What is the evidence-base for atopic eczema treatments? A summary of published randomised controlled trials

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What's already known about this topic?

- The evidence base for atopic eczema (AE) treatments is broad and limited by poor quality trials
- The last systematic review to provide an overview of all published AE randomised controlled trials (RCTs) was conducted in 2000

What does this study add?

- Over 500 RCTs have been published on treatments for AE, but many research gaps remain
- This summary highlights treatment for which there is reasonable evidence of benefit, and those for which there is reasonable evidence of no benefit
- Future research priorities that have no current RCT evidence include the role of allergy testing (followed by allergen avoidance), and modified bathing habits in the management of AE

Summary (Abstract)

Atopic eczema (AE) is a common chronic inflammatory skin condition. Whilst many AE treatment options are available, the evidence to support their efficacy varies in depth and quality. In 2000, an NIHR HTA systematic review identified and evaluated existing randomised controlled trials (RCTs) of AE treatments. To ensure continuing utility, the NIHR commissioned an update to the review. Here, we present an overview of the updated report and key findings.

Systematic reviews and RCTs of AE treatments that included participants with AE (criteria based or diagnosed) were identified using: MEDLINE, EMBASE, CENTRAL, LILACS, AMED, CINAHL and Cochrane Skin Group Specialised Register (searched to August 31st 2013 (RCTs) and 31st December 2015 (systematic reviews)). Outcome measures included: symptoms, AE severity, quality-of-life, and adverse effects. Study quality was assessed using the Cochrane Collaboration risk of bias tool.

Of the 287 new RCTs identified, only 22 (8%) were judged to be low risk of bias. When combined with RCTs from the previous review (n= 254), we found 'reasonable evidence of benefit' for corticosteroids, calcineurin inhibitors, Atopiclair™, ciclosporin, azathioprine, ultraviolet light and education programmes.
Interventions with reasonable evidence of ''no benefit' included some dietary interventions, ion exchange water softeners, multiple daily applications of topical corticosteroids and antibiotic-containing corticosteroids for non-infected AE. Many common treatments lack evidence of efficacy and warrant further evaluation.

The evidence base for AE is still hampered by poor trial design and reporting. The trials included in this review were used to establish the Global Resource of Eczema Trials (GREAT) Database.

Introduction

Atopic eczema (AE) (syn. atopic dermatitis), is a chronic inflammatory skin condition characterised by an itchy red rash that affects all age groups[1]. AE has one of the highest burdens compared to other skin diseases.[2]

The evidence-base for AE treatments is extensive, but has limitations in terms of quality and relevance.[3] This is exemplified by the 'Systematic Review of Treatments for Atopic Eczema', published by the National Institute for Health Research (NIHR), which identified 254 RCTs of AE treatment covering 47 interventions.[4] The encompassing nature of the review, and critical appraisal of the evidence therein, has helped to inform clinical guidelines on an international level for over a decade and the report has been heavily cited, with more than 650 citations listed in Google Scholar at time of writing.[5-8]

To ensure its continuing utility, the NIHR commissioned an update of the systematic scoping review as part of a programme of work on the prevention and treatment of skin disease,[9] with the aim of summarising the evidence-base for AE treatments for guideline writers, healthcare professionals and patients. This review will also help in identifying research gaps to be addressed in the future, and in identifying topics suitable for specific targeted systematic reviews.

The current paper provides a summary of the updated scoping review (which is freely available through the NIHR Journal series)[9], with a specific focus on the overall findings and conclusions.

Methods used for the scoping review

The following section briefly described the methodology employed to create the scoping review, which can be viewed in its entirety in the methods section of the full report. [9]

Design

This was a systematic scoping review of all systematic reviews and randomised controlled trials (RCTs) for AE treatments. A scoping review attempts to systematically map existing evidence on a given topic and identify potential gaps in the literature to inform future research priorities. It differs from a clinically-focussed systematic review in that it often covers a much broader topic area, summarises the evidence in a qualitative format and offers limited critical appraisal.[10]

Type of studies included

As systematic reviews and RCTs represent the best source of unbiased evidence on the effectiveness of treatments, we only included these types of studies. Studies were required to contain at least one clinical outcome. Prevention studies, provocation studies, changes in blood biochemistry and evaluations of cellular mechanisms were excluded.

Participants

Studies were included if participants (of any age) had AE, as diagnosed by a physician, or that met with a diagnostic criteria (e.g. Hanifin and Rajka,[11] UK working party[12] or similar).

Main outcome measures

Outcome measures chosen for the review were deliberately broad, in order to reflect those commonly used in AE trials.[13,14] Changes in patient-rated symptoms such as itching (pruritus) or sleep loss were extracted where possible. Global severity, as rated by patients or their physician, was also sought. Other outcomes included changes in AE severity rating scales; quality of life; and adverse events (encompassing adverse events and adverse reactions depending on how these were reported in the original RCTs).

Search strategy

We searched the following electronic databases (search dates end of 1999 to 31st August 2013) - MEDLINE; EMBASE; CENTRAL; The Cochrane Skin Group Specialised Trials Register; Latin American and Caribbean Health Sciences database (LILACS); Allied and Complementary Medicine Database (AMED); Cumulative Index to Nursing and Allied Health Literature (CINAHL) (Supplementary Figure 1). We also searched www.controlled-trials.com for completed and ongoing RCTs using the terms atopic dermatitis, atopic eczema and eczema as well as using our extensive contacts in the field of AE research to identify other ongoing studies.

Systematic reviews on AE treatments were searched for up until Dec 2015 using PubMed, EMBASE, the Cochrane Library and NHS Evidence. Where appropriate the results of these specific systematic reviews are presented alongside the RCT evidence.

