 to 12.8; $P < 0.001$).^[40]

Corticosteroids versus pimecrolimus:

[See benefits of pimecrolimus, p 13 .](#)

Pimecrolimus plus corticosteroids versus vehicle cream plus corticosteroids:

[See benefits of pimecrolimus, p 13 .](#)

Pimecrolimus versus vehicle, plus topical corticosteroids for flares:

[See benefits of pimecrolimus, p 13 .](#)

Corticosteroids versus tacrolimus:

See benefits of tacrolimus, p 19 .

Corticosteroids plus tacrolimus versus corticosteroids alone:

See benefits of tacrolimus, p 19 .

Corticosteroids plus tacrolimus versus tacrolimus alone:

We found two RCTs comparing corticosteroids plus tacrolimus versus tacrolimus alone. ^[41] ^[42]

Symptom severity

The first three-arm open-label RCT (45 children with eczema) compared three interventions: the moderate corticosteroid clobetasone butyrate 0.05% once daily plus tacrolimus 0.03% once daily, tacrolimus 0.03% twice daily, and clobetasone butyrate 0.05% twice daily for 4 weeks. ^[41] It found that combined treatment significantly improved the median percentage improvement in the modified Eczema Area and Severity Index (mEASI; scale of 0–90, where 90 is worst symptoms and body area affected) compared with tacrolimus 0.03% alone at 4 weeks (median percentage improvement in mEASI: 98.7% with tacrolimus 0.03% plus clobetasone butyrate 0.05% v 81.9% with tacrolimus 0.03%; mean difference in percentage reduction in EASI 19.0%, 95% CI 10.5% to 27.6%; P = 0.001).

The second RCT (82 adults with eczema) compared the potent corticosteroid desoximetasone 0.25% plus tacrolimus 0.1% versus tacrolimus 0.1% alone. ^[42] The RCT was within-participant design; each participant was randomised to receive either tacrolimus plus desoximetasone or tacrolimus alone to one side of the body, and the alternative medication to the other side. The RCT found that desoximetasone 0.25% plus tacrolimus 0.1% significantly improved symptom scores and the Physician's Global Assessment (PGA) compared with tacrolimus 0.1% alone at 21 days (reduction in symptom score [scale 0–15, with 15 being the most severe symptoms]: 8.1 with tacrolimus 0.1% plus desoximetasone 0.25% v 7.3 with tacrolimus 0.1% alone; mean difference 0.8, 95% CI 0.4 to 1.2; P = 0.0002; PGA [scale 0–6, with 6 being flare of eczema]: 1.9 with tacrolimus 0.1% plus desoximetasone 0.25% v 2.2 with tacrolimus 0.1% alone; mean difference 0.3, 95% CI 0.1 to 0.5; P = 0.004).

The RCT also found that tacrolimus 0.1% plus desoximetasone 0.25% significantly improved the proportion of people with no pruritus compared with tacrolimus 0.1% alone at 3 days (58/69 [84%] with tacrolimus 0.1% plus desoximetasone 0.25% v 49/69 [71%] with tacrolimus 0.1% alone; P = 0.04). ^[42]

Harms:

Corticosteroids versus placebo:

The systematic review found that trials that specifically gathered data on skin thinning and suppression of the pituitary–adrenal axis failed to find any evidence of harm (numbers not reported). ^[21] Minor adverse effects, such as burning, stinging, irritation, folliculitis, hypertrichosis, contact dermatitis, and pigmentary disturbances, occurred in <10% of the people.

The first subsequent RCT did not report any harms. ^[30]

The second subsequent RCT found that the proportion of people reporting adverse events was lower with hydrocortisone butyrate 0.1% than with vehicle, but significance was not assessed (48/139 [35%] with hydrocortisone butyrate 0.1% v 56/145 [39%] with vehicle; significance not assessed). Most adverse events were mild to moderate and not related to study medication. ^[31] The most common adverse events were nasopharyngitis, application-site burning, pyrexia, upper respiratory tract infection, ear infection, application-site pruritus, and cough. Telangiectasia, skin atrophy, and striae were not reported in either group.

The third subsequent RCT reported 40 adverse effects, which were comparable among groups (absolute results not reported). ^[32] Seven adverse effects were considered possibly or probably related to study medication (4/96 [4%] with clobetasol propionate 0.05% lotion v 1/100 [1%] with clobetasol propionate 0.05% emollient v 2/33 [6%] with vehicle; significance not assessed). Most adverse effects were mild or moderate; details about the type of adverse effects were not reported. There were no cases of clinically significant skin atrophy or telangiectasia.

Different frequencies of corticosteroid application versus each other:

One RCT identified by the review reported no clinically important skin thinning. ^[35]

Different formulations of corticosteroid versus each other:

See harms of corticosteroids versus placebo.

Different corticosteroids versus each other:

The first RCT involved two studies of identical design. In the first RCT, 20/67 (29%) of people applying fluticasone propionate 0.05% and 21/67 (31%) applying hydrocortisone 1% reported adverse events, the most common (>5%) of which were general symptoms.^[36] In the second RCT, 28/59 (42%) of people applying fluticasone propionate 0.05% and 22/54 (35%) applying hydrocortisone 0.1% butyrate reported adverse events, the most common (>5%) of which was respiratory tract infection. The second RCT found no clinically significant skin thinning.^[37]

Corticosteroids plus emollients versus emollients alone:

One RCT found that adverse events occurred in 17/112 (15%) people with topical corticosteroids plus emollient compared with 26/109 (24%) people with emollient alone; significance was not assessed.^[39] The types of adverse events were not specified, but no adverse events were considered to be related to study medication. Worsening of eczema was reported for 6/112 (5%) people with topical corticosteroids plus emollient compared with 15/109 (14%) people with emollient alone; significance not assessed.

Corticosteroids versus emollients:

The systematic review and RCT gave no information on adverse effects.^[35]^[24] The additional RCT found no clinically significant skin thinning.^[40] It also found that fluticasone propionate cream or ointment exerted no significant effect of HPA-axis function during short or longer term treatments (up to 20 weeks).^[40]

Corticosteroids versus pimecrolimus:

See harms of pimecrolimus, p 13 .

Pimecrolimus plus corticosteroids versus vehicle cream plus corticosteroids:

See harms of pimecrolimus, p 13 .

Pimecrolimus versus vehicle, plus topical corticosteroids for flares:

See harms of pimecrolimus, p 13 .

Corticosteroids versus tacrolimus:

See harms of tacrolimus, p 19 .

Corticosteroids plus tacrolimus versus corticosteroids alone:

See harms of tacrolimus, p 19 .

Corticosteroids plus tacrolimus versus tacrolimus alone:

The first RCT found that tacrolimus 0.03% alone significantly increased the proportion of people with skin burning compared with tacrolimus 0.03% plus clobetasone butyrate 0.05% (7/15 [47%] with 0.03% tacrolimus versus 2/15 [13%] with tacrolimus 0.03% plus clobetasone butyrate 0.05%; $P = 0.042$).^[41] The RCT found no significant difference in the proportion of people with increased itching among the three groups (20% with tacrolimus 0.03% v 13.3% with clobetasone butyrate 0.05% v 6.7% with tacrolimus 0.03% plus clobetasone butyrate 0.05%; P among groups = 0.562; absolute numbers not reported). The second RCT did not report on adverse effects.^[42]

Comment:**Corticosteroids versus placebo:**

Most of these studies were done between 1960 and 1980, when studies of this nature were often poorly designed. Some only reported preference data, making it difficult to interpret the size of effect. Those that did report treatment effect found that it was large. However, none of the studies compared betamethasone 17-valerate versus placebo, despite the fact that this is considered as the standard comparator for new corticosteroids in modern studies. Nearly all studies were of <4 weeks' duration.^[21] There is insufficient evidence to discern the "best" topical corticosteroids because most trials have only compared one against another, but seldom against the same one and never all together. There is a general lack of industry-independent studies comparing topical corticosteroids against each other, and studies are usually too short to inform clinical practice on long-term control. Overall, studies found little difference in the number of people responding to treatment between once- and twice-daily application of potent corticosteroids.

Clinical guide:

In general terms, the lowest potency topical corticosteroid that achieves a good response is used, and the strength of preparation will depend on the age, body site, and severity of lesions to be treated. Because children may be more prone to skin thinning than are adults, particular care is taken to avoid the use of potent preparations to sensitive sites such as the face, axillae, or nappy area. Children may need short bursts of potent corticosteroids to bring their eczema into remission, which is then maintained by emollients and weaker corticosteroid preparations. Adults usually need potent corticosteroids to control eczema on their body and limbs — typically used in short bursts

of a few days to a week, followed by a break period when emollients only are used. Patients' adherence to corticosteroids may be limited by perceived risks of skin thinning and systemic adverse effects. Therefore, patients, carers, and possibly general practitioners need to be provided adequate information concerning the safety, potency, and appropriate use of topical corticosteroids.

OPTION PIMECROLIMUS

Symptom severity

Compared with vehicle Pimecrolimus 1.0% is more effective at improving clearance of eczema at 3 to 6 weeks, and improving pruritus at 1 or 6 weeks ([high-quality evidence](#)).

Compared with vehicle, plus topical corticosteroids for flares Pimecrolimus 1.0% plus topical corticosteroids for flares seems more effective at improving clearance at 1 week, but we don't know if it is more effective in the longer term ([moderate-quality evidence](#)).

Compared with corticosteroids Pimecrolimus 1.0% may be less effective at improving clearance at 1 week, and at improving pruritus at 1 or 3 weeks ([low-quality evidence](#)).

Compared with tacrolimus We don't know whether pimecrolimus 1.0% is more effective than tacrolimus 0.03% at improving clearance or pruritus at 1, 3, or 6 weeks, or if it is more effective than tacrolimus 0.1% at improving clearance at 1 week, but pimecrolimus 1.0% may be less effective than tacrolimus 0.1% at improving clearance at 3 or 6 weeks ([low-quality evidence](#)).

Different frequencies of application of pimecrolimus versus each other Pimecrolimus 0.1% 4 times daily seems no more effective than pimecrolimus 1.0% two times daily at improving clearance or pruritus at 3 weeks ([moderate-quality evidence](#)).

Relapse rates

Compared with vehicle, plus topical corticosteroids for flares Pimecrolimus 1.0% plus topical corticosteroids for flares may be more effective at reducing the number of flares ([low-quality evidence](#)).

Quality of life

Compared with vehicle Pimecrolimus 1.0% may be more effective at improving the quality of life of parents with children with eczema at 29 days ([low-quality evidence](#)).

Compared with vehicle, plus topical corticosteroids for flares Pimecrolimus 1.0% seems to be more effective at improving quality of life in adults with eczema flares who also use corticosteroids as needed ([moderate-quality evidence](#)).

Note

There seems to be similar rates of adverse effects (application-site skin burning and skin infections) with pimecrolimus 1% and vehicle, pimecrolimus 1% and tacrolimus 0.03% and 0.1%, and with different frequencies of application of pimecrolimus 1%; however, pimecrolimus may cause more application-site skin burning than betamethasone valerate. There is a potential cancer risk from the use of pimecrolimus and tacrolimus, but published RCTs did not identify any cases of cancer, and there have been no long-term observational studies investigating the risk.

For GRADE evaluation of interventions for eczema, [see table, p 39](#).

Benefits:

Pimecrolimus versus vehicle:

We found one systematic review (search date 2006) ^[43] and one subsequent RCT ^[44] comparing pimecrolimus 1.0% versus vehicle. The systematic review included people with a broad range of ages (infants, children, and adults).

Symptom severity

The systematic review ^[43] found that pimecrolimus 1.0% twice daily significantly increased the proportion of people with complete or almost complete clearance according to the Investigator's Global Assessment (IGA) compared with vehicle twice daily at 3 and 6 weeks (3 weeks: 5 RCTs, 783 people; 169/506 [33%] with pimecrolimus 1.0% v 29/277 [10%] with vehicle; RR 2.72, 95% CI 1.84 to 4.03; 6 weeks: 3 RCTs, 589 people; 160/390 [41%] with pimecrolimus 1.0% v 40/199 [20%] with vehicle; RR 2.03, 95% CI 1.50 to 2.74). Of the 5 RCTs in these analyses, the diagnosis of eczema was not certain in one RCT, and the follow-up was poor in two RCTs.

The review also found that pimecrolimus 1.0% twice daily significantly increased the proportion of people with mild or absent pruritus (0 or 1 measured on a pruritus score) compared with vehicle twice daily at 1, 3, and 6 weeks (1 week: 3 RCTs, 472 people; 167/268 [62%] with pimecrolimus v 64/204 [31%] with vehicle; RR 1.89, 95% CI 1.51 to 2.35; 3 weeks: 5 RCTs, 783 people; 333/506 [66%] with pimecrolimus v 87/277 [31%] with vehicle; RR 2.02, 95% CI 1.69 to 2.42; 6 weeks: 3

RCTs, 589 people; 240/390 [62%] with pimecrolimus v 67/199 [34%] with vehicle; RR 1.82, 95% CI 1.48 to 2.25).^[43]

The subsequent RCT (200 people aged >12 years with mild to moderate facial eczema) compared pimecrolimus 1.0% twice daily versus vehicle twice daily.^[44] The use of topical corticosteroids was not permitted in the RCT. The discontinuation rate in this RCT was high (27/101 [27%] with pimecrolimus 1% v 60/99 [61%] with vehicle; significance not assessed); the main reason for discontinuation was unsatisfactory effect. The results presented here are for the intention-to-treat analysis (people randomised to treatment who took at least one dose and who had at least one post-baseline measurement). It found that pimecrolimus 1.0% significantly increased the proportion of people with clear or almost clear facial eczema according to the IGA compared with vehicle at 6 weeks (47% with pimecrolimus 1.0% v 16% with vehicle; $P < 0.001$; absolute numbers not reported). It also found that pimecrolimus 1.0% significantly decreased the proportion of people with eyelid dermatitis between baseline and 6 weeks compared with vehicle (81% at baseline and 55% at 6 weeks with pimecrolimus 1.0% v 85% at baseline and 81% at 6 weeks with vehicle; $P < 0.001$; absolute numbers not reported).