We used the following disease terms for AE: atopic dermatitis, atopic eczema, eczema, neurodermatitis, infantile eczema, childhood eczema, or Besniers' prurigo. No language restrictions were applied; data from non-English papers was extracted by international colleagues. References were screened by one author (either SS or HN), with discussion with a second author as required (HW, KT or SB). Those studies using terms that were definitely not AE, such as allergic contact eczema, were excluded. Terms that were considered possibly AE, such as 'childhood eczema', were scrutinised and only included if the description of the participants clearly indicated AE.

Data assessment and study quality

Data was independently extracted by two authors (HN and SB or SS) with discrepancies resolved by consensus or by an arbitrator (HCW, KST or FMD). Although primarily a scoping review, trial quality (specifically randomisation, allocation concealment and blinding) was evaluated. This was done using Cochrane collaboration's risk of bias assessment tool.[15] The overall risk of bias for the included studies was summarised according to defined criteria (Supplementary Table 1). Authors were not blinded to the identity of the RCT authors, and a more detailed quality assessment (such as GRADE[16]) was unfeasible given the number of included studies.

Presentation of the results

Results are presented according to broad categories of treatments: i) topical corticosteroids and topical immunomodulators; ii) emollients and other topical treatments (including bath additives and oils); iii) antimicrobials including antibiotics, antiseptics and antifungals; iv) antihistamines and mast cell stabilisers; v) dietary interventions (including probiotics, essential fatty acids, vitamins, cows' milk substitutes); vi) non-pharmacological interventions (including education, psychological therapies, different ways of providing AE care, allergen avoidance followed by allergen avoidance or re-introduction and medical devices); vi) phototherapy; vii) systemic immunomodulatory agents; viii) complementary therapies (homeopathy, aromatherapy, hypnotherapy, Chinese herbal medicine, St John's Wort, acupuncture, balneotherapy, relaxation); ix) other.

For clarity of interpretation, results are also summarised according to categories of evidence:

i) treatments for which there is reasonable *evidence of benefit*

ii) treatments for which there is reasonable evidence of *no-clinically useful benefit*

iii) treatments for which there is *insufficient evidence to inform clinical decision-making*

iv) treatments with an *absence of RCT evidence*.

Classification of treatment options into these four categories was a qualitative judgement on the part of the authors based on availability and quality of the evidence, and the likelihood of clinically important effects. It is not intended to signify that all uncertainty has been resolved in those areas classed as having reasonable evidence of benefit or reasonable evidence of no benefit – simply that there is a reasonable body of evidence that may usefully inform clinical decision-making. In this paper, we have not tried to summarise the possible

harms of all included studies, but harms and drawbacks of treatments are included for all treatment categories in the main report.

Pooling of the trial results using meta-analysis was not possible due to the very wide nature of interventions included, and the very heterogeneous nature of study participants and outcomes. However, interventions with evidence of benefit or evidence of no benefit have been mapped to the latest relevant systematic reviews on these topics where they exist.

Results of the review

Summary of trials

In addition to the 254 RCTs identified in the original 2000 scoping review, this updated includes an additional 287 new RCTs, making 541 RCTs in total covering 92 different interventions for treating AE. The number of RCTs published according to broad treatment categories is shown (Figure 1), with further details provided in Supplementary Figure 2.

The size of the newly identified RCTs varied widely from seven randomised participants to 972 participants. Most of the trials were conducted in secondary care, and tended to include participants with either moderate to severe disease, or mild to moderate disease. Very few RCTs included all severities of AE.

Reporting was generally poor, with “unclear” categories dominating the assessments: randomisation method (2% high, 36% low and 62% unclear risk of bias), allocation concealment (3% high, 15% low and 82% unclear risk of bias), and blinding or masking of the intervention (15% high, 28% low, 57% unclear risk of bias). Only 22/287 (8%) were considered to be at low risk of bias for all three quality criteria (randomisation, allocation concealment and blinding). Overall agreement between the team members on the availability and quality of the evidence, and the likelihood of clinically important effects was good.