The RCT found that pimecrolimus 1.0% significantly increased the proportion of people with no or mild pruritus on the head or neck (scale 0 [no pruritus] to 3 [severe pruritus]) compared with vehicle at 6 weeks (70% with pimecrolimus 1.0% v 34% with vehicle; $P < 0.001$; absolute numbers not reported).^[44]

Quality of life

The systematic review^[43] identified one RCT^[45] that met *Clinical Evidence* reporting criteria.

The RCT (195 infants with mild to severe eczema) compared pimecrolimus (129 children) versus vehicle (66 children).^[45] It only assessed quality of life of parents, not of the children receiving treatment. It found that pimecrolimus significantly improved parents' quality of life, as measured by the Parents' Quality of Life Index Atopic Dermatitis (PQoL-AD; includes 5 domains, a higher score indicates better quality of life) between baseline and 29 days compared with vehicle cream (mean percentage change in PQoL-AD from baseline: psychosomatic well-being subscale: 15% with pimecrolimus 1% v 6% with vehicle; effects on social life subscale: 7% with pimecrolimus 1% v 2% with vehicle; confidence in medical treatment subscale: 10% with pimecrolimus 1% v 4% with vehicle; emotional coping subscale: 16% with pimecrolimus 1% v 6% with vehicle; acceptance of disease subscale: 20% with pimecrolimus 1% v 7% with vehicle; $P < 0.05$ for each subscale comparison). The discontinuation rate in this RCT was high (13/130 [10%] with pimecrolimus 1% v 25/66 [38%] with vehicle; significance not assessed); the main reason for discontinuation was unsatisfactory effect, so these results should be interpreted with caution. The results presented here are for the intention-to-treat analysis (last observation carried forward for parents of 195 children randomised to treatment who took at least one dose and who had at least one post-baseline measurement).^[45]

Pimecrolimus versus vehicle, plus topical corticosteroids for flares:

We found one systematic review (search date 2006)^[43] and three subsequent RCTs^[46] ^[47] ^[48] comparing pimecrolimus 1.0% versus vehicle, plus topical corticosteroids for flares.

Symptom severity

The systematic review^[43] found that pimecrolimus 1.0% twice daily plus topical corticosteroids for flares significantly increased the proportion of people with complete or almost complete clearance according to the IGA at 1 week compared with vehicle twice daily plus topical corticosteroids for flares (2 RCTs, 526 people; 126/387 [33%] with pimecrolimus 1.0% v 11/139 [8%] with vehicle; RR 3.45, 95% CI 1.66 to 7.14). Follow-up was poor in both RCTs.

Relapse rates

The systematic review^[43] found that pimecrolimus 1.0% significantly increased the proportion of people with no flares at 6 months and 12 months compared with vehicle twice daily plus topical corticosteroids for flares (6 months: 9 RCTs, 3091 people; 1122/1835 [61%] with pimecrolimus 1.0% v 503/1256 [40%] with vehicle; RR 1.47, 95% CI 1.32 to 1.64; 12 months: 2 RCTs, 962 people; 453/678 [67%] with pimecrolimus 1.0% v 115/284 [40%] with vehicle; RR 1.69, 95% CI 1.45 to 1.96). Of the 9 RCTs, in these analyses, the diagnosis of eczema was not certain in 5 RCTs, and the follow-up was poor in the other 4 RCTs.

Two RCTs identified by the review^[43] comparing pimecrolimus versus vehicle, with moderately potent topical corticosteroids for flares, provided data at 12 months; both RCTs found that the proportion of people requiring corticosteroids was significantly reduced with pimecrolimus 1.0% twice daily at 12 months compared with vehicle (437/678 [64%] with pimecrolimus 1.0% v 104/284 [37%] with vehicle; RR 1.76, 95% CI 1.50 to 2.08).

The first subsequent RCT (184 children aged 2–17 years with a history of severe eczema) compared pimecrolimus 1% twice daily versus vehicle cream twice daily while symptoms were present.^[46] The trial was designed to assess corticosteroid-sparing effects. During flares (unacceptable itching/scratching or onset of oozing), treatment with prednicarbate 0.25% was used as rescue medication and study medication was discontinued. The trial intended to include only children with active severe disease, but at screening only 48% had active severe disease. The RCT found that, in the complete trial population, there was no significant difference in the number of days requiring topical corticosteroid use between pimecrolimus and vehicle at 24 weeks (29 days with pimecrolimus 1% v 35 days with vehicle; $P = 0.18$).^[46] In the subgroup of children with severe active disease at baseline, pimecrolimus significantly reduced the number of days requiring topical corticosteroids at 24 weeks (28 days with pimecrolimus 1% v 45 days with vehicle; $P = 0.002$). The proportion of children followed up from randomisation to the end of the study was not clear.

The second subsequent RCT (543 adults with a history of mild or moderate atopic dermatitis who were clear or almost clear of symptoms at baseline) found that pimecrolimus 1% applied at the onset of relapse significantly increased the mean number of days without use of topical corticosteroids for flares compared with vehicle cream over 26 weeks (152 days with pimecrolimus v 139 days with vehicle cream; $P < 0.001$).^[47] It also found that pimecrolimus significantly decreased the number of flares requiring use of topical corticosteroids compared with vehicle cream over 26 weeks (0.97 flares with pimecrolimus v 1.39 flares with vehicle cream; $P = 0.0014$).

The third subsequent RCT (521 children aged 2–17 years with a history of mild or moderate atopic dermatitis who were clear or almost clear of symptoms at baseline) found that pimecrolimus 1% at the onset of relapse significantly increased the mean number of days without use of topical corticosteroids for flares compared with vehicle cream over 26 weeks (160 days with pimecrolimus v 138 days with vehicle cream; $P < 0.001$).^[48] It also found that pimecrolimus significantly decreased the number of flares requiring use of topical corticosteroids compared with vehicle cream over 26 weeks (0.84 flares with pimecrolimus v 1.68 flares with vehicle cream; $P < 0.001$).

Quality of life

The review^[43] did not perform a meta-analysis because of differences in outcome measures; we therefore report only the one RCT assessing this outcome that met *Clinical Evidence* reporting criteria.^[49]

The RCT (192 adults with eczema) compared pimecrolimus 1% twice daily versus vehicle twice daily used at the first signs or symptoms of flares.^[49] Emollients and reactive use of topical corticosteroids were permitted. The RCT found that pimecrolimus 1% significantly improved quality of life, as measured by the Quality of Life Index for Atopic Dermatitis (QoLIAD; scale 0–25, higher score indicates impaired quality of life) and the Dermatology Life Quality Index (DLQI; scale 0–30, higher score indicates impaired quality of life) compared with vehicle at 24 weeks (mean percentage decrease in QoLIAD: 26% with pimecrolimus v 7% with vehicle; $P = 0.002$; mean percentage decrease in DLQI: 22% with pimecrolimus v 7% with vehicle; $P = 0.01$; absolute results not reported).

Pimecrolimus plus corticosteroids versus corticosteroids alone:

We found one RCT (47 adults and children with severe eczema on 2 symmetric extremities) comparing pimecrolimus 1% twice daily plus fluticasone 0.05% once daily with vehicle cream once daily plus fluticasone 0.05% twice daily.^[50] The RCT was within-participant design; each participant was randomised to receive either pimecrolimus plus fluticasone or vehicle plus fluticasone to target sites on one side of the body, and the alternative medication to target sites on the other side.

Symptom severity

The RCT found that there was no significant difference between pimecrolimus plus fluticasone and vehicle plus fluticasone in the modified Eczema Area and Severity Index (mEASI) at 15 days (results displayed graphically; $P = 0.26$).^[50] It also found that there was no significant difference between the two groups in the proportion of target sites clear or almost clear according to the IGA of disease severity at 15 days (18/45 [40%] with pimecrolimus plus fluticasone v 17/45 [38%] with vehicle plus fluticasone; $P = 0.51$).

Pimecrolimus versus corticosteroids:

We found one systematic review (search date 2006) comparing pimecrolimus 1.0% versus topical corticosteroids.^[43] The systematic review identified no RCTs that met *Clinical Evidence* reporting criteria comparing pimecrolimus versus mild corticosteroids, or comparing pimecrolimus versus mid-potency corticosteroids; however, it identified one RCT (87 adults, aged 18–71 years) comparing pimecrolimus 1.0% twice daily versus the potent corticosteroid betamethasone valerate 0.1% twice daily, which we report below.

Symptom severity

The systematic review reported that betamethasone valerate 0.1% significantly increased the proportion of people with >50% improvement on the Physician's Global Assessment compared with pimecrolimus 1.0% twice daily at 3 weeks (24/45 [53%] with pimecrolimus 1.0% v 37/42 [88%] with betamethasone valerate 0.1%; RR 0.61, 95% CI 0.45 to 0.81).^[43]

The review also found that betamethasone valerate 0.1% twice daily significantly increased the proportion of people with mild or absent pruritus (0 or 1 measured on a pruritus score) compared with pimecrolimus 1.0% twice daily at 1 week and 3 weeks (1 week: 1 RCT, 87 people; 18/45 [40%] with pimecrolimus 1.0% v 33/42 [79%] with betamethasone valerate 0.1%; RR 0.51, 95% CI 0.34 to 0.75; 3 weeks: 1 RCT, 87 people; 21/45 [47%] with pimecrolimus 1.0% v 34/42 [81%] with betamethasone valerate 0.1%; RR 0.58, 95% CI 0.41 to 0.81).^[43]

Pimecrolimus versus tacrolimus:

We found one systematic review (search date 2006)^[43] and one subsequent RCT^[51] comparing pimecrolimus 1.0% versus tacrolimus. The systematic review performed separate meta-analyses for comparisons with two different doses of tacrolimus; pimecrolimus 1.0% twice daily versus tacrolimus 0.03% twice daily and pimecrolimus 1.0% twice daily versus tacrolimus 0.1% twice daily.

Symptom severity

The systematic review^[43] found no significant difference between pimecrolimus 1.0% twice daily and tacrolimus 0.03% twice daily in the proportion of people with complete or almost complete clearance according to the IGA at 1, 3, and 6 weeks, although there was a trend in favour of tacrolimus (1 week: 2 RCTs, 567 children; 45/288 [16%] with pimecrolimus 1.0% v 48/279 [17%] with tacrolimus 0.03%; RR 0.91, 95% CI 0.63 to 1.31; 3 weeks: 2 RCTs, 567 people; 76/288 [26%] with pimecrolimus 1.0% v 88/279 [32%] with tacrolimus 0.03%; RR 0.82, 95% CI 0.58 to 1.15; 6 weeks: 2 RCTs, 567 people; 109/288 [38%] with pimecrolimus 1.0% v 126/279 [45%] with tacrolimus 0.03%; RR 0.84, 0.69 to 1.02). The diagnosis of eczema was not certain in one RCT.

The systematic review^[43] found no significant difference between pimecrolimus 1.0% twice daily and tacrolimus 0.1% twice daily in the proportion of people with complete or almost complete clearance according to the IGA at 1 week; however, tacrolimus 0.1% twice daily significantly increased the proportion of people with complete or almost complete clearance according to the IGA at 3 weeks and 6 weeks compared with pimecrolimus 1.0% twice daily (1 week: 2 RCTs, 639 people; 29/317 [9%] with pimecrolimus 1.0% v 35/322 [11%] with tacrolimus 0.1%; RR 0.85, 95% CI 0.53 to 1.34; 3 weeks: 2 RCTs, 639 people; 47/317 [15%] with pimecrolimus 1.0% v 86/322 [27%] with tacrolimus 0.1%; RR 0.56, 95% CI 0.41 to 0.77; 6 weeks: 2 RCTs, 639 people; 75/317 [24%] with pimecrolimus 1.0% v 132/322 [41%] with tacrolimus 0.1%; RR 0.58, 95% CI 0.46 to 0.74). Both RCTs had poor follow-up.

The review^[43] identified one RCT (141 people) assessing pruritus. The RCT found no significant difference between pimecrolimus 1.0% twice daily and tacrolimus 0.03% twice daily in the proportion of people with mild or absent pruritus at 1 week and 6 weeks, although tacrolimus 0.03% significantly improved the proportion with mild or absent pruritus at 3 weeks compared with pimecrolimus 1.0% (1 week: 39/71 [55%] with pimecrolimus 1.0% v 48/70 [69%] with tacrolimus 0.03%; RR 0.80, 95% CI 0.62 to 1.04; 3 weeks: 41/71 [58%] with pimecrolimus 1.0% v 52/70 [74%] with tacrolimus 0.03%; RR 0.78, 95% CI 0.61 to 0.99; 6 weeks: 45/71 [63%] with pimecrolimus 1.0% v 48/70 [69%] with tacrolimus 0.03%; RR 0.92, 95% CI 0.73 to 1.17). The diagnosis of eczema was not certain in the RCT.

The subsequent RCT (188 people >16 years with moderate eczema) compared pimecrolimus 1% twice daily with tacrolimus 0.1% twice daily.^[51] It found that tacrolimus 0.1% significantly improved the change between baseline and 6 weeks in the Eczema Area Severity Index (EASI) score compared with pimecrolimus 1% (percentage reduction in EASI [scale 0–72, where higher score indicates more severe eczema]: 43% reduction with pimecrolimus 1% v 59% reduction with tacrolimus 0.1%; $P = 0.01$; absolute results not reported). It also found that tacrolimus 0.1% significantly increased the proportion of people with an improvement of 1 or more grades in the Investigator Global Atopic Dermatitis Assessment (IGADA) between baseline and 6 weeks, and also the proportion of people with clear or almost clear disease according to the IGADA at 6 weeks, compared with pimecrolimus (proportion of people with improvement in 1 or more grades of the IGADA [symptom severity score ranging from 0 {clear} to 5 {very severe}]: 62% with pimecrolimus 1% v 79% with tacrolimus 0.1%; $P < 0.02$; proportion of people with clear or almost clear eczema on the IGADA: 31% with pimecrolimus 1% v 45% with tacrolimus 0.1%; $P = 0.04$; absolute results for both outcomes presented graphically). This RCT had a withdrawal rate of 21% (premature withdrawal: 18/98 [18%] with tacrolimus 0.1% v 21/90 [23%] with pimecrolimus 1%; significance not assessed).

Different frequencies of application of pimecrolimus versus each other:

Symptom severity

We found one systematic review (search date 2006),^[43] which identified one crossover RCT^[52] that met *Clinical Evidence* reporting criteria comparing pimecrolimus 1.0% twice daily and pimecrolimus 1.0% 4 times daily.

The review^[43] reported no significant difference between pimecrolimus 1.0% twice daily and pimecrolimus 1.0% 4 times daily in the proportion of people with complete or almost complete clearance according to the IGA at 3 weeks (1 RCT, 49 people; 7/24 [29%] with pimecrolimus 1.0% twice daily v 7/25 [28%] with pimecrolimus 1.0% 4 times daily; RR 1.04, 95% CI 0.43 to 2.52).

The review^[43] also found no significant difference between pimecrolimus 1.0% twice daily and pimecrolimus 1.0% twice daily in the proportion of people with mild or absent pruritus at 3 weeks (1 RCT, 49 people; 12/24 [50%] with pimecrolimus 1.0% twice daily v 13/25 [52%] with pimecrolimus 1.0% 4 times daily; RR 0.96, 95% CI 0.56 to 1.67).

Harms:

Pimecrolimus versus vehicle:

The systematic review^[43] found no significant difference between pimecrolimus 1.0% twice daily and vehicle twice daily in overall adverse effects or application-site skin burning (overall adverse effects: 4 RCTs, 827 people; 261/480 [54.4%] with pimecrolimus 1.0% v 188/347 [54.2%] with vehicle; RR 0.92, 95% CI 0.82 to 1.02; application-site skin burning: 5 RCTs, 914 people; 34/507 [7%] with pimecrolimus 1.0% v 22/407 [5%] with vehicle; RR 1.40, 95% CI 0.90 to 2.18).

The subsequent RCT found that adverse effects were more common with pimecrolimus 1.0% than with vehicle, but significance was not assessed (proportion of people with at least 1 adverse effect: 72/101 [71%] with pimecrolimus v 60/99 [61%] with vehicle).^[44] The most common adverse effect was application-site irritation (27/101 [27%] with pimecrolimus v 22/99 [22%] with vehicle).

Pimecrolimus versus vehicle, plus topical corticosteroids for flares:

The systematic review^[43] found no significant difference between pimecrolimus 1.0% twice daily plus topical corticosteroids for flares and vehicle twice daily plus topical corticosteroids for flares in overall adverse effects, skin infections, viral skin infections, bacterial skin infections, or application-site skin burning (overall adverse effects: 4 RCTs, 1398 people; 480/702 [68%] with pimecrolimus 1.0% v 444/696 [64%] with vehicle; RR 1.07, 95% CI 1.00 to 1.16; skin infections: 3 RCTs, 718 people; 105/483 [22%] with pimecrolimus 1.0% v 39/235 [17%] with vehicle; RR 1.14, 95% CI 0.75 to 1.72; viral skin infection: 3 RCTs, 718 people; 39/483 [8%] with pimecrolimus 1.0% v 9/235 [4%] with vehicle; RR 1.79, 95% CI 0.89 to 3.61; bacterial skin infections: 4 RCTs, 982 people; 41/659 [6%] with pimecrolimus 1.0% v 23/323 [7%] with vehicle; RR 0.84, 95% CI 0.51 to 1.39; application-site skin burning: 3 RCTs, 999 people; 29/549 [5%] with pimecrolimus 1.0% v 5/450 [1%] with vehicle; RR 4.36, 95% CI 1.75 to 10.85).

The first subsequent RCT found that adverse effects occurred in 86% of children in the pimecrolimus 1% group compared with 85% in the vehicle group (absolute results not reported; significance not assessed).^[46] The most common adverse effect was respiratory tract infection. Adverse effects suspected to be drug related occurred in 5/95 [5%] with pimecrolimus (5 events) compared with 4/89 (4%) with vehicle (10 events; significance between groups not assessed). Drug-related adverse effects included application-site burning, herpes simplex virus, impetigo, molluscum contagiosum, allergic eye disorders, and contact dermatitis.

The second subsequent RCT found that the most common adverse effects were nasopharyngitis, headache, and influenza (nasopharyngitis: 54/264 [21%] with pimecrolimus 1% v 38/254 [15%] with vehicle; reported as not significant; P value not reported; headache: 52/264 [20%] with pimecrolimus v 34/254 [13%] with vehicle; significance not assessed; influenza: 17/264 [6%] with pimecrolimus v 17/254 [7%] with vehicle; significance not assessed).^[47] Application-site burning occurred in 11/264 (4%) people with pimecrolimus versus 2/254 (0.8%) people with vehicle cream; significance was not assessed.

The third subsequent RCT found that the most common adverse effects were nasopharyngitis, pyrexia, and influenza (nasopharyngitis: 57/246 [23%] with pimecrolimus v 39/260 [15%] with vehicle; pyrexia: 19/246 [8%] with pimecrolimus v 11/260 [4%] with vehicle; influenza: 17/246 [7%] with pimecrolimus v 16/260 [6%] with vehicle; significance for all outcomes not assessed).^[53] Application-site burning occurred in 3/246 (1%) children with pimecrolimus versus 8/260 (3%) children with vehicle; significance was not assessed.

Pimecrolimus plus corticosteroids versus corticosteroids alone:

The RCT did not directly compare adverse effects with combination treatment versus corticosteroids alone; it found that 10 adverse effects occurred across groups, including one local event (superinfected eczema) at a non-target site (no further data reported).^[50]

Pimecrolimus versus corticosteroids:

The systematic review^[43] found that pimecrolimus 1.0% twice daily significantly increased overall adverse effects and application-site skin burning compared with betamethasone valerate 0.1% twice daily (overall adverse effects: 1 RCT, 87 people; 32/45 [71%] with pimecrolimus 1.0% v 19/42 [45%] with betamethasone valerate 0.1%; RR 1.57, 95% CI 1.07 to 2.30; application-site skin burning: 1 RCT, 87 people; 22/45 [49%] with pimecrolimus 1.0% v 4/42 [10%] with betamethasone valerate 0.1%; RR 5.13, 95% CI 1.93 to 13.66).

One RCT^[54] identified by the review^[43] assessed long-term safety and tolerability of unrestricted continuous use of corticosteroids for 1 year. The RCT (658 adults with moderate to severe atopic dermatitis) compared pimecrolimus 1% cream versus topical corticosteroids (potent for limbs and trunk; weak for face). It found that 3/330 (1%) people taking topical corticosteroids developed striae and 36/330 (11%) developed burning.^[54] Similar studies in children are lacking.

Pimecrolimus versus tacrolimus:

The systematic review^[43] performed separate meta-analyses for comparisons with two different doses of tacrolimus; pimecrolimus 1.0% twice daily versus tacrolimus 0.03% twice daily and pimecrolimus 1.0% twice daily versus tacrolimus 0.1% twice daily. It found no significant difference between pimecrolimus 1.0% twice daily and tacrolimus 0.03% twice daily in overall adverse effects, skin infections, bacterial skin infections, viral skin infections, and application-site burning (overall adverse effects: 2 RCTs, 567 people; 97/288 [34%] with pimecrolimus 1.0% v 91/279 [33%] with tacrolimus 0.03%; RR 1.03, 95% CI 0.90 to 1.17; skin infections: 2 RCTs, 567 people; 5/288 [2%] with pimecrolimus 1.0% v 2/279 [1%] with tacrolimus 0.03%; RR 1.65, 95% CI 0.12 to 22.75; bacterial skin infections: 1 RCT, 141 people; 3/71 [4%] with pimecrolimus 1.0% v 0/70 [0%] with tacrolimus 0.03%; RR 6.90, 95% CI 0.36 to 131.23; viral skin infections: 2 RCTs, 567 people; 2/288 [0.7%] with pimecrolimus 1.0% v 2/279 [0.7%] with tacrolimus 0.03%; RR 1.03, 95% CI 0.15 to 6.96; application-site skin burning: 2 RCTs, 567 people; 34/288 [12%] with pimecrolimus 1.0% v 28/279 [10%] with tacrolimus 0.03%; RR 1.17, 95% CI 0.55 to 2.49).

The systematic review^[43] found no significant difference between pimecrolimus 1.0% twice daily and tacrolimus 0.1% twice daily in overall adverse effects, skin infections, viral skin infections and application-site skin burning (overall adverse effects: 2 RCTs, 639 people; 70/317 [22%] with pimecrolimus 1.0% v 81/322 [25%] with tacrolimus 0.1%; RR 1.04, 95% CI 0.47 to 2.26; skin infections: 2 RCTs, 639 people; 5/317 [2%] with pimecrolimus 1.0% v 3/322 [1%] with tacrolimus 0.1%; RR 1.60, 95% CI 0.37 to 6.99; viral skin infections: 1 RCT, 413 people; 1/203 [0.5%] with pimecrolimus 1.0% v 1/210 [0.5%] with tacrolimus 0.1%; RR 1.03, 95% CI 0.07 to 16.43; application-site skin burning: 31/317 [10%] with pimecrolimus 1.0% v 47/322 [15%] with tacrolimus 0.1%; RR 0.76, 95% CI 0.36 to 1.62).

The subsequent RCT found that there was no significant difference between pimecrolimus 1% and tacrolimus 0.1% in adverse effects at 6 weeks (21/90 [23%] with pimecrolimus 1% v 32/98 [33%] with tacrolimus 0.1%; P = 0.19).^[51] The most common adverse effects were application-site burning and itching in both groups.

Different frequencies of application of pimecrolimus versus each other:

The systematic review^[43] found no significant difference between pimecrolimus 1.0% twice daily and pimecrolimus 1.0% 4 times daily in overall adverse effects and application-site skin burning (overall adverse effects: 1 RCT, 49 people; 4/24 [17%] with pimecrolimus 1.0% twice daily v 3/25 [12%] with pimecrolimus 1.0% 4 times daily; RR 1.39, 95% CI 0.35 to 5.57; application-site skin burning: 1 RCT, 49 people; 3/24 [13%] with pimecrolimus 1.0% twice daily v 3/25 [12%] with pimecrolimus 1.0% 4 times daily; RR 1.04, 95% CI 0.23 to 4.66).

Harms alerts:

The FDA has issued a public health advisory to inform people about a potential cancer risk from the use of topical pimecrolimus and tacrolimus (www.fda.gov). This concern is based on information from animal studies, case reports in a small number of people, and knowledge of how drugs in this class work. It may take human studies of 10 years or longer to determine if use of pimecrolimus or tacrolimus is linked to cancer. In the meantime, this risk is uncertain, and the FDA advises that pimecrolimus and tacrolimus should be used only as labelled, after other prescription treatments have failed to work or cannot be tolerated.^[55]

Comment: The systematic review^[43] did not identify any trials that assessed the effects of topical pimecrolimus compared with topical corticosteroids, of topical pimecrolimus compared with topical tacrolimus, or of different frequencies of application of pimecrolimus 1% on health-related quality of life.

Clinical guide:

In the UK, NICE recommends that topical pimecrolimus is used as a second-line option for resistant head and neck eczema.^[56] German guidelines, however, recommend topical pimecrolimus as first-line treatment at sensitive sites.^[57] It may be used in children (older than 2 years of age) and adults, and may be useful for people who become dependent on topical corticosteroids at sensitive sites such as the face, where there is a significant risk of skin thinning. Pimecrolimus is licensed as a second-line agent in the US, although the site of application is not restricted. In practice, pimecrolimus is being aimed at people with mild eczema; however, this is being done in the absence of RCTs that compare it with existing therapy for such a group. Pimecrolimus is generally well tolerated. Published RCTs did not confirm the theoretical risk of skin cancer and lymphoma associated with pimecrolimus. However, adequate epidemiological investigations are missing, so this important question remains unclear.

OPTION TACROLIMUS

Symptom severity

Compared with vehicle Tacrolimus 0.03% and 0.1% seem more effective at clearing eczema and improving disease severity and pruritus ([moderate-quality evidence](#)).

Tacrolimus plus corticosteroids compared with corticosteroids alone We don't know whether tacrolimus 0.03% plus corticosteroids (moderate) is more effective than corticosteroids (moderate) alone at improving disease severity scores ([low-quality evidence](#)).

Compared with corticosteroids Tacrolimus 0.03% and 0.1% seem to be more effective than hydrocortisone acetate (mild) at improving disease severity, but we don't know whether tacrolimus 0.03% and 0.1% are more effective than clobetasone butyrate (moderate), hydrocortisone butyrate (potent), and methylprednisolone aceponate (potent) (moderate-quality evidence).

Tacrolimus 0.03% compared with tacrolimus 0.1% Tacrolimus 0.03% may be as effective as tacrolimus 0.1% in clearing eczema at 3 weeks but may be less effective at 12 weeks (low-quality evidence).

Compared with pimecrolimus 1.0% We don't know whether tacrolimus 0.03% is more effective at improving clearance or pruritus at 1, 3, or 6 weeks, or if tacrolimus 0.1% is more effective at improving clearance at 1 week, but tacrolimus 0.1% may be more effective than pimecrolimus 1.0% at improving clearance at 3 or 6 weeks (low-quality evidence).

Compared with corticosteroids plus tacrolimus Tacrolimus alone may be less effective than corticosteroids (moderate and potent) plus tacrolimus at improving disease severity ([very low-quality evidence](#)).

Relapse rates

Compared with vehicle Tacrolimus 0.03% may be more effective at preventing relapse (low-quality evidence).

Quality of life

Compared with vehicle Tacrolimus 0.03% and 0.1% seem more effective at improving quality of life (moderate-quality evidence).

Tacrolimus 0.03% compared with tacrolimus 0.1% Tacrolimus 0.03% may be more effective at improving quality of life in adults, but we don't know if it is more effective at improving quality of life in children (very low-quality evidence).

Note

Tacrolimus 0.1% and 0.03% may be associated with an increased risk of application-site skin burning compared with vehicle and corticosteroids. There is a potential cancer risk from the use of pimecrolimus and tacrolimus, but published RCTs did not identify any cases of cancer, and there have been no long-term observational studies investigating the risk.

For GRADE evaluation of interventions for eczema, [see table, p 39](#).

Benefits:

Tacrolimus versus vehicle:

We found two systematic reviews (search dates 2004^[58] and 2006^[59]), one subsequent report of two RCTs,^[60] and 4 subsequent RCTs^{[61] [62] [63] [64]} comparing tacrolimus versus vehicle. The two systematic reviews performed similar meta-analyses, so we report the meta-analyses from the most recent systematic review here.^[59] However, the reviews^{[58] [59]} identified additional RCTs that were not included in the meta-analyses; these RCTs are reported separately.