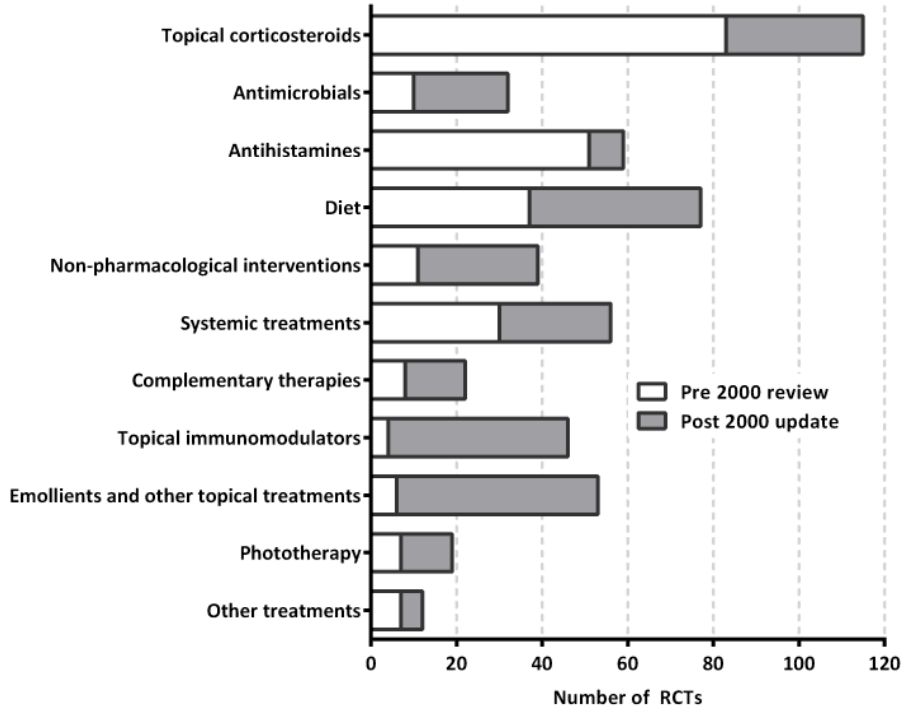

Figure 1: Number of included RCTs per treatment category

Treatments with reasonable evidence of benefit

Fourteen interventions or treatment approaches were felt to have reasonable evidence of benefit (Table 1). These include the use of topical corticosteroids and topical calcineurin inhibitors, both for the treatment of active AE, and as intermittent proactive (maintenance) therapy for the prevention of AE flares. Other interventions including Atopiclair™ emollient, ultraviolet light therapy, azathioprine and ciclosporin, all had reasonable evidence of benefit compared to placebo/vehicle. Similarly, RCT and systematic review evidence suggested that education may be beneficial, although the exact components of a successful education programme in different clinical settings is still unclear.

Of the 14 interventions with reasonable evidence of benefit, 10/14 (71%) have been the subject of more detailed, treatment-specific systematic reviews (Table 1).

Treatments with evidence of no clinically useful benefit

Nine interventions were deemed to have a reasonable level of evidence of no benefit in treating AE (Table 2): topical corticosteroids containing an antibiotic for the treatment of AE that is not infected; *Mycobacterium vaccae* vaccine; probiotics; ion exchange water softeners; evening primrose oil and borage oil.

Treatments which require more research

There are many treatments for AE that have insufficient or contradictory RCT evidence, for which further research is required (Table 3). Some of the treatments have been trialled many times, however, the quality of reporting means that evidence for these treatments is not yet strong enough.

Treatments with an absence of RCT evidence

The scoping review has helped to identify areas for which there is currently no RCT evidence for commonly used practices for the treatment of AE including: dilution of topical corticosteroids, order of application of topical corticosteroids and emollients, impregnated bandages (zinc or ichthammol paste bandages), modified bathing habits (non-antiseptic bath additives, soap avoidance, frequency of bathing), and the role of routine allergy testing followed by allergen avoidance or re-introduction.

Discussion

Main findings

The systematic scoping review findings indicated there were only a small number of treatments with evidence of benefit (Table 1) and some treatments with evidence of no benefit (Table 2). For the majority of treatments, however, further but better designed research is needed (see Table 3). It is disappointing that there was a lack of strong evidence base for some of the most widely used AE treatments, such as emollients and bandages. However, stopping or restricting the use of these treatments on the basis of lack of RCT evidence would not benefit patients. Although information on treatment drawbacks and harms are included for each intervention in the main review, we have not tried to summarise them in this report due to their diverse and treatment-specific nature. Generally, harms were reported less well than treatment benefits resulting in an asymmetry of information to inform patient choices.

In addition to the established approach for treating AE flares with topical corticosteroids, perhaps the single largest advance in AE treatment since the 2000 review has been the strong evidence supporting the value of a proactive approach for maintaining AE remission through the use of twice weekly topical corticosteroids or calcineurin inhibitors.[17] Educational approaches have also emerged as a potentially promising intervention, although further work is needed to establish the most important components of the intervention, and the most cost-effective ways of delivering education in different health settings.

The finding that Atopiclair™ emollient has emerged as a potentially useful intervention for AE in four out of five industry-sponsored trials is difficult to interpret at this time. High-quality, independent trials are now needed that compare Atopiclair™ to other commonly used (and cheaper) emollients.

The understanding that some interventions now have sufficient evidence to suggest little or no benefit for AE patients is equally important. These interventions provide options for disinvestment, ensuring that available funds are channelled to the most effective treatments. Possible areas to consider for disinvestment include: the application of topical corticosteroids twice a day, as once-daily application has been shown to be equally effective; topical corticosteroids containing antibiotics when used for the management of non-infected AE; use of ion exchange water softeners; and dietary supplements (probiotics, borage oil, evening primrose oil).

Implications for research

There is a lack of AE treatment trials conducted in a primary care setting, where most patients are seen. The research questions being investigated often fail to reflect the most pressing questions for clinicians and patients. A recent James Lind Alliance Priority Setting Partnership [3] identified the most important treatment uncertainties as judged by patients and clinicians. When set in the context of the updated evidence base from the review, the following areas identified from the Priority Setting Partnership seem to be most pressing:

Priority areas with no current RCT evidence

- What role might allergy tests play in treating AE?
- What is the best way for people with AE to wash?

- Which should be applied first when treating AE – emollients or topical corticosteroids?

Priority areas with limited RCT evidence

- What is the best and safest way of using topical corticosteroids for AE?
- What is the long-term safety of applying topical steroids to the skin for AE?
- Which emollient is the most effective and safe in treating AE?
- What is the best psychological treatment for itching/scratching in AE?
- What are the best and safest 'natural' products to apply to the skin?
- How much does avoidance of irritants and allergens help people with AE?
- What is the role of diet in treating AE (exclusion diets and nutritional supplements)
- Which is more effective in the management of AE: education programmes, GP care, nurse-led care, dermatology-led care of multi-disciplinary teams?
- Which is safer and more effective in treating AE: topical corticosteroids or calcineurin inhibitors (especially for proactive flare prevention)?
- How effective are interventions to reduce skin infections in the management of AE?
- What is the best and safest way of using drugs that suppress the immune system (particularly in children)

Some important topics have already been picked up by NIHR funding bodies, and large pragmatic trials are currently underway in the UK evaluating the role of topical and oral antibiotics for the treatment of infected AE (CREAM) (UKCRN ID 11233), silk clothing for the management of moderate to severe AE (CLOTHES) (UKCRN ID 15132), the role of bath emollients in the management of AE (BATHE: UKCRN ID 17348) and a feasibility trial of emollient clinical and cost effectiveness (COMET: UKCRN ID 16571).

Methodological research

One of the most pressing concerns identified by this review is the continued preponderance of small, poorly reported and poorly conducted trials. Greater efforts to work collaboratively to conduct large, well designed studies that address important questions, can only be of benefit to patients and healthcare providers.

Similarly, the ability to combine study results in meta-analysis continues to be hampered by the wide variation in outcome measures used. The move towards using the same core outcome sets as encouraged by the Harmonising Outcome Measures for Eczema (HOME) initiative[18-20] (www.homeforeczema.org) are likely to be beneficial for future clinical interpretation and evidence syntheses.

Strengths and limitations of the review

The updated review has used a clear methodology for identifying RCTs for inclusion, which has minimised potential selection bias. However, despite searching the main bibliographic databases (MEDLINE and EMBASE) and several smaller, specialist databases (CINAHL, AMED and LILACS), it is possible that we might have missed some RCTs. Many of the treatments that are lacking in RCT evidence have nevertheless been studied using uncontrolled designs, which may provide additional useful information. Similarly, large cohort studies are required to detect rare treatment adverse effects.

Whilst masking the identity of the trial authors from the review team was not practical, this may have introduced bias when summarising qualitative aspects of the results. Given the very wide scope of the review and heterogeneous nature of participants, interventions and outcomes, it was not practical to undertake detailed meta-analysis for single interventions. These will need to be conducted (where appropriate) within much narrower intervention-specific systematic reviews in the future.

Our classification of treatment options into categories such as "evidence of benefit to support" is not tantamount to a positive recommendation for widespread use or otherwise, as that is the remit of guideline developers and depends on factors such as magnitude of benefit, adverse effects, how the treatment compares with existing active treatments, availability, cost effectiveness and population most likely to benefit.

As with all systematic reviews, the evidence presented will become out of date quite rapidly for some topics, and readers of the review are also directed to our free to access database of AE RCTs Global Resource of EczemA Trials (GREAT Database, accessible at http://www.greatdatabase.org.uk), which contains details of all the studies in the scoping review and can be used by readers who wish to investigate particular included or excluded studies further.

Conclusion

The number of RCTs for AE has increased substantially since the year 2000[4] yet most are still small, poorly reported, and do not address questions of clinical importance to patients and healthcare professionals

We hope that our work provides an easily accessible guide for patients and clinicians wishing to research treatment effects, and that it will be used by guideline developers to prevent duplication of effort in collating and evaluating the available evidence base for AE treatments. AE researchers will be able to identify potential research gaps and systematic reviews that require further work.

Table and figure legends

Figure 1: Number of included RCTs per treatment category

Table 1: Treatments with reasonable evidence of benefit for AE patients

Table 2: Treatments with reasonable evidence of no benefit for AE patients

Table 3: Treatments which require more research

Supplementary Figure 1: Search strategy used to identify trials

Supplementary Table 1: Criteria used for discussing the risk of bias in the summaries of treatment categories

Evidence of benefit: at least one good quality RCT or a large body of evidence and a clinically useful finding. We defined a 'good quality' trial as well designed and well reported and with a magnitude of benefit deemed by the authors to be clinically relevant, and 'large body of evidence' as enough trials with consistent evidence of clinically relevant benefit, despite some limitations in reporting					
Intervention and severity of AE	**Population**	**Trials (n)**	**Participants (n)**	**Risk of bias**	**Systematic Review(s)**
Topical Corticosteroids					
Corticosteroids (various strengths) are superior to vehicle for AE of all severities	Adults and children	23 [21-42]	3857	Mostly unclear	None
Topical Calcineurin Inhibitors					
Pimecrolimus (1%) is superior to vehicle for mild to moderate AE	Mainly children	16[43-57]	3149	Mostly unclear	Chen (2011)[58] Number of included studies: 6 (<18 years only) Meta-analysis: OR 3.21, 95% CI 2.48 to 4.14
Tacrolimus (0.03, 0.1, 0.3%) is superior to vehicle for moderate to severe AE	Adults and children	9 [59-65]	2089	Mostly unclear	Chen (2011)[58] Number of included studies: 4 (<18 years only) Meta-analysis: OR 4.56, 95% CI 2.80 to 7.44
Tacrolimus (0.03, 0.1%) is superior to hydrocortisone acetate (1%) for moderate-to severe AE	Children	2[66,67]	1184	Unclear	Martins (2015)[68] Number of included studies: 2 Tacrolimus 0.03%: RR 2.58, 95% CI 1.96 to 3.38 Number of included studies:1 Tacrolimus 1%: RR 3.09, 95% CI 2.14 to 4.45
Tacrolimus (0.1%) superior to fluticasone propionate ointment (0.005%) for moderate to severe facial AE	Adults	1[69]	568	Mostly unclear	*Not applicable*
Tacrolimus (0.1, 0.03%) is superior to pimecrolimus (1%) for AE of all severities	Adults and children	5[70-72]*	1243	Mostly low	Martins (2015)[68] Number of included studies: 3 Meta-analysis: RR 1.80, 95% CI 1.35 to 2.42
Proactive (maintenance) topical therapy for preventing flares					
Corticosteroids applied twice a week are superior to vehicle for moderate to severe AE	Adults and children	4[73-76]	929	Mostly unclear	Schmitt (2011)[17] Number of included studies: 4 Meta-analysis: RR 0.46, 95% CI 0.38-0.55
Tacrolimus (0.1, 0.03%) applied twice a week is superior to vehicle for mild to severe AE	Adults and children	4[77-80]	741	Mostly unclear	Schmitt (2011)[17] Number of included studies: 3 Meta-analysis: RR 0.78, 95% CI 0.60-1.00
Pimecrolimus (1%) applied twice a week is superior to vehicle for AE of all severities	Mainly children	2[44,81]	251	Mostly low	None
Systemic Therapies					
Ciclosporin superior to placebo for severe AE	Adults	4[82-85]	113	Mostly unclear	Schmitt 2007[86] Number of included studies: 12 Meta-analysis: Included non-RCTs
Azathioprine superior to placebo for moderate to severe AE	Adults	2[87,88]	100	Mostly low	Schram 2011[89] Number of included studies: 2 Meta-analysis: not done
Ultra-violet Light Therapy					
NB-UVB superior to placebo (visible light) for moderate to severe AE	Adults	2[90,91]	116	Mostly unclear	Dogra 2015[92] Number of included studies: 13 (included non-RCTs) Meta-analysis: not done Gambichler 2005[93] Number of included studies: 3 (included non-RCTs) Meta-analysis: not done
Other					
Atopiclair™ superior to vehicle for mild to moderate AE	Adults and children	4[94-98]	489	Mixed	None
Education superior to no-education for moderate to severe AE	Mainly children	7[99-105]	1076	Mixed	Ersser 2014 [106] Number of included studies:10 Meta-analysis: not done