Symptom severity

The systematic review performed an analysis of effects of tacrolimus 0.03% at 3 weeks.^[59] It found that tacrolimus 0.03% significantly improved the proportion of people with a Physician's Global Evaluation of 90% improvement or better compared with vehicle at 3 weeks (1 RCT, 87 children aged 7–16 years, with moderate/severe atopic dermatitis: 25/43 [58%] with tacrolimus 0.03% v 12/44 [27%] with vehicle; RR 2.13, 95% CI 1.24 to 3.68).

A further analysis performed by the review assessing effects of tacrolimus 0.1% at 3 weeks found no significant difference between tacrolimus 0.1% and vehicle in the proportion of people with a Physician's Global Evaluation of 90% improvement or better at 3 weeks (1 RCT, 93 children aged 7–16 years, with moderate/severe atopic dermatitis: 21/49 [43%] with tacrolimus 0.1% v 12/44 [27%] with vehicle; RR 1.57, 95% CI 0.88 to 2.81).^[59]

A meta-analysis performed by the review assessing effects of tacrolimus 0.03% at 12 weeks found that tacrolimus 0.03% significantly improved the proportion of people with a Physician's Global Evaluation of 90% improvement or better compared with vehicle at 12 weeks (2 RCTs, 983 adults and children with moderate to severe eczema: 100/328 [30%] with tacrolimus 0.03% v 22/328 [7%] with vehicle; RR 4.53, 95% CI 2.93 to 7.00).^[59]

A meta-analysis performed by the review assessing effects of tacrolimus 0.1% at 12 weeks found that tacrolimus 0.1% significantly improved the proportion of people with a Physician's Global Evaluation of 90% improvement or better compared with vehicle at 12 weeks (2 RCTs, 983 adults and children with moderate to severe eczema: 125/327 [38%] with tacrolimus 0.03% v 22/328 [8%] with vehicle; RR 5.69, 95% CI 3.72 to 8.72).^[59]

A subgroup analysis assessing tacrolimus 0.1% at 3 weeks found no significant difference between tacrolimus 0.1% and vehicle in the proportion of people with a Physician's Global Evaluation of 90% improvement or better at 3 weeks (1 RCT, 93 children aged 7–16 years, with moderate/severe atopic dermatitis: 21/49 [43%] with tacrolimus 0.1% v 12/44 [27%] with vehicle; RR 1.57, 95% CI 0.88 to 2.81).^[59]

One additional RCT (317 children and adolescents aged 2–15 years with mild to moderate eczema) identified by the reviews found that tacrolimus 0.03% twice daily was superior to vehicle in inducing significant improvement in itch at day 4 and at 6 weeks (mean improvement on 10-cm visual analogue scale; at day 4: 1.7 cm with tacrolimus v 1.0 cm with vehicle; $P = 0.001$; at 6 weeks: 2.8 cm with tacrolimus v 1.2 cm with vehicle; $P < 0.001$).^[65]

The subsequent report of two identically designed RCTs (one paediatric RCT [aged 2–15 years] and one adult RCT [aged 16 years or older]; combined population of 618 people with mild to moderate eczema) compared tacrolimus 0.03% with vehicle cream, both twice daily for up to 6 weeks.^[60] The discontinuation rate in the RCTs was high, but was significantly lower with vehicle than with tacrolimus 0.03% (50/310 [16%] with tacrolimus 0.03% v 102/308 [33%] with vehicle; $P < 0.0001$); the main reasons for discontinuation were loss to follow-up, adverse events, lack of efficacy, voluntary withdrawal, and major protocol violation. The results presented here are for all people randomised (617 people). The RCTs found that tacrolimus 0.03% significantly increased the proportion of people with an Investigator's Global Assessment (IGA) score of "clear" or "almost clear" at 6 weeks (154/310 [50%] with tacrolimus 0.03% v 89/307 [29%] with vehicle; $P > 0.0001$). They also found that tacrolimus 0.03% significantly reduced the percentage improvement in the Eczema Area Severity Index (EASI; score 0–72, with higher score indicating more severe disease) compared with vehicle between baseline and 6 weeks (percentage improvement in EASI: 55% with tacrolimus 0.03% v 25% with vehicle; $P < 0.0001$).

The subsequent report also found that tacrolimus 0.03% significantly improved patient's perception of itch (as measured by a 10-cm visual analogue scale, increasing score indicates worse itch) compared with vehicle at 6 weeks (2.4 cm with tacrolimus 0.03% v 3.7 cm with vehicle; $P < 0.0001$).^[60]

Relapse rates

The first subsequent RCT (250 children aged 2–15 years with mild to severe eczema) compared tacrolimus 0.03% versus vehicle; each intervention was applied once daily 2 times a week for 12 months.^[61] Before being randomised, all participants had been treated using open-label tacrolimus 0.03% for 8 days to 6 weeks; only when an IGA score of 2 or less was achieved were participants randomised into the double-blind disease control period. If the children had a disease exacerbation during the 12-month disease control period, tacrolimus 0.03% was applied twice daily for 1 to 6 weeks until flare resolution; after resolution, children went back to the treatment that they had been allocated to. The discontinuation rate in this RCT was high (30/125 [24%] with tacrolimus 0.03% v 43/125 [34%] with vehicle; significance not assessed); the main reasons for discontinuation were

lack of flare resolution within 6 weeks, lack of efficacy, and withdrawal of consent. The results presented here are for the full analysis set (all 250 children). The RCT found that tacrolimus 0.03% significantly increased the proportion of children with no flares over 12 months compared with vehicle (proportion of children with no flares: 63/125 [50%] with tacrolimus 0.03% v 37/125 [30%] with vehicle; $P < 0.001$).

The second subsequent RCT (224 people aged >16 years with mild to severe eczema) compared tacrolimus 0.03% versus vehicle; each intervention was applied once daily 2 times a week for 12 months.^[62] Before being randomised, all participants had been treated using open-label tacrolimus 0.03% for 8 days to 6 weeks; only when an IGA score of 2 or less was achieved were participants randomised into the double-blind disease control period. If the participants had a disease exacerbation during the 12-month disease control period, tacrolimus 0.03% was applied twice daily for 1 to 6 weeks until flare resolution; after resolution, participants went back to the treatment that they had been allocated to. The discontinuation rate in this RCT was high (35/116 [30%] with tacrolimus 0.03% v 53/108 [49%] with vehicle; significance not assessed); the main reasons for discontinuation were lack of flare resolution within 6 weeks and withdrawal of consent. The results presented here are for the full analysis set (all 224 participants). The RCT found that tacrolimus 0.03% significantly increased the proportion of people with no flares over 12 months compared with vehicle (proportion of people with no flares: 66/116 [57%] with tacrolimus 0.03% v 32/108 [30%] with vehicle; $P < 0.001$).

The third subsequent RCT (105 children aged 2–15 years with moderate to severe eczema) compared tacrolimus 0.03% versus vehicle; each intervention was applied once daily three times a week for up to 40 weeks.^[63] Before being randomised, all children had been treated using open-label tacrolimus 0.03% for up to 16 weeks as needed, and had randomly received either tacrolimus 0.03% or alclometasone dipropionate 0.05% ointment twice daily for 4 days at the beginning of the 16-week period; only when children were clear or almost clear of disease were they randomised into the double-blind disease control period; however, one child without clear or almost clear disease was randomly assigned, but was not included in the efficacy analysis. If the children had a disease exacerbation during the 40-week disease control period, tacrolimus 0.03% was applied twice daily for up to 8 weeks until flare resolution; after resolution, children went back to the treatment that they had been allocated to. Non-medicated topical agents were permitted during the control period, including emollients. The discontinuation rate in this RCT was high (29/68 [43%] with tacrolimus 0.03% v 26/37 [70%] with vehicle; significance not assessed); the reasons for discontinuation were loss to follow-up, voluntary withdrawal, lack of flare resolution within 8 weeks, lack of efficacy, and administrative reasons (not specified). The results presented here are for all children who received at least one application of study medication and who were clear or almost clear of disease at randomisation (103 children). The RCT found that tacrolimus 0.03% significantly increased the number of disease-free days compared with vehicle over 40 weeks (174 days with tacrolimus v 107 days with vehicle; $P = 0.0008$). It also found that tacrolimus 0.03% significantly increased the median time to first relapse compared with vehicle (116 days with tacrolimus 0.03% v 31 days with vehicle; $P = 0.04$). The RCT reported that the proportion of children with at least one relapse of disease was similar in both groups (72%; absolute results not reported; significance not reported).

The fourth subsequent RCT (197 people aged >2 years [53% aged 2–15 years; 47% aged 16 years or older] with moderate to severe eczema) compared tacrolimus 0.03% or 0.1% (depending on age; 0.03% for children <16 years, 0.1% for people 16 years or older) versus vehicle; each intervention was applied once daily three times a week for up to 40 weeks.^[64] Before being randomised, all participants had been treated using open-label tacrolimus for up to 16 weeks as needed, and had randomly received either tacrolimus or corticosteroids (alclometasone dipropionate ointment 0.05% for children and triamcinolone acetonide ointment 0.1% for adults) twice daily for 4 days at the beginning of the 16-week period; only when participants were clear or almost clear of disease were they randomised into the double-blind disease control period. If the participants had a disease exacerbation during the 40-week disease control period, tacrolimus was applied twice daily for up to 8 weeks until flare resolution; after resolution, participants went back to the treatment that they had been allocated to. Non-medicated topical agents were permitted during the control period, including emollients. The discontinuation rate in this RCT was high (55/125 [44%] with tacrolimus v 28/72 [39%] with vehicle; significance not assessed); the reasons for discontinuation were voluntary withdrawal, loss to follow-up, lack of flare resolution within 8 weeks, lack of efficacy, adverse events, and administrative reasons (not specified). The results presented here are for all people who received at least one application of study medication, who were clear or almost clear of disease at randomisation, and who had one post-baseline evaluation (195 people). The RCT found that tacrolimus significantly increased the number of flare-free treatment days compared with vehicle over 40 weeks (177 days with tacrolimus v 134 days with vehicle; $P = 0.003$). It also found that tacrolimus significantly increased the median time to first relapse compared with vehicle (169 days with tacrolimus v 43 days with vehicle; $P = 0.037$). It found no significant difference between tacrolimus and vehicle in the proportion of people with at least one flare at 40 weeks, although there was a

trend in favour of tacrolimus (77/124 [62%] with tacrolimus v 47/71 [66%] with vehicle; $P = 0.539$). The RCT did not report results for subgroups by age.

Quality of life

The first systematic review^[58] identified one report^[66] that comprised three separate RCTs assessing quality of life in three populations: adults, children, and toddlers (using the dermatology life quality index in adults, the children's dermatology life quality index, and a modified version of this instrument in toddlers). It found that both tacrolimus 0.03% and 0.1% significantly improved quality of life at 12 weeks (985 people, 50% of children and adults, and two-thirds of children with severe atopic dermatitis, with similar baseline quality of life scores in each age group; mean change in quality of life change scores: adults: -5.6 with vehicle v -21.1 with tacrolimus 0.03% v -27.1 with tacrolimus 0.1%; $P < 0.005$ for all comparisons; children: -8.1 with vehicle v -24.4 with tacrolimus 0.03% v -24.1 with tacrolimus 0.1%; $P < 0.000$ for both doses of tacrolimus versus vehicle; toddlers: -7.9 with vehicle v -30.8 with tacrolimus 0.03% v -35.6 with tacrolimus 0.1%; $P < 0.000$ for both doses of tacrolimus versus vehicle).^[66]

One subsequent RCT found that quality of life (as measured by the Infants' Dermatology Life Quality Index [IDLQI]; scale 0–30, where higher score indicates impaired quality of life) was similar with tacrolimus 0.03% and vehicle at 12 months, although significance was not assessed (IDLQI for children aged 2–4 years: 4.0 with tacrolimus 0.03% v 3.8 with vehicle; IDLQI for children aged 5–15 years: 4.6 with tacrolimus 0.03% v 4.8 with vehicle; significance not assessed).^[61]

Tacrolimus plus corticosteroids versus corticosteroids alone:

We found one three-arm open-label RCT (45 children with eczema) comparing three interventions: tacrolimus 0.03% twice daily, the moderate corticosteroid clobetasone butyrate 0.05% twice daily, and tacrolimus 0.03% once daily plus clobetasone butyrate 0.05% once daily for 4 weeks.^[41] The RCT found no significant difference between tacrolimus 0.03% plus clobetasone butyrate 0.05% and clobetasone butyrate 0.05% alone in the median percentage improvement in the modified Eczema Area and Severity Index (mEASI; scale 0–90, where 90 is worst symptoms and body area affected) at 4 weeks (98.7% with tacrolimus 0.03% plus clobetasone butyrate 0.05% v 95.1% with clobetasone butyrate 0.05%; mean difference +6.5%, 95% CI -2.0% to +15.1%; $P = 0.128$).

Tacrolimus versus corticosteroids:

We found two systematic reviews (search dates 2004^[58] and 2006^[59]) and two subsequent RCTs^[67]^[41] comparing tacrolimus versus corticosteroids. The two systematic reviews performed similar meta-analyses, so we report the meta-analyses from the most recent systematic review here.^[59] However, the first systematic review^[58] identified additional RCTs that were not included in the meta-analyses; these RCTs are reported separately.

Symptom severity

The systematic review performed a meta-analysis comparing mild potency corticosteroids versus tacrolimus 0.03% at 3 weeks. It found that tacrolimus 0.03% significantly increased the proportion of people with a Physician's Global Evaluation of 90% improvement or better compared with hydrocortisone acetate 1% at 3 weeks (2 RCTs, 1184 children with moderate to severe eczema; 149/399 [37%] with tacrolimus 0.03% v 57/392 [15%] with hydrocortisone acetate 1%; RR 2.56, 95% CI 1.95 to 3.3).^[59]

One analysis from the systematic review assessing mild potency corticosteroids versus tacrolimus 0.1% at 3 weeks found that tacrolimus 0.1% significantly increased the proportion of people with a Physician's Global Evaluation of 90% improvement or better compared with hydrocortisone acetate 1% at 3 weeks (1 RCT, 560 children with moderate to severe eczema: 90/186 [48%] with tacrolimus 0.1% v 29/185 [16%] with hydrocortisone acetate 1%; RR 3.09, 95% CI 2.14 to 4.4).^[59]

The first subsequent RCT was a three-arm open-label RCT (45 children with eczema) comparing three interventions: tacrolimus 0.03% twice daily, the moderate corticosteroid clobetasone butyrate 0.05% twice daily, and tacrolimus 0.03% once daily plus clobetasone butyrate 0.05% once daily for 4 weeks.^[41] It found that tacrolimus 0.03% was significantly less effective than clobetasone butyrate 0.05% at increasing the median percentage improvement in the modified Eczema Area and Severity Index (mEASI; scale of 0–90, where 90 is worst symptoms and body area affected) at 4 weeks (82% with tacrolimus v 95% with clobetasone butyrate; mean difference 12.5%, 95% CI 2.4% to 22.7%; $P = 0.018$).