Table 1: Treatments with reasonable evidence of benefit for AE patients

* Please note, 3 studies were included within one paper

Evidence of no benefit: at least one good quality RCT or several less well reported RCTs which consistently failed to show a convincing benefit on overall disease activity. We defined a 'good quality' trial as well designed and well reported, and large enough to exclude a clinically useful benefit or several trials with no evidence of benefit to give confidence in there being no clinically relevant benefit, despite less clear reporting					
Intervention and severity of AE	**Population**	**Trials (n)**	**Participants (n)**	**Risk of bias**	**Systematic Review(s)**
Twice daily versus once daily topical corticosteroids	Adults and children	3[34,107,108]	617	Mostly unclear	Green (2005)[109] Number of included studies: 10 Meta-analysis: not preformed (heterogeneity)
Antibiotic-containing corticosteroids versus corticosteroids alone for mild to severe non-infected AE	Mainly unspecified	5[110-114]	352	Mostly unclear	Bath-Hextall (2010) [115] Number of included studies: 2 Meta-analysis: RR 0.52, 95% CI 0.23 to 1.16
Probiotics for treating AE versus placebo	Mainly children	20[116-135]	1513	Mostly unclear	Boyle (2009) [136] Number of included studies: 5 Meta-analysis: mean difference -0.90, 95% CI -2.84 to 1.04
Dietary supplements rich in linoleic acid (evening primrose oil and borage oil) versus placebo	Mainly adults	23[137-158]	1448	Mostly unclear	Bamford (2013) [159] Number of included studies: evening primrose oil (7 trials) Meta-analysis for Evening Primrose Oil mean difference -2.22, 95% CI -10.48 to 6.04. Number of included studies: borage oil (8 trials) Meta-analysis for borage oil: not preformed (heterogeneity)
Protease inhibitor SRD441 versus vehicle in for mild to moderate AE	Adults	1[160]	93	Mostly low	SR not applicable
Emollient with furfuryl palmitate versus emollient alone for mild to moderate AE	Children	1[161]	117	Low	SR not applicable
Ion exchange water softening devices versus no water softening for moderate to severe AE	Children	1[162]	336	Low	SR not applicable
Cipamfylline cream versus vehicle	Adults	1[163]	103	Mostly low	SR not applicable
Mycobacterium vaccae vaccine versus no vaccine for moderate to severe AE	Mainly children	4[164-167]	372	Low	None

Table 2: Treatments with reasonable evidence of no benefit for AE patients

Intervention	Number of trials	Number of participants
Emollients	20[168-186]	1664
Dietary interventions including prebiotics, dietary restrictions, and synbiotics	13[187-199]	711
Non-pharmacological interventions, including: specialised clothing (silk or synthetic fibres with or without antibiotics); environmental interventions (house dust mite reduction, desensitisation); staying in a different climate; different approaches to organisation of care such as additional visits to the doctors or nurse led clinics; support groups; e-health management; psychological therapies (stress reduction or habit reversal techniques); balneotherapy (salt baths); biofeedback	33[200-232]	2447
Oral antibiotics for clinically infected or uninfected AE	3[233-235]	125
Topical corticosteroids combined with topical antibiotics for infected AE	2[110,236]	660
Wet wraps in addition to topical corticosteroids	5[237-241]	153
Antiseptic and non-antiseptic bath additives	4[242-245]	97
Systemic and topical antifungals	4[246-249]	202
Topical treatments including: topical vitamin B12; topical coal tar; camellia oil; SRD441 (protease inhibitor); WBI-1001 (an inhibitor of T cell inflammatory cytokine secretion); hippophe rhamnoides; black seed oil; pill mask; rosmarinic acid; vitreoscilla filiformis; shale oil; miltefosine; opiate receptor antagonist; carbohydrate derived fulvic acid; raffinose; farnesol and xylitol, bacterial antigens; camomile extract; heparin and levomenol; 15(R/S)-Methyl-lipoxin A4, N-acetyl-l-hydroxyproline; nalmefene hydrochloride monohydrate (SRD174)	27[250-276]	1340
Systemic treatments including: oral prednisolone; methotrexate; mycophenolate mofetil; biological therapies (omalizumab; mepolizumab); intravenous immunoglobulin; montelukast	22[277-298]	900
Oral antihistamines	29[297,299-326]	4201
Other less commonly used interventions including: oral pimecrolimus; oral naltrexone; autologous blood therapy; tandospirone citrate; full spectrum light therapy; excimer laser; nitrazepam; theophylline; topical salbutamol; papaverine and suplatast tosilate	14[327-338]	481
Complementary therapies including: Chinese Herbal treatment; hypnotherapy; massage therapy; aromatherapy; acupuncture; acupressure; and other herbal treatments	17[339-354]	604