One analysis from the systematic review, assessing potent corticosteroids versus tacrolimus 0.03% at 3 weeks, found that tacrolimus 0.03% was significantly less effective at increasing the proportion of people with a Physician's Global Evaluation of 90% improvement or better compared with hydrocortisone butyrate 0.1% at 3 weeks (1 RCT, 379 adults with moderate to severe eczema; 73/193

[38%] with tacrolimus 0.03% v 95/186 [51%] with hydrocortisone butyrate 0.1%; RR 0.74, 95% CI 0.59 to 0.9).^[59]

One analysis from the review, assessing potent corticosteroids versus tacrolimus 0.1% at 3 weeks, found no significant difference between tacrolimus 0.1% and hydrocortisone butyrate 0.1% in the proportion of people with a Physician's Global Evaluation of 90% improvement or better at 3 weeks (1 RCT, 377 adults with moderate to severe eczema; 94/193 [49%] with tacrolimus 0.03% v 95/186 [51%] with hydrocortisone butyrate 0.1%; RR 0.96, 95% CI 0.79 to 1.1).^[59]

One analysis from the review, assessing potent corticosteroids (trunk and extremities) plus mild corticosteroids (head and neck) versus tacrolimus 0.1% found that tacrolimus 0.1% significantly increased the proportion of people with a Physician's Global Evaluation of 90% improvement or better compared with a combined topical corticosteroids regimen (potent corticosteroids hydrocortisone butyrate 0.1% for trunk and extremities plus mild corticosteroids hydrocortisone acetate 1% for head and neck) at 6 months (1 RCT, 972 adults with moderate/severe eczema; 298/487 [61%] with tacrolimus 0.1% v 225/486 [46%] with corticosteroids; RR 1.32, 95% CI 1.17 to 1.4; P < 0.0001).^[59]

The second subsequent RCT (265 children aged 2–15 years with an acute flare of severe eczema) compared three interventions: tacrolimus 0.03% twice daily versus the potent corticosteroid methylprednisolone aceponate once daily plus placebo once daily for 2 to 3 weeks.^[67] It found no significant difference between tacrolimus 0.03% and methylprednisolone aceponate 0.1% in the proportion of people with an IGA score of "clear" or "almost clear" at 3 weeks (91/136 [66.9%] with tacrolimus 0.03% v 86/129 [66.7%] with methylprednisolone aceponate 0.1%; P = 0.9314). It also found no significant difference between tacrolimus 0.03% and methylprednisolone aceponate 0.1% in the mean percentage improvement in the Eczema Area and Severity Index at 3 weeks (85.3% with tacrolimus 0.03% v 89.7% with methylprednisolone aceponate 0.1%; P = 0.0667).

The RCT also found that tacrolimus 0.03% was significantly less effective at improving itch compared with methylprednisolone aceponate 0.1% at 3 weeks (mean improvement in itch measured by visual analogue scale [0 mm = no itch, 100 mm = worst itch imaginable]: −49.8 mm with tacrolimus 0.03% v −61.7 mm with methylprednisolone aceponate 0.1%; P = 0.0004).^[67]

Tacrolimus plus corticosteroids versus tacrolimus alone:

See [benefits of corticosteroids](#), p 6 .

Tacrolimus 0.03% versus tacrolimus 0.1%:

We found one systematic review (search date 2004)^[58] comparing tacrolimus 0.03% with tacrolimus 0.1%; the review identified 6 RCTs.

Symptom severity

Pooled analysis for three RCTs (696 children aged 2–17 years, 570 adults with moderate to severe eczema)^[68] ^[69] ^[70] found no significant difference between 0.03% and 0.1% tacrolimus in people clear or achieving an excellent improvement at 3 weeks (168/423 [40%] with tacrolimus 0.03% v 202/424 [48%] with tacrolimus 0.1%; RR 0.89, 95% CI 0.67 to 1.19). The other three RCTs found that, compared with tacrolimus 0.03%, tacrolimus 0.1% significantly increased the proportion of people clear or achieving an excellent improvement at 12 weeks (100/328 [30%] with tacrolimus 0.03% v 125/327 [38%] with tacrolimus 0.1%; RR 0.80, 95% CI 0.65 to 0.99). The review found that there was no significant difference between tacrolimus 0.03% and tacrolimus 0.1% in participants' global assessment of response (better or much better) at 3 weeks and 12 weeks (3 weeks: 0.84, 95% CI 0.69 to 1.00; 12 weeks: 0.93, 95% CI 0.83 to 1.03; absolute numbers not reported).

Quality of life

The systematic review^[58] identified one study^[66] that comprised three separate RCTs assessing quality of life in three populations: adults, children, and toddlers (using the dermatology life quality index in adults, the children's dermatology life quality index, and a modified version of this instrument in toddlers). It found that, compared with tacrolimus 0.03%, tacrolimus 0.1% significantly improved quality of life in adults (P < 0.000). No significant difference was found between 0.03% and 0.1% tacrolimus in quality of life in infants or children (P = 0.937 in children; P = 0.224 in toddlers).

Tacrolimus versus pimecrolimus:

See [benefits of pimecrolimus](#), p 13 .

Tacrolimus compared with corticosteroids plus tacrolimus:

See [benefits of corticosteroids](#), p 6 .

Harms:**Tacrolimus versus vehicle:**

The first systematic review found that tacrolimus 0.03% and 0.1% significantly increased the proportion of people with skin burning compared with vehicle (173/425 [40%] with tacrolimus 0.03% v 92/426 [22%] with vehicle; RR 1.89, 95% CI 1.43 to 2.50; 187/430 [43%] with tacrolimus 0.1% v 90/426 [21%] with vehicle; RR 2.08, 95% CI 1.35 to 3.18).^[58] The systematic review did not report on adverse effects.^[59]

The subsequent report of the two RCTs found that the overall incidence of adverse effects was similar in both groups (46% with tacrolimus 0.03% v 52% with vehicle; absolute results not reported; significance not assessed).^[60] The most frequently reported adverse effects were skin burning or itching, increased itching, and skin erythema (skin burning or itching: 85/310 [27%] with tacrolimus 0.03% v 76/307 [25%] with vehicle; significance not assessed; increased itching: 90/310 [27%] with tacrolimus 0.03% v 115/307 [38%] with vehicle; P = 0.03; skin erythema: 40/310 [13%] with tacrolimus 0.03% v 74/307 [24%] with vehicle; P = 0.0003).

One subsequent RCT found that adverse events related to the study ointment were more common in the tacrolimus 0.03% group than in the vehicle group, although significance was not assessed (40/125 [32%] with tacrolimus 0.03% v 37/125 [30%] with vehicle; significance not assessed).^[61] Adverse effects included application-site pruritus, nasopharyngitis, and impetigo. Serious adverse events occurred in 7/125 (6%) people with tacrolimus 0.03% (bronchopneumonia, eczema herpeticum, infected eczema, gastroenteritis, staphylococcal infection, and asthma in 2 people) versus 1/125 (1%) with vehicle (sleep apnoea); significance not assessed.

Another subsequent RCT found that adverse events related to the study ointment were more common in the tacrolimus 0.03% group than in the vehicle group, although significance was not assessed (47/116 [41%] with tacrolimus 0.03% v 38/108 [35%] with vehicle).^[62] The most common adverse effects were application-site pruritus and folliculitis. Serious adverse events occurred in 5/116 (4%) people with tacrolimus 0.03% versus 3/108 (3%) with vehicle; significance was not assessed. Only two serious adverse events were considered to be probably related to study medication; application-site infection in the tacrolimus 0.03% group and eczema herpeticum in the vehicle group.

Another subsequent RCT reported that the incidence of adverse effects was similar in both groups (8/68 [12%] with tacrolimus 0.03% v 4/36 [11%] with vehicle; significance not assessed).^[63] The most frequently reported adverse effects were burning, pruritus, and skin infections (burning: 2/68 [2.9%] with tacrolimus 0.03% v 1/36 [2.8%] with vehicle; pruritus: 1/68 [1%] with tacrolimus 0.03% v 2/36 [6%] with vehicle; skin infections: 1/68 [1%] with tacrolimus 0.03% v 1/36 [3%] with vehicle).

Another subsequent RCT reported that the incidence of adverse effects was similar in both groups (10/125 [8.0%] with tacrolimus v 6/71 [8.5%] with vehicle; significance not assessed).^[64] The most frequently reported adverse effects were burning, pruritus, and skin infections (burning: 2/125 [2%] with tacrolimus v 1/71 [1%] with vehicle; pruritus: 1/125 [1%] with tacrolimus v 2/71 [3%] with vehicle; skin infections: 1/125 [0.8%] with tacrolimus v 1/71 [1.4%] with vehicle). The RCT reported malignancy in two people (1 person in the tacrolimus group, treatment group not stated for the other person); neither event was determined by the investigator to be treatment related.

Tacrolimus plus topical corticosteroids versus topical corticosteroids alone:

The RCT found that tacrolimus 0.03% plus clobetasone butyrate 0.05% increased the proportion of people with skin burning compared with clobetasone butyrate 0.05% alone, although significance was not assessed (2/15 [13%] with tacrolimus 0.03% plus clobetasone butyrate 0.05% v 1/15 [7%] with clobetasone butyrate 0.05%; P value not reported).^[41] The RCT found no significant difference in the proportion of people with increased itching among the three groups (20% with 0.03% tacrolimus v 13.3% with 0.05% clobetasone butyrate v 6.7% with 0.03% tacrolimus plus 0.05% clobetasone butyrate; P among groups = 0.562; absolute numbers not reported).

Tacrolimus versus corticosteroids:

The first systematic review found that tacrolimus 0.03% and 0.1% significantly increased the proportion of people with skin burning than did mild or potent topical corticosteroids.^[58] The systematic review did not report on adverse effects.^[59]

The first subsequent RCT found that tacrolimus 0.03% significantly increased the proportion of people with skin burning compared with clobetasone butyrate 0.05% (7/15 [47%] with tacrolimus 0.03% v 1/15 [7%] with clobetasone butyrate 0.05%; P = 0.010).^[41] The RCT found no significant difference in the proportion of people with increased itching among the three groups (20% with 0.03% tacrolimus v 13.3% with 0.05% clobetasone butyrate v 6.7% with 0.03% tacrolimus plus 0.05% clobetasone butyrate; P among groups = 0.562; absolute numbers not reported).

The second subsequent RCT found that adverse events occurred more frequently in the tacrolimus group than in the methylprednisolone aceponate group (6/136 [4%] with tacrolimus 0.03% v 0/129 [0%] with methylprednisolone aceponate 0.1%; significance not assessed). Adverse events included pruritus, erythema, skin burning, and hot flushes. ^[67]

Tacrolimus plus corticosteroids versus tacrolimus alone:

See [harms of corticosteroids](#), p 6 .

Tacrolimus 0.03% versus tacrolimus 0.1%:

The systematic review found that there was no significant difference in skin infections and skin burning between tacrolimus 0.1% and 0.03% (skin infections: 22/513 [4%] with tacrolimus 0.1% v 38/517 [7%] with tacrolimus 0.03%; RR 0.60, 95% CI 0.35 to 1.02; skin burning: 338/807 [42%] with tacrolimus 0.1% v 295/807 [37%] with tacrolimus 0.03%; RR 1.14, 95% CI 0.95 to 1.35). ^[58]

Tacrolimus versus pimecrolimus:

See [harms of pimecrolimus](#), p 13 .

Tacrolimus compared with corticosteroids plus tacrolimus:

See [harms of corticosteroids](#), p 6 .

Harms alerts:

The FDA issued a public health advisory to inform people about a potential cancer risk from the use of pimecrolimus and tacrolimus (www.fda.gov). This concern is based on information from animal studies, case reports in a small number of people, and knowledge of how drugs in this class work. ^[55]

We found one study that assessed the risk of non-melanoma skin cancer (NMSC) in 9813 patients (5052 people aged 2–19 years; 2144 people aged 20–39 years; 1929 people aged 40–59 years; 688 people aged 60 years or older) who were treated with tacrolimus 0.03% or 0.1% twice daily in US studies done between 1995 and 2001. ^[71] In total, 300/9813 (3%) people were followed up for 3 years or longer. During follow-up, 13 cases of NMSC were observed (10 basal cell carcinomas, 3 squamous cell carcinomas); 95% CI in patients age 40 years or older 361 to 1217 per 100,000 patient-years. As this range was similar to the age-specific incidence of first NMSC (adjusted to the 1988–1992 US white male population; 533/100,000 person-years) the authors concluded that the study does not indicate an increased risk of NMSC associated with tacrolimus treatment for eczema.

It may take human studies with a duration of 10 years or longer to determine if use of pimecrolimus or tacrolimus is linked to cancer. In the meantime, this risk is uncertain, and the FDA advises that pimecrolimus and tacrolimus should be used only as labelled, for people after other prescription treatments have failed to work or cannot be tolerated. ^[55]

Comment:

We also found one systematic review, written in Chinese; we are awaiting translation to assess it for inclusion. ^[72]

Clinical guide:

Tacrolimus 0.1% may be as effective as potent topical corticosteroids, although the results from RCTs are inconsistent, and may be more effective than mild topical corticosteroids. For patients whose eczema clears during treatment with tacrolimus twice daily, continued treatment of previously inflamed sites twice or three times a week may prevent disease exacerbation. Similarly to pimecrolimus, tacrolimus preparations are recommended as second-line treatments for children and adults with eczema because of their unknown long-term adverse effects. Topical tacrolimus may be useful for resistant eczema at sensitive sites such as the face, where the use of more potent topical corticosteroids carries a high risk of thinning of the skin and telangiectasia.

QUESTION

What are the effects of dietary interventions in adults with established eczema?