338 **Table 3: Treatments which require more research**

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Table 1: Treatments with reasonable evidence of benefit for eczema patients

Intervention and severity of AE	Population	Trials (n)	Participants (n)	Risk of bias	Systematic Review(s)
Topical Corticosteroids					
Corticosteroids (various strengths) are superior to vehicle for AE of all severities	Adults and children	23 [1-22]	3857	Mostly unclear	None
Topical Calcineurin Inhibitors					
Pimecrolimus (1%) is superior to vehicle for mild to moderate AE	Mainly children	16[23-37]	3149	Mostly unclear	Chen (2011)[38] Number of included studies: 6 Meta-analysis: OR 3.21, 95% CI 2.48 to 4.14
Tacrolimus (0.03, 0.1, 0.3%) is superior to vehicle for moderate to severe AE	Adults and children	9 [39-45]	2089	Mostly unclear	Chen (2011)[38] Number of included studies: 4 Meta-analysis: OR 4.56, 95% CI 2.80 to 7.44
Tacrolimus (0.03, 0.1%) is superior to hydrocortisone acetate (1%) for moderate-to severe AE	Children	2[46,47]	1184	Unclear	Ashcroft (2005)[48] Number of included studies: 2 Meta-analysis: unsure
Tacrolimus (0.1%) superior to fluticasone propionate ointment (0.005%) for moderate to severe facial AE	Adults	1[49]	568	Mostly unclear	*Not applicable*
Tacrolimus (0.1, 0.03%) is superior to pimecrolimus (1%) for AE of all severities	Adults and children	5[50-52]	1243	Mostly low	Martins (2015)[53] Number of included studies: 3 Meta-analysis: RR 1.80, 95% CI 1.35 to 2.42
Proactive (maintenance) topical therapy for preventing flares					
Corticosteroids applied twice a week are superior to vehicle for moderate to severe AE	Adults and children	4[54-57]	929	Mostly unclear	Schmitt (2011)[58] Number of included studies: 4 Meta-analysis: RR 0.46, 95% CI 0.38-0.55
Tacrolimus (0.1, 0.03%) applied twice a week is superior to vehicle for mild to severe AE	Adults and children	4[59-62]	741	Mostly unclear	Schmitt (2011)[58] Number of included studies: 3 Meta-analysis: RR 0.78, 95% CI 0.60-1.00
Pimecrolimus (1%) applied twice a week is superior to vehicle for AE of all severities	Mainly children	2[24,63]	251	Mostly low	None
Systemic Therapies					
Ciclosporin superior to placebo for severe AE	Adults	4[64-67]	113	Mostly unclear	Schmitt 2007[68] Number of included studies: (12) Meta-analysis: (included non-RCTs)
Azathioprine superior to placebo for moderate to severe AE	Adults	2[69,70]	100	Mostly low	Schram 2011[71] Number of included studies: Meta-analysis:
Ultra-violet Light Therapy					
NB-UVB superior to placebo (visible light) for moderate to severe AE	Adults	2[72,73]	116	Mostly unclear	Gambichler 2005[74] Number of included studies: Meta-analysis: Dogra 2015
Other					
Atopiclair™ superior to vehicle for mild to moderate AE	Adults and children	4[75-79]	489	Mixed	None
Education superior to no-education for moderate to severe AE	Mainly children	7[80-86]	1076	Mixed	Pickett (2015) [87] Number of included studies:7 Meta-analysis: not performed (heterogeneity) Ersser 2014 [88] Number of studies:10 Meta-analysis: not performed (lack of data)

Table 2: Treatments with reasonable evidence of no benefit for eczema patients

Evidence of no benefit: at least one good quality RCT or several less well reported RCTs which consistently failed to show a convincing benefit on overall disease activity. We defined a 'good quality' trial as well designed and well reported, and large enough to exclude a clinically useful benefit or several trials with no evidence of benefit to give confidence in there being no clinically relevant benefit, despite less clear reporting						
Intervention	**No. of Trials**	**No. of Participants**	**Risk of bias**	**Population applied to**	**Severity of AE**	**Relevant systematic reviews**
Twice daily versus once daily topical corticosteroids	3[14,89,90]	617	Mainly unclear risk of bias	Adults and children	Mainly unspecified	Green (2005)[91] Number of included studies: 10 Meta-analysis: not preformed (heterogeneity)
Topical corticosteroids in combination with antibiotics for AE that is not clinically infected versus topical corticosteroid only	5[92-96]	352	Mainly low or unclear risk of bias	Mainly unspecified	Mild to severe	Bath-Hextall (2010) [97] Number of included studies: 2 Meta-analysis: RR 0.52, 95% CI 0.23 to 1.16
Probiotics for treating established AE versus placebo	20[98-117]	1513	Mainly unclear risk of bias	Mainly children	Unspecified	Boyle (2009) [118] Number of included studies: 5 Meta-analysis: mean difference -0.90, 95% CI -2.84 to 1.04
Dietary supplements rich in linoleic acid such as evening primrose oil and borage oil versus placebo	23[119-140]	1448	Mainly unclear risk of bias	Mainly adults	Unspecified	Bamford (2013) [141] Number of included studies: evening primrose oil (7 trials) Meta-analysis for Evening Primrose Oil mean difference -2.22, 95% CI -10.48 to 6.04. Number of included studies: borage oil (8 trials) Meta-analysis for borage oil: not preformed (heterogeneity)
Other topical treatment: protease inhibitor SRD441 versus vehicle in adults with mild to moderate AE	1[142]	93	Mainly low risk of bias	Adults	Mild to moderate	SR not applicable
Other topical treatment: emollient with furfuryl palmitate versus emollient only	1[143]	117	Low risk of bias	Children	Unspecified	SR not applicable
Ion exchange water softening devices versus no water softening	1[144]	336	Low risk of bias	Children	Moderate to severe	SR not applicable
Other topical treatment: cipamfylline cream versus vehicle	1[145]	103	Mainly low risk of bias	Adults	Unspecified	SR not applicable
Mycobacterium vaccae vaccine versus no vaccine	4[146-149]	372	Low risk of bias	Mainly children	Moderate to severe	None

Table 3: Treatments which require more research

Intervention	Number of trials	Number of participants
Emollients	20[150-168]	1664
Dietary interventions including prebiotics, dietary restrictions, and synbiotics	13[169-181]	711
Non-pharmacological interventions, including: specialised clothing (silk or synthetic fibres with or without antibiotics); environmental interventions (house dust mite reduction, desensitisation); staying in a different climate; different approaches to organisation of care such as additional visits to the doctors or nurse led clinics; support groups; e-health management; psychological therapies (stress reduction or habit reversal techniques); balneotherapy (salt baths); biofeedback	33[182-214]	2447
Oral antibiotics for clinically infected or uninfected AE	3[215-217]	125
Topical corticosteroids combined with topical antibiotics for infected AE	2[92,218]	660
Wet wraps in addition to topical corticosteroids	5[219-223]	153
Antiseptic bath additives	3[224-226]	66
Systemic and topical antifungals	4[227-230]	202
Topical treatments including: topical vitamin B12; topical coal tar; camellia oil; SRD441 (protease inhibitor); WBI-1001 (an inhibitor of T cell inflammatory cytokine secretion); hippophe rhamnoides; black seed oil; pill mask; rosmarinic acid; vitreoscilla filiformis; shale oil; miltefosine; opiate receptor antagonist; carbohydrate derived fulvic acid; raffinose; farnesol and xylitol, bacterial antigens; camomile extract; heparin and levomenol; 15(R/S)-Methyl-lipoxin A4, N-acetyl-l-hydroxyproline; nalmefene hydrochloride monohydrate (SRD174)	27[231-257]	1340
Systemic treatments including: oral prednisolone; methotrexate; mycophenolate mofetil; biological therapies (omalizumab; mepolizumab); intravenous immunoglobulin; montelukast	22[258-279]	900
Oral antihistamines	29[278,280-307]	4201
Other less commonly used interventions including: oral pimecrolimus; oral naltrexone; autologous blood therapy; tandospirone citrate; full spectrum light therapy; excimer laser; nitrazepam; theophylline; topical salbutamol; papaverine and suplatast tosilate	14[308-319]	481
Complementary therapies including: Chinese Herbal treatment; hypnotherapy; massage therapy; aromatherapy; acupuncture; acupressure; and other herbal treatments	17[320-335]	604

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Supplementary Table 1: Search strategy (see separate file)

Supplementary Table 2: Criteria used for discussing the risk of bias in the summaries of treatment categories

Risk of bias description in the chapter summaries Collective risk of bias descriptions for summary statements	Basis for description
Overall low risk of bias	Method of generating the randomisation sequence, concealment of the allocation sequence, and blinding were assessed as low risk for all the trials summarised
Overall unclear risk of bias	Method of generating the randomisation sequence, concealment of the allocation sequence, and blinding were assessed as unclear risk for all the trials summarised
Overall high risk of bias	Method of generating the randomisation sequence, concealment of the allocation sequence, and blinding were assessed as high risk for all the trials summarised
Mostly low risk of bias	A clear majority of the method of generating the randomisation sequence, concealment of the allocation sequence, and blinding
Mostly unclear risk of bias	A clear majority of the method of generating the randomisation sequence, concealment of the allocation sequence, and blinding
Mostly high risk of bias	A clear majority of the method of generating the randomisation sequence, concealment of the allocation sequence, and blinding
A high risk of bias for (randomisation/allocation concealment/blinding)	One of method of generating the randomisation sequence, concealment of the allocation sequence, and blinding assessed as high for all, or in the case of many trials, almost all trials summarised.
A mixed risk of bias	The assessments were a fairly even distribution of risk of bias for method of generating the randomisation sequence, concealment of the allocation sequence, and blinding for the trials summarised.

Supplementary Table 1: Criteria used for discussing the risk of bias in the summaries of treatment categories

Risk of bias description in the chapter summaries	
Collective risk of bias descriptions for summary statements	**Basis for description**
Low	Method of generating the randomisation sequence, concealment of the allocation sequence, and blinding were assessed as being low risk for all the trials summarised
Unclear	Method of generating the randomisation sequence, concealment of the allocation sequence, and blinding were assessed as being unclear risk for all the trials summarised
High	Method of generating the randomisation sequence, concealment of the allocation sequence, and blinding were assessed as being high risk for all the trials summarised
Mostly low	A clear majority of the method of generating the randomisation sequence, concealment of the allocation sequence, and blinding were assessed as being low risk for the trials summarised
Mostly unclear	A clear majority of the method of generating the randomisation sequence, concealment of the allocation sequence, and blinding were assessed as being unclear risk for the trials summarised
Mostly high	A clear majority of the method of generating the randomisation sequence, concealment of the allocation sequence, and blinding were assessed as being high risk for the trials summarised
Mixed	A fairly even distribution of risk of bias for method of generating the randomisation sequence, concealment of the allocation sequence, and blinding for the trials summarised.