OPTION

VITAMIN E AND MULTIVITAMINS

Symptom severity

Vitamin E compared with placebo We don't know if vitamin E is more effective at reducing disease severity at 12 weeks to 8 months compared with placebo or selenium ([very low-quality evidence](#)).

Vitamins E or B alone compared with vitamin E plus vitamin B Vitamin E plus vitamin B2 may be more effective in reducing disease severity at 4 weeks compared with vitamins E or B alone ([very low-quality evidence](#)).

For GRADE evaluation of interventions for eczema, see [table](#), p 39 .

Benefits: **Vitamin E versus placebo:**
We found one RCT. ^[73]

Symptom severity

The RCT (96 adults and children, aged 10–60 years, with moderate/severe eczema involving 30–70% of the body surface) compared vitamin E supplementation versus placebo over 8 months. ^[73] The clinical assessment of pruritus was performed using the [SCORing Atopic Dermatitis](#) (SCORAD) index. It found that, compared with placebo, vitamin E significantly improved the proportion of people with "great improvement" (23/50 [46%] with vitamin E versus 1/46 [2%] with placebo; significance assessment not performed). It also found that, compared with placebo, vitamin E increased the proportion of people who went into almost complete remission (7/50 [14%] with vitamin E v 0/46 [0%] with placebo).

Vitamin E or vitamin B versus both vitamins combined:

We found one systematic review (search date 1999 ^[21]), which identified one RCT. ^[74]

Symptom severity

The RCT ^[74] (59 people with mild/moderate eczema of the dry type) identified by the review ^[21] had three arms: vitamin E (100 mg) alone versus vitamin B2 (riboflavin butyrate 20 mg) alone versus vitamin E plus vitamin B2 over 4 weeks. It found that, compared with vitamin E or vitamin B2 alone, vitamin E plus vitamin B2 significantly increased the proportion of people with an improved physicians' global assessment at 4 weeks (significance assessment not performed). However, the clinical significance of these results is difficult to interpret in the absence of a placebo. ^[74]

Harms: The RCTs did not report on harms. ^[73] ^[74]

Comment: It is likely that the results are generalisable to both adults and children.

QUESTION What are the effects of dietary interventions in children with established eczema?

OPTION EGG AND COW'S MILK EXCLUSION DIET

Symptom severity

Compared with hydrolysed cow's milk formulae We don't know whether amino-acid-based formulae is more effective at improving symptom severity at 2 to 3 months and 6 to 8 months in infants with cow's milk allergy/intolerance ([very low-quality evidence](#)).

Compared with normal diet Egg exclusion diet may be more effective at improving symptom severity at 4 weeks in infants with egg allergy ([very low-quality evidence](#)).

Adverse effects

Calcium, protein, and calorie deficiency are a risk in dairy-free diets.

For GRADE evaluation of interventions for eczema, [see table, p 39](#).

Benefits: We found one systematic review (search date 2006) ^[75] comparing egg and cow's milk exclusion diet versus other diets. The review identified 6 RCTs comparing cow's milk or egg exclusion diet versus a normal diet; however, it was only able to meta-analyse two RCTs because of differences in study design, populations, and outcome measures. Of the remaining RCTs, only one RCT ^[76] met *Clinical Evidence* reporting criteria; this RCT compared egg exclusion diet versus normal diet and is reported below.

Cow's milk exclusion diet versus normal diet:

Symptom severity

The systematic review found no significant difference between amino-acid-based formulae and hydrolysed cow's milk formulae in symptom severity (as assessed by the [SCORing Atopic Dermatitis index](#) [SCORAD]; scale 0–103, with higher score indicating more severe disease) at 2 to 3 months or 6 to 8 months (2 RCTs, 118 infants aged 1–10 months with eczema and cow's milk allergy/intolerance; 2–3 months: mean difference 0, 95% CI –4.87 to +4.87; 6–8 months: mean difference +1.06, 95% CI –1.67 to +3.80; mean combined scores not reported). ^[75] The follow-up and type of analysis (per protocol or intention to treat) was unclear in one RCT, and both RCTs had unclear allocation generation, allocation concealment, and masking.

Egg exclusion diet versus normal diet:

Symptom severity

The systematic review identified one RCT (62 young children, aged 11–17 months, with positive IgE antibodies to egg) that compared egg exclusion diet versus normal diet in infants with suspected

egg allergy.^[76] The RCT found that egg exclusion diet significantly increased the number of infants with reduced body surface area with eczema compared with normal diet at 4 weeks (25/28 [89%] with egg exclusion v 16/27 [59%] with normal diet; RR [calculated by review] 1.51, 95% CI 1.07 to 2.11; $P = 0.04$). Egg exclusion diet also significantly reduced eczema severity (assessed on 6 clinical features on a scale of 0–3 units at 16 body sites) compared with normal diet over 4 weeks (change in severity score of 9.4 points with egg exclusion v 3.3 points with normal diet; mean difference [calculated by review] 6.10, 95% CI 0.06 to 12.14). The two groups were not comparable at baseline; the egg exclusion group had more extensive and severe involvement than the normal diet group.

Harms: Calcium, protein, and calorie deficiency are always a risk in dairy-free diets in children. Three RCTs in the systematic review^[75] used potentially allergenic soya-based milk substitute, which itself can be allergenic in atopic eczema.

Comment: The clinical importance of changes in severity scores obtained in many studies is unknown. Drop-out rates are particularly high for elimination diets and those containing hydrolysate milk substitutes.^[21]

OPTION PROBIOTICS

Symptom severity

Compared with placebo or no treatment Probiotics seem no more effective at reducing parent-reported, participant-reported, or investigator-reported eczema severity (*moderate-quality evidence*).

Quality of life

Compared with placebo or no treatment We don't know whether probiotics are more effective at improving quality of life in parents of children with eczema (*very low-quality evidence*).

Note

Commercially available heat-inactivated lactobacillus may increase episodes of diarrhoea and bowel ischaemia, but regimens used in clinical trials have not been associated with adverse effects.

For GRADE evaluation of interventions for eczema, see table, p 39 .

Benefits: We found one systematic review (search date 2008, 12 RCTs, 781 children^[77]) comparing probiotics plus co-interventions (extensively hydrolysed infant formula or prebiotic preparations) versus control (co-intervention alone or microcrystalline cellulose).

Symptom severity

The systematic review found no significant difference between probiotics and control in participant-reported and parent-reported eczema symptoms (as measured using SCORing Atopic Dermatitis index [SCORAD] part C; scale 1–20, with higher score indicating worse symptoms) at the end of treatment (5 RCTs, 313 children; mean difference –0.40 [in favour of probiotics], 95% CI –1.30 to +0.50; combined scores for each group not reported). There was significant heterogeneity for this outcome ($I^2 = 77\%$); the reason for this is not clear, but it may be related to use of different probiotic strains.^[77] The systematic review also found no significant difference between probiotics and control in investigator-rated eczema severity (using total SCORAD scores; scale 0–103, with higher score indicating worse symptoms) at the end of study treatment (7 RCTs, 588 children; –0.67 [in favour of probiotics], 95% CI –2.91 to 1.57). There was significant heterogeneity for this outcome ($I^2 = 76\%$); the reason for this is not clear, but it may be related to differences in methodological quality, setting location, or sample size. One RCT in both analyses had poor follow-up and no intention-to-treat analysis. Subgroup analyses for trial design (crossover or parallel), type of probiotic, children's age, disease severity, allergic sensitisation, and food allergy did not change these conclusions.

Quality of life

The systematic review identified two RCTs^{[78] [79]} that assessed quality of life. The review did not perform a meta-analysis because of differences in the quality of life scores used. One RCT (56 children aged 6–18 months) found similar median changes in quality of life (as measured by the Dermatitis Family Impact Questionnaire; scale 0–30, where a higher score indicates greater impact on quality of life) during treatment (change over 8 weeks) and 4 weeks after treatment cessation (change over 16 weeks) between probiotic and placebo (change at 8 weeks: –2 with probiotic v –2 with placebo; change at 16 weeks: –2.5 with probiotic v +3 with placebo; significance not assessed).^[78] The systematic review reported that the differences between groups were not significant (P value not reported).^[77] The other RCT (54 children aged 1–55 months) found no significant difference between probiotics and placebo in change in parents' quality of life (psychosomatic well-being, effects on social life, satisfaction with medical care, dealing emotionally with eczema, accep-

tance of eczema) over 8 weeks (combined score for all 5 domains: 19.9 at baseline and 19.9 at 8 weeks with probiotic v 19.4 at baseline and 19.1 at 8 weeks; reported as not significant; P value not reported). Whether a high or low score on the scale indicates improved quality of life was not clear.^[79]

Harms: The systematic review found no significant difference between probiotics and control in gastrointestinal adverse effects (5 RCTs, 304 children; 25/150 [17%] with probiotics v 18/154 [12%] with control; RR 1.57, 95% CI 0.78 to 3.15). The systematic review also performed a harms search, and found 42 cases of suspected or confirmed probiotic sepsis in case reports and review articles; a probiotic origin could not be definitively identified in all 42 cases, and it was not possible to quantify the risk of sepsis. The review also identified a report of increased risk of fatal bowel ischaemia in critically ill patients treated with one particular combination of probiotics.^[77]

Comment: No convincing evidence exists to suggest that probiotic supplementation is an effective treatment for established eczema. Future RCTs could explore combinations of different strains and doses of lactobacilli.

OPTION FEW-FOODS DIET

We found no direct information from RCTs about whether few-foods diets are better than no active treatment in people with eczema. Few-foods diets are difficult to follow and are unpalatable.

For GRADE evaluation of interventions for eczema, see table, p 39 .

Benefits: We found one systematic review (search date 2006),^[75] which identified no RCTs that met *Clinical Evidence* reporting criteria.

Harms: We found no RCTs.

Comment: **Clinical guide:**
At present, there is no RCT evidence to support the use of a few-foods diet; the diet is difficult to follow and is unpalatable.

OPTION ELEMENTAL DIET

We found no direct information from RCTs about whether elemental diets are better than no active treatment in people with eczema. Elemental food diets are difficult to follow and are unpalatable.

For GRADE evaluation of interventions for eczema, see table, p 39 .

Benefits: We found one systematic review (search date 2006),^[75] which identified no RCTs that met *Clinical Evidence* reporting criteria.

Harms: We found no RCTs.

Comment: At present, there is no RCT evidence to support the use of an elemental diet; the diet is difficult to follow and is unpalatable.

OPTION ZINC SUPPLEMENTATION

Symptom severity

Compared with placebo Zinc sulphate supplements may be no more effective at reducing disease severity scores at 8 weeks (low-quality evidence).

For GRADE evaluation of interventions for eczema, see table, p 39 .

Benefits: **Zinc sulphate versus placebo:**
Symptom severity
We found one RCT (50 children, aged 1–16 years), which compared zinc sulphate (185.4 mg/day) versus placebo.^[80] It found no significant difference in combined disease severity score between zinc sulphate and placebo (mean combined disease severity score [0–70, higher is worse]: 36.1 at baseline and 48.7 at 8 weeks with zinc sulphate v 34.6 at baseline and 39.3 at 8 weeks with placebo; P = 0.64 for between-group comparison).

Harms: The RCT found that 6 people stopped taking the capsules, one (placebo) because of loose stools, one (zinc sulphate) because of severe exacerbation of eczema (attributed to the capsules by the parent), three (1 zinc, 2 placebo) developed a widespread itchy maculopapular rash 6 to 15 days

after starting treatment, and one (placebo) developed a herpes simplex virus skin infection recurrence.^[80]

Comment: None.

OPTION	PYRIDOXINE (VITAMIN B6)
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Symptom severity

Compared with placebo Pyridoxine (vitamin B6) may be no more effective at reducing disease severity scores at 4 weeks (*low-quality evidence*).

For GRADE evaluation of interventions for eczema, see table, p 39 .

Benefits: **Pyridoxine versus placebo:**
Symptom severity

We found one systematic review (search date 1999, 2 RCTs).^[21] The first RCT identified by the review was too small to be considered. The second RCT identified by the review (48 children with moderate/severe eczema) found no significant difference between pyridoxine and placebo in skin severity score at 4 weeks (median skin severity score [total area affected × overall degree of erythema, with a possible range 0–500] 92.3 at baseline and 109.0 at 4 weeks with pyridoxine v 125.5 at baseline and 77.0 at 4 weeks with placebo; reported as not significant).

Harms: One child developed a non-specific erythematous rash while taking pyridoxine.^[21]

Comment: There is insufficient RCT evidence to support the benefit of pyridoxine in the treatment of eczema.

OPTION	ESSENTIAL FATTY ACIDS (EVENING PRIMROSE OIL, BLACKCURRANT SEED OIL, FISH OIL)
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Symptom severity

Compared with placebo Essential fatty acids (evening primrose oil, blackcurrant seed oil, borage oil, or fish oil) may be no more effective at reducing disease severity scores (*low-quality evidence*).

For GRADE evaluation of interventions for eczema, see table, p 39 .

Benefits: **Essential fatty acids versus placebo:**
Symptom severity

We found one systematic review (search date 2002, 20 RCTs, 1357 people, aged 0.6–78 years, including 6 RCTs in adults only [293 adults], 9 RCTs in adults and children [679 people], and 5 RCTs in children [385 people])^[81] and one subsequent RCT.^[82] Effect size could not be calculated for 8 studies because of insufficient data on overall severity or component subscales of eczema. The review found no significant difference between essential fatty acids (evening primrose oil, borage oil, blackcurrant seed oil, fish oil) and placebo in physician-assessed overall severity (see table 3, p 38). The subsequent RCT found no significant difference in mean improvement in eczema between borage oil capsules (gamma linolenic acid 920 mg) and placebo at 12 weeks (see table 3, p 38).^[82]

Harms: The systematic review did not report on harms.^[81] The subsequent RCT found lower rates of adverse events with borage oil compared with placebo (diarrhoea: 6/85 [4%] with borage oil v 6/55 [11%] with placebo; nausea, vomiting, or both: 3/85 [4%] with borage oil v 5/55 [9%] with placebo; headache: 1/85 [1%] with borage oil v 4/55 [7%] with placebo; influenza-like symptoms: 22/85 [26%] with borage oil v 21/55 [38%] with placebo; significance assessment not performed).^[82]

Comment: Borage oil, blackcurrant oil, and evening primrose oil are all sources of gamma linolenic acid.^[81] It is likely that the results are generalisable to both adults and children.

QUESTION	What are the primary preventive effects of breastfeeding in predisposed infants?
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OPTION	PROLONGED BREASTFEEDING BY MOTHER STRAIGHT AFTER BIRTH
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We found no direct information from RCTs on the effects of breastfeeding straight after birth on the development of eczema in infants.

Note

Observational data suggest that exclusive breastfeeding for at least 3 months does not reduce eczema risk and there is no evidence to suggest that exclusive breastfeeding alleviates eczema symptoms, unless a child is allergic to cow's milk protein.

For GRADE evaluation of interventions for eczema, see table, p 39 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: We found one systematic review (search date 2008, 21 prospective cohort studies), which did not meet the inclusion criteria for this review. When assessing all studies, the review found no significant reduction in the risk of eczema with breastfeeding (OR 0.89, 95% CI 0.76 to 1.04).^[83] There was significant heterogeneity among studies ($P < 0.001$). Sensitivity analyses omitting studies that were outliers did not alter the results. Breastfeeding was associated with a decreased risk of eczema (OR 0.70, 95% CI 0.50 to 0.99) when analysis was restricted to the studies comparing breastfeeding with conventional formula feeding, although the difference between groups was of borderline significance. There was also no significant reduction in the risk of eczema with breastfeeding in study populations with atopic heredity (OR 0.78, 95% CI 0.58 to 1.05). Prolonged self-selected breastfeeding may be associated with unknown protective factors, leading to bias. It is unlikely that an RCT will be conducted in this area, for ethical reasons.

Clinical guide

Observational evidence suggests that exclusive breastfeeding for at least 3 months does not reduce eczema risk and there is no evidence to suggest that exclusive breastfeeding alleviates eczema symptoms, unless a child is allergic to cow's milk protein.

QUESTION What are the primary preventive effects of reducing allergens in predisposed infants?

OPTION CONTROL OF HOUSE DUST MITE

Development of eczema

House dust mite reduction compared with an education package on allergen avoidance or basic information about allergies Mite reduction using an impermeable mattress cover for the child's bed may be no more effective at reducing the incidence of children developing eczema at 24 months compared with advice for allergen avoidance, or information on allergies (low-quality evidence).

For GRADE evaluation of interventions for eczema, see table, p 39 .

Benefits: House dust mite reduction versus an education package on allergen avoidance or basic information about allergies:

Development of eczema

We found one RCT (696 newborn children, at high risk of developing allergies). It found no significant difference in the development of eczema between use of a mite impermeable mattress encasing for the child's bed versus a simple educational package on allergen avoidance versus basic information about allergies at 24 months.^[84]

Harms: The RCT gave no information on adverse effects.^[84]

Comment: Clinical guide:

House dust mite avoidance did not show a protective effect on the development of sensitisation to house dust mites or symptomatic allergy in children at 24 months.

QUESTION What are the primary preventive effects of dietary interventions in infants?

OPTION MATERNAL DIETARY RESTRICTION DURING PREGNANCY AND LACTATION

Development of eczema

Maternal antigen avoidance diet compared with normal diet We don't know whether maternal antigen avoidance diets during pregnancy or lactation are effective in reducing the incidence of infants developing eczema during their first 12 to 18 months of life compared with normal diets (very low-quality evidence).

Note

Maternal antigen avoidance diets may decrease mean gestational weight gain by 1.8 kg for a 60-kg woman, and may be associated with a higher risk of preterm birth.

For GRADE evaluation of interventions for eczema, see table, p 39 .

Benefits:	Maternal allergen avoidance versus no avoidance: Development of eczema We found one systematic review (search date 2006, 4 RCTs, 334 pregnant women on antigen avoidance diet during pregnancy or during both pregnancy and lactation).^[85] RCTs identified by the review were found to be of poor methodological quality, with the exception of one. One RCT did not include the number of women randomised and so was not included in the meta-analysis. The review found no significant difference between maternal antigen avoidance and no avoidance during pregnancy in the incidence of atopic eczema during the first 12 to 18 months of life (2 RCTs; 35/157 [22.2%] with avoidance v 39/177 [20.0%] with no avoidance; RR 1.01, 95% CI 0.57 to 1.79). The systematic review also included two trials of antigen avoidance during lactation (43 lactating women). The methodological quality of these trials was also poor and two of the trials began the diet during pregnancy. Randomisation was unclear for all of the trials, and analysis was not based on intention to treat. Only one trial^[86] gave details of compliance and blinding of the physicians who examined the children for eczema. The review also found no significant difference between maternal avoidance during lactation and no avoidance in the proportion of children developing eczema during their first 12 to 18 months of life (1 RCT; 5/12 [42%] with avoidance v 8/14 [57%] with no avoidance; RR 0.73, 95% CI 0.32 to 1.64). The RCT may have been underpowered to detect clinically important differences between groups.
Harms:	One RCT identified by the review found that, compared with no avoidance, maternal antigen avoidance significantly decreased mean gestational weight gain by a small amount (WMD -3.0, 95% CI -5.21 to -0.79, percentage of pre-pregnancy weight [i.e., 1.8 kg for a 60-kg woman]).^[85]
Comment:	Clinical guide More data are necessary on potential adverse effects of maternal antigen avoidance on gestational weight gain, fetal growth, and preterm birth. Antigen avoidance diets for women during pregnancy with a history of atopy are unlikely to substantially reduce risk of giving birth to an atopic child.

OPTION	EARLY INTRODUCTION OF PROBIOTICS (IN LAST TRIMESTER AND/OR SHORTLY AFTER BIRTH)
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Development of eczema

Early introduction of probiotics compared with placebo Probiotics taken during the last trimester of pregnancy and for up to 1 year after birth may reduce the risk of eczema development at up to 2 years (low-quality evidence).

For GRADE evaluation of interventions for eczema, see table, p 39 .

Benefits:	Probiotics versus no probiotics: We found two systematic reviews (search date 2007, 5 RCTs, 1581 infants;^[87] and search date 2007, 6 RCTs, 2080 infants^[88]) and two subsequent RCTs^[89] ^[90] comparing probiotics versus no probiotics. The analyses were similar in both systematic reviews, and the RCTs identified by first review were included in the most recent systematic review; we therefore report only the most recent systematic review here.^[88]
	Development of eczema The review compared probiotic supplementation versus no supplementation. Probiotics were given antenatally and postnatally (antenatally: 2 RCTs with <i>Lactobacillus rhamnosus</i>; one RCT with <i>Lactobacillus reuteri</i>; one RCT with a combination of 4 probiotic strains; postnatally: one RCT with <i>L. rhamnosus</i>; one RCT with <i>Lactobacillus acidophilus</i>).^[88] Of the 6 RCTs in the review, 5 RCTs were in children with a high risk of developing eczema (infants with at least 1 first-degree relative with a history of allergy or food hypersensitivity). The review found that probiotics significantly reduced the incidence of eczema up to 2 years of age (5 RCTs, 1477 infants; 211/735 [29%] with probiotics v 261/742 [35%] with no probiotics; RR 0.82, 95% CI 0.70 to 0.95). However, there was significant heterogeneity for this outcome. When the definition of eczema was restricted to atopic eczema, there was no significant difference between groups in incidence of eczema within the first 2 years of life, although there was a trend in favour of probiotics (4 RCTs, 1356 infants; 97/674 [14%] with probiotics v 123/682 [18%] with no probiotics; RR 0.80, 95% CI 0.62 to 1.02). Again there was significant heterogeneity for this outcome. The review did not provide reasons for heterogeneity in either analysis. The loss to follow-up was >20% in two RCTs (24% and 61%). The first subsequent RCT (512 infants with a first-degree relative with a history of asthma, eczema, or hay fever) compared <i>L. rhamnosus</i>, <i>Bifidobacterium animalis</i>, and placebo.^[89] The infants' pregnant mothers received one of the three regimens from 35 weeks' gestation, and continued for

6 months after birth while breastfeeding. Infants also received one of the three regimens from between 2 and 16 days after birth up to age 2 years; capsules were diluted in water or milk, and were sprinkled over food if eating solids. The RCT found that *L. rhamnosus* significantly reduced the proportion of children with eczema at 2 years (14.8% with *L. rhamnosus* v 26.8% with placebo; HR 0.51, 95% CI 0.30 to 0.85; $P = 0.01$; absolute results not reported). However, it found no significant difference between *B. animalis* and placebo in the proportion of children with eczema at 2 years (HR 0.90, 95% CI 0.58 to 1.41; $P = 0.64$; absolute results presented graphically).

The second subsequent RCT (253 Asian infants with a first-degree relative with a history of allergy or food hypersensitivity) compared 60 mL of a cow's milk formula plus a probiotic supplement (*Bifidobacterium longum*) daily versus 60 mL daily of a cow's milk formula alone from 12 hours after birth to 6 months.^[90] The remainder of infant feeds could be trial formula, other formula, or breast milk. Mothers did not take probiotics antenatally. The RCT found no significant difference between probiotic and no probiotic in the proportion of infants with eczema at 1 year (27/124 [22%] with probiotic v 30/121 [25%] with no probiotic; OR 0.82, 95% CI 0.44 to 1.52). Although the two groups were not balanced with regard to a number of potential confounding factors (sex, birth order, type of food between birth and 6 months, and antenatal smoking exposure), adjustment for these confounders did not significantly affect the results.

Harms:

Probiotics versus no probiotics:

Of the 6 RCTs identified by the review assessing the incidence of eczema, 4 assessed adverse effects.^[88] The systematic review reported that one RCT found no significant difference in the cumulative incidence of mild adverse effects (spitting-up, colic, and constipation) during the first 12 months of age, and reported no serious adverse effects. One RCT found no significant difference between probiotics and control in infant vomiting, total duration of crying, duration of fussing, and consistency of stools in infants. Another RCT found no significant difference in adverse effects (abdominal discomfort, vomiting, or excess crying) between probiotics and placebo. The other RCT reported no adverse effects.

Three additional RCTs in the systematic review comparing probiotics versus no probiotics also assessed adverse effects (although they did not assess eczema incidence).^[88] The first RCT found that necrotising enterocolitis, death, or both was significantly reduced in preterm infants receiving probiotics compared with no probiotics (6/73 [8%] with probiotics v 17/72 [23%] with no probiotics; $P = 0.025$). The second RCT found that none of the positive blood cultures grew *Lactobacillus* or *Bifidobacterium* species, and sepsis was significantly lower with probiotics than with no probiotics (22/180 [12%] with probiotics v 36/187 [19%] with no probiotics; $P = 0.03$). The third RCT found that colic and irritability occurred less frequently with probiotics than with no probiotics, and there was no significant difference in stool frequency or consistency, vomiting or fever with diarrhoea, discomfort with bowel movement, healthcare attention for illness, or day-care absenteeism between groups.^[88]

The two subsequent RCTs did not report on adverse effects.^{[89] [90]}

Comment:

There is some evidence to suggest that probiotic supplementation antenatally and postnatally can reduce eczema risk in infants from high-risk families. However, direct comparability between trials is hampered by use of different probiotic strains.

GLOSSARY

Atopic Inherited tendency to develop allergic reactions associated with an immunoglobulin E response.

Corticosteroids Synthetic glucocorticoids (similar to hormones) are used to treat atopic eczema, among other diseases, to suppress inflammation, allergy, and immune responses.

Dry skin area and severity index A newly proposed system for dry skin and ichthyosis, where the score is calculated as the product of the sum of severity scores and area affected in 4 body regions.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

SASSAD index The Six Area, Six Sign Atopic Dermatitis severity index is a scoring system to measure the severity of atopic eczema. Six sites of the body are assessed for each of six features, each one scoring 0 to 3 for increasing severity.

SCORAD index The SCORing Atopic Dermatitis (SCORAD) index is a scoring system designed by the European Task Force on Atopic Dermatitis to measure the severity of atopic eczema. It has 5 clinical signs: erythema, vesicu-

lation, excoriation, crusting, and oedema. Each of these signs has 4 scores: 0 = absent; 1 = mild, 2 = moderate, and 3 = severe.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Corticosteroids (alone or used concurrently with emollients) Two RCTs added comparing corticosteroids versus vehicle; [31] [32] one RCT assessed a potent corticosteroid [31] and one assessed a very potent corticosteroid. [32] The RCTs found that corticosteroids increased eczema clearance and improved disease severity compared with vehicle. One further RCT added comparing potent corticosteroids plus emollient versus emollient alone. [39] It found that potent corticosteroids plus emollient reduced the relapse rate compared with emollient alone. Two further RCTs added comparing corticosteroids plus tacrolimus versus tacrolimus alone; [41] [42] one RCT assessed a moderate corticosteroid [41] and one assessed a potent corticosteroid. [42] The two RCTs found that corticosteroids plus tacrolimus improved disease severity compared with tacrolimus alone. Categorisation unchanged (Beneficial).

Early introduction of probiotics (in last trimester and/or shortly after birth) for the prevention of eczema One systematic review (search date 2007) [88] and two subsequent RCTs added, which compared probiotics versus no probiotics given both antenatally and postnatally to prevent eczema in infants at risk. [89] [90] The systematic review found that probiotics reduced the incidence of eczema when all participants were analysed, but results were no longer significant if the definition of eczema was restricted to atopic eczema. [88] The first subsequent RCT found that *Lactobacillus rhamnosus* reduced the proportion of children with eczema at 2 years; however, it found no significant difference between *Bifidobacterium animalis* and placebo. [89] The second subsequent RCT found no significant difference between *Bifidobacterium longum* and no probiotic in the proportion of infants with eczema at 1 year. Categorisation unchanged (Likely to be beneficial).

Egg and cow's milk exclusion diet One systematic review added (search date 2006), [75] which compared egg and cow's milk exclusion diets versus normal diet. It found no significant difference between amino-acid-based formulae and hydrolysed cow's milk formulae in symptom severity in infants with cow's milk allergy/intolerance; however, it found that egg exclusion diet was more effective than normal diet at improving symptom severity in infants with egg allergy, although the RCT was of low quality. Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to judge the effectiveness of this intervention.

Elemental diet One systematic review added (search date 2006), [75] which identified no RCTs that met *Clinical Evidence* reporting criteria. Categorisation unchanged (Unknown effectiveness).