Supplementary figure 2: Summary of included interventions

Topical treatments

Calcineurin Inhibitors
Pimecrolimus (Elidel®)
Tacrolimus (Protopic®)

Corticosteroids
Alclometasone dipropionate (Aclovate®)
Betamethasone (Betnovate®)
Clobetasol propionate (Dermovate®)
Clobetasone butyrate (Eumovate®)
Desonide hydrogel (Desonate®)
Desoximetasone (Topicort®)
Fluocinolone acetonide (Derma-Smoothe/FS®)
Fluocinonide (Vanos®)
Fluticasone propionate (Cutivate®)
Hydrocortisone acetate (Hc45®)
Hydrocortisone butyrate (Locoid lipocream®)
Hydrocortisone solution (Hydrogelan®)
Methylprednisolone Aceponate (Advantan®)
Mometasone furoate (Elocon®)
Prednicarbate
Triamcinolone acetonide (Aristocort® A)

Corticosteroids with Antibiotics/Antifungals
Fusidic acid and betamethasone-17-valerate (Fucicort®)
Hydrocortisone and miconazole (Daktacort®)
Triamcinolone acetonide and tetracycline

Antibiotics/antifungals
Ciclopirox olamine (Batrafen®)
Fusidic acid (Fucidin®)
Mupirocin (Bactroban®)

Bathing-related
Eucalyptus and oat extract mixture bath additive
Sodium hypochlorite (bleach) bath additive
Triclosan (Safeguard®) soap bar

Emollients (unbranded)
Farnesol and xylitol-containing
Furfuryl palmitate-containing
Glycerine-containing
Triclosan-containing leave-on emollient
Urea-containing

Emollients (branded)
A-Derma®
Albolene®
Aquaphor®
Atopiclair™
Axera™
Canoderm®
Cetaphil™
EpiCeram®
Eucerin®
Exomega milk®
Hyaltopic™
Lipiderm®
Miglyol®
MimyX™
Restoraderm®
Stelatopia®
Tefirax®

Other Topical
Atopico®
Black seed oil
Carbohydrate-derived fulvic acid
Cipamfylline
Cyanocobalamin
Doxepin
Hydroxyproline
Kamillosan®
Lipoxin A4
Miltefosine (Miltex®)
Nalmefene (SRD174)
Naltrexone
Rosmarinic acid
Sea buckthorn extract
Sensicutan® with heparin and levomenol
Shale oil
Sodium bituminosulfonate (Ichthosin®)
Sodium cromoglycate (Altoderm®)
Sorbityl furfural palmitate (AR-GG27®)
SRD441
St John's wort
Vitreoscilla filiformis extract
WBI-1001

Oral treatments

Immunosupressants
Azathioprine
Ciclosporin (Neoral®)
Methotrexate
Mycophenolate sodium
Prednisolone

Antihistamines
Cetirizine (Zirtek®)
Chlorpheniramine (Piriton®)
Epinastine hydrochloride
Fexofenadine (Telfast®)
Ketotifen fumarate (Zaditen®)
Loratidine (Clarityn®)
Olopatadine hydrochloride

Antifungals
Itraconazole
Ketoconazole (Nizoral®)

Other Oral
Anapsos®
Chinese herbal medicine (various)
Hochu-ekki-to
Naltrexone
Montelukast (Singulair®)
Pimecrolimus
Tandospirone citrate

Dietary
Borage oil
Evening primrose oil
Fish oil
Hempseed oil
Milk replacements
Prebiotics
Probiotics
Synbiotics
Vitamin D2 and D3
Vitamin E

Other types of treatment

Immunoglobulins
Intravenous immunoglobulin
Mepolizumab (intravenous)
Omalizumab (subcutaneous)

Phototherapy
Full spectrum light therapy
Ultraviolet-A
Ultraviolet-B

Clothing
Ethylene-vinyl alcohol (Mediele®)
Silk (Dermasilk®)
Silver filaments (Padycare®)
Silver coated (X-Static®)
Tourmaline coated

Interaction-based
Additional visits to healthcare professionals
Educational
E-health portal
Psychological
Support groups

Complementary
Acupuncture
Acupressure
Aromatherapy and massage
Hypnotherapy
Progressive muscle relaxation

Enviromental
Balneotherapy
House dust mite reduction
Ion-exchange water softeners
Visiting a different climate

Supplementary Figure 1: Search strategy used to identify trials

MEDLINE (Ovid) Cochrane Collaboration Highly sensitive search string

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross-over$).mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. (assign$ or allocat$).mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp Dermatitis, Atopic/
15. atopic dermatitis.mp.
16. atopic eczema.mp.
17. exp NEURODERMATITIS/
18. neurodermatitis.mp.
19. infantile eczema.mp.
20. childhood eczema.mp.
21. (besnier$ and prurigo).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
22. eczema.mp. or exp Eczema/
23. 21 or 17 or 20 or 15 or 14 or 22 or 18 or 16 or 19
24. 23 and 13

EMBASE search string (Ovid)

1. random$.mp.
2. factorial$.mp.
3. crossover$.mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
7. assign$.mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12