Emollients (alone or plus topical corticosteroids) One RCT added comparing emollient versus placebo cream, [25] and three RCTs added comparing emollient plus corticosteroids versus corticosteroids alone. [26] [27] [28] The RCT comparing emollient versus placebo found no significant difference between groups in local severity. The three RCTs comparing emollient plus corticosteroids versus corticosteroids alone also found no significant difference between groups in disease severity. Categorisation unchanged (Likely to be beneficial based on consensus).

Few-foods diet One systematic review added (search date 2006), [75] which identified no RCTs that met *Clinical Evidence* reporting criteria. Categorisation unchanged (Unknown effectiveness).

Pimecrolimus One systematic review (search date 2006) [43] and 6 subsequent RCTs [44] [46] [47] [48] [50] [51] added assessing pimecrolimus. The systematic review and RCTs found that pimecrolimus 1.0% was more effective than vehicle and betamethasone valerate 0.1% at improving clearance and improving pruritus, and was more effective than vehicle at improving quality of life and reducing relapse rates. However, pimecrolimus 1.0% was less effective than tacrolimus 0.1% at improving clearance. There was no significant difference in application-site skin burning and skin infections between pimecrolimus 1% and vehicle, and between pimecrolimus and tacrolimus; however, pimecrolimus may cause more application-site skin burning than betamethasone valerate 0.1%. There is a potential cancer risk from the use of pimecrolimus, but the review and RCTs did not identify any cases of cancer. Categorisation unchanged (Beneficial).

Tacrolimus One systematic review [59] and 6 RCTs added comparing tacrolimus with vehicle cream. [60] [61] [62] [63] [64] The systematic review [59] and two RCTs [60] found that tacrolimus 0.03% or 0.1% improved disease severity compared with vehicle, and the other 4 RCTs found that tacrolimus 0.03% prevented relapse compared with vehicle. The systematic review [59] and two further RCTs [41] [67] also compared tacrolimus with corticosteroids. The review and RCTs found that tacrolimus 0.03% and 0.1% improve disease severity compared with hydrocortisone acetate (mild), but the effects of tacrolimus 0.03% and 0.1% compared with clobetasone butyrate (moderate), hydrocortisone butyrate (potent), and methylprednisolone aceponate (potent) were not clear. Categorisation unchanged (Beneficial).

Probiotics One systematic review added (search date 2007), [77] which identified 12 RCTs comparing probiotics versus placebo or no treatment. The review found no significant difference between probiotics and placebo or no treatment in parent-reported, participant-reported, or investigator-reported eczema severity. It also found no significant difference between probiotics compared with no treatment in patients' quality of life. Therefore, categorisation changed from Unknown effectiveness to Unlikely to be beneficial.

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TABLE 1 UK Working Party Diagnostic Criteria for Atopic Dermatitis ^[2]

An individual must have an itchy skin condition (or parental report of scratching or rubbing) in the last 12 months, plus three or more of the following: (i) a history of involvement of the skin creases (fronts of elbows, behind knees, fronts of ankles, around neck, or around eyes) (ii) a personal history of asthma or hay fever (or history of atopic disease in a first-degree relative if a child is aged under 4 years) (iii) a history of a generally dry skin in the last year (iv) onset under the age of 2 years (not used if a child is aged under 4 years) or visible flexural dermatitis (including dermatitis affecting cheeks or forehead and outer aspects of limbs in children under 4 years)
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TABLE 2 Research criteria for assessing severity in eczema

Symptom severity scoring systems

The SCORing Atopic Dermatitis (SCORAD) index

Total score is calculated from:

Extent of affected areas: calculated as a percentage of total body area (from chart)

Intensity of a typical lesion (each scored 0 = none, 1 = mild, 2 = moderate, 3 = severe):

Erythema

Oedema/papulation

Oozing/crust

Excoriation

Lichenification

Dryness of unaffected areas

Subjective symptoms:

Pruritus (0–10 visual analogue scale)

Sleep loss (0–10 visual analogue scale)

SCORAD = extent score/5 + 7 × intensity score/2 + subjective symptoms score

Half of all people with eczema score between 28 and 54 points. For a simple guide to using SCORAD in practice, see http://adserver.sante.univ-nantes.fr/Scorad_Course/How.html (last accessed 8 March 2011)

Six Area, Six Sign Atopic Dermatitis severity index (SASSAD)

Six sites of the body are assessed for each of 6 features, each one scoring 0 to 3 for increasing severity:

Erythema

Exudation

Excoriation

Dryness

Cracking

Lichenification

The SASSAD scale correlates with global assessments of disease severity, but not with quality-of-life scores

Symptom severity scoring systems

Eczema Area and Severity Index (EASI)

Includes an assessment of the extent of disease of different anatomic sites on a Likert scale

Includes an assessment of the intensity of lesions, i.e., erythema, oedema/induration/papulation, excoriation, and lichenification, each one scoring 0 to 3 for increasing severity

Total EASI score ranges from 0 to 72 with higher scores indicating more severe eczema

Patient-oriented Eczema Measure (POEM)

Measures the frequency of occurrence of the following eczema signs and symptoms during the previous week

Dryness

Itching

Flaking

Cracking

Sleep loss

Bleeding

Weeping

POEM score ranges from 0 to 28, with higher scores indicating more severe eczema

TABLE 3 RCTs comparing essential fatty acids versus placebo

Study	Methods	Participants	Outcomes	Results
[81]	Systematic review pooled data: 5 RCTs for borage oil; 11 RCTs and 1 controlled clinical trial of evening primrose oil; 1 RCT of blackcurrant seed oil; and 4 RCTs and 1 controlled clinical trial of fish oil	3 RCTs (243 adults), 4 RCTs (159 children), 4 RCTs (299 adults and children)	Pooled effect size for evening primrose oil and borage seed oil	+0.15, 95% CI -0.02 to +0.32; P = 0.09
[81]	Systematic review pooled data: 5 RCTs for borage oil; 11 RCTs and 1 controlled clinical trial of evening primrose oil; 1 RCT for blackcurrant seed oil; and 4 RCTs and 1 controlled clinical trial of fish oil	2 RCTs (176 adults), 1 RCT in 82 adults and children	Pooled effect size for fish oils	-0.01, 95% CI -0.27 to +0.30; P value not reported
[82]	Borage oil capsules (gamma linolenic acid 920 mg) versus placebo over 12 weeks	151 participants including 69 children	Mean physician assessed improvement in eczema (Six Area, Six Sign Atopic Dermatitis severity index [SASSAD] score)	+1.4, 95% CI -2.2 to +5.0; P = 0.45

TABLE GRADE evaluation of interventions for eczema

Important outcomes		Symptom severity, relapse rate, development of atopic eczema, quality of life, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment	
What are the effects of self-care treatments in adults and children with established atopic eczema?										
5 (528) ^{[21] [22] [23] [24] [25]}	Symptom severity	Emollients v placebo	4	−2	0	−1	0	Very low	Quality points deducted for poor methodology and incomplete reporting of results. Directness point deducted for assessing different outcomes	
3 (311) ^{[26] [27] [28]}	Symptom severity	Emollient plus corticosteroids v corticosteroids alone	4	−1	0	−2	0	Very low	Quality point deducted for poor follow-up. Directness points deducted for different regimens of corticosteroids and lack of direct comparisons between groups	
2 (259) ^{[26] [27]}	Quality of life	Emollient plus corticosteroids v corticosteroids alone	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for different regimens of corticosteroids	
3 (356) ^{[21] [22] [23]}	Symptom severity	Different emollients v each other	4	−2	0	−1	0	Very low	Quality points deducted for poor methodology and incomplete reporting of results. Directness point deducted for unclear relevance of comparators used	
3 (607) ^{[30] [31] [32]}	Symptom severity	Corticosteroids v placebo	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for different regimens of corticosteroids	
1 (376) ^[35]	Symptom severity	Different frequencies of corticosteroid application v each other	4	−1	0	−1	0	Low	Quality point deducted for multiple comparisons. Directness point deducted for narrow population	
1 (196) ^[32]	Symptom severity	Different formulations of corticosteroids v each other	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results	
2 (439) ^{[36] [37]}	Symptom severity	Different corticosteroids v each other	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results	
2 (439) ^{[36] [37]}	Relapse rates	Different corticosteroids v each other	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and multiple comparisons	
2 (312) ^{[38] [39]}	Symptom severity	Corticosteroids plus emollients v emollients alone	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different regimens of corticosteroids	
1 (221) ^[39]	Relapse rates	Corticosteroids plus emollients v emollients alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results	
1 (72) ^[24]	Symptom severity	Corticosteroids v emollients	4	−3	0	−1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and short follow-up. Directness point deducted for few comparators	
2 (643) ^{[40] [35]}	Relapse rates	Corticosteroids v emollients	4	−2	+1	−1	0	Low	Quality points deducted for uncertainty of assessment score and incomplete reporting. Consistency point added for dose response. Directness point deducted for unclear relevance of comparator used	

Important outcomes		Symptom severity, relapse rate, development of atopic eczema, quality of life, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (127) ^[41] ^[42]	Symptom severity	Corticosteroids plus tacrolimus v tacrolimus alone	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and open-label RCT. Consistency point deducted for different regimens of tacrolimus and corticosteroids in the RCTs
6 (983) ^[43] ^[44]	Symptom severity	Pimecrolimus v vehicle cream	4	−1	0	0	+1	High	Quality point deducted for poor follow-up. Effect-size point added for effect size >2
1 (196) ^[43] ^[45]	Quality of life	Pimecrolimus v vehicle cream	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for high level of treatment discontinuation
2 (526) ^[43]	Symptom severity	Pimecrolimus v vehicle, plus topical corticosteroids for flares	4	−1	0	0	0	Moderate	Quality point deducted for poor follow-up
12 (4339) ^[43] ^[46] ^[47] ^[48]	Relapse rates	Pimecrolimus v vehicle, plus topical corticosteroids for flares	4	−1	0	−1	0	Low	Quality point deducted for poor follow-up. Directness point deducted for uncertainty about diagnosis of eczema
1 (192) ^[49]	Quality of life	Pimecrolimus v vehicle, plus topical corticosteroids for flares	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
1 (47) ^[50]	Symptom severity	Pimecrolimus plus topical corticosteroids v topical corticosteroids alone	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for narrowness of population
1 (87) ^[43]	Symptom severity	Pimecrolimus v corticosteroids	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for comparison with potent corticosteroids only
5 (1394) ^[43] ^[51]	Symptom severity	Pimecrolimus v tacrolimus	4	−1	0	−1	0	Low	Quality point deducted for poor follow-up. Directness point deducted for uncertainty about diagnosis
6 (1781) ^[59] ^[60]	Symptom severity	Tacrolimus v vehicle	4	−1	0	0	0	Moderate	Quality point deducted for high discontinuation in 2 RCTs
4 (776) ^[61] ^[62] ^[63] ^[64]	Relapse rates	Tacrolimus v vehicle	4	−2	0	0	0	Low	Quality points deducted for high discontinuation rates and incomplete reporting of results
4 (1235) ^[61] ^[66]	Quality of life	Tacrolimus v vehicle	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting
1 (45) ^[41]	Symptom severity	Tacrolimus plus corticosteroids v corticosteroids alone	4	−2	0	0	0	Low	Quality points deducted for open-label study and sparse data
6 (3036) ^[41] ^[59] ^[67]	Symptom severity	Tacrolimus v corticosteroids	4	−1	0	0	0	Moderate	Quality point deducted for open-label study
6 (1351) ^[68] ^[69] ^[70]	Symptom severity	Lower tacrolimus dose v higher dose	4	0	−1	−1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for assessing different outcomes
3 (number of participants unclear) ^[66]	Quality of life	Lower tacrolimus dose v higher dose	4	−2	0	−1	0	Very low	Quality points deducted for uncertainty about the size of population and incomplete reporting of results. Directness point deducted for different outcome measures
What are the effects of dietary interventions in adults with established atopic eczema?									
1 (96) ^[73]	Symptom severity	Vitamin E v placebo	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertain clinical importance of outcome
1 (59) ^[74]	Symptom severity	Vitamins B and E alone v vitamin E plus vitamin B2	4	−3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and poor follow-up

Important outcomes		Symptom severity, relapse rate, development of atopic eczema, quality of life, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of dietary interventions in children with established atopic eczema?									
2 (118) ^[75]	Symptom severity	Cow's milk formula v amino-acid-based formula	4	−3	0	−1	0	Very low	Quality points deducted for sparse data; incomplete reporting of results; poor follow-up; and unclear allocation generation, concealment, and masking. Directness point deducted for narrowness of population
1 (62) ^[76]	Symptom severity	Egg exclusion diet v normal diet	4	−1	0	−2	0	Very low	Quality point deducted for sparse data. Directness points deducted for baseline differences between groups and for narrowness of population
7 (588) ^[77]	Symptom severity	Probiotics v placebo or no treatment	4	0	0	−1	0	Moderate	Directness point deducted for statistical heterogeneity
2 (110) ^{[78] [79]}	Quality of life	Probiotics v placebo or no treatment	4	−3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and uncertainty about outcome scale
1 (50) ^[80]	Symptom severity	Zinc supplements v placebo	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for short-term follow-up
1 (48) ^[21]	Symptom severity	Pyridoxine v placebo	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
21 (1508) ^{[81] [82]}	Symptom severity	Essential fatty acids v placebo	4	−2	0	0	0	Low	Quality point deducted for incomplete results and inclusion of CCTs
What are the primary preventive effects of reducing allergens in predisposed infants?									
1 (696) ^[84]	Development of eczema	House dust mite reduction v education package on allergen avoidance advice v basic information about allergies	4	−1	0	−1	0	Moderate	Quality point deducted for incomplete reporting of results. Directness point deducted for unclear comparators (may include house mite reduction measures)
What are the primary preventive effects of dietary interventions in infants?									
9 (1227) ^{[85] [86]}	Development of eczema	Maternal antigen avoidance diet v no avoidance	4	−3	−1	0	0	Very low	Quality points deducted for uncertainty of randomisation, methodological flaws, and no intention-to-treat analysis. Consistency point deducted for conflicting results
7 (2242) ^{[88] [89] [90]}	Development of eczema	Early introduction of probiotics v placebo	4	0	−2	0	0	Low	Consistency points deducted for heterogeneity across trials and different results for different probiotic strains
Type of evidence: 4 = RCT; 2 = observational. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes. Effect size: based on relative risk or odds ratio.									