

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

45 **Summary (Abstract)**

46
47 Atopic eczema (AE) is a common chronic inflammatory skin condition. Whilst many AE treatment options are
48 available, the evidence to support their efficacy varies in depth and quality. In 2000, an NIHR HTA systematic
49 review identified and evaluated existing randomised controlled trials (RCTs) of AE treatments. To ensure
50 continuing utility, the NIHR commissioned an update to the review. Here, we present an overview of the
51 updated report and key findings.

52
53 Systematic reviews and RCTs of AE treatments that included participants with AE (criteria based or diagnosed)
54 were identified using: MEDLINE, EMBASE, CENTRAL, LILACS, AMED, CINAHL and Cochrane Skin Group
55 Specialised Register (searched to August 31st 2013 (RCTs) and 31st December 2015 (systematic reviews)).
56 Outcome measures included: symptoms, AE severity, quality-of-life, and adverse effects. Study quality was
57 assessed using the Cochrane Collaboration risk of bias tool.

58
59 Of the 287 new RCTs identified, only 22 (8%) were judged to be low risk of bias. When combined with RCTs
60 from the previous review (n= 254), we found 'reasonable evidence of benefit' for corticosteroids, calcineurin
61 inhibitors, Atopiclair™, ciclosporin, azathioprine, ultraviolet light and education programmes.

62 Interventions with reasonable evidence of "no benefit" included some dietary interventions, ion exchange
63 water softeners, multiple daily applications of topical corticosteroids and antibiotic-containing corticosteroids
64 for non-infected AE. Many common treatments lack evidence of efficacy and warrant further evaluation.

65
66 The evidence base for AE is still hampered by poor trial design and reporting. The trials included in this review
67 were used to establish the Global Resource of Eczema Trials (GREAT) Database.

68 **Introduction**

69 Atopic eczema (AE) (syn. atopic dermatitis), is a chronic inflammatory skin condition characterised by an itchy
70 red rash that affects all age groups¹. AE has one of the highest burdens compared to other skin diseases.²

71

72 The evidence-base for AE treatments is extensive, but has limitations in terms of quality and relevance.³ This is
73 exemplified by the 'Systematic Review of Treatments for Atopic Eczema', published by the National Institute
74 for Health Research (NIHR), which identified 254 RCTs of AE treatment covering 47 interventions.⁴ The
75 encompassing nature of the review, and critical appraisal of the evidence therein, has helped to inform clinical
76 guidelines on an international level for over a decade and the report has been heavily cited, with more than
77 650 citations listed in Google Scholar at time of writing.⁵⁻⁸

78

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

84

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

87

88

89 **Methods used for the scoping review**

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

92 **Design**

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

98 **Type of studies included**

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

103 **Participants**

104 Studies were included if participants (of any age) had AE, as diagnosed by a physician, or that met with a
105 diagnostic criteria (e.g. Hanifin and Rajka,¹¹ UK working party¹² or similar).

106 **Main outcome measures**

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

112 **Search strategy**

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

119
120 Systematic reviews on AE treatments were searched for up until Dec 2015 using PubMed, EMBASE, the
121 Cochrane Library and NHS Evidence. Where appropriate the results of these specific systematic reviews are
122 presented alongside the RCT evidence.

123

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

131 **Data assessment and study quality**

132 Data was independently extracted by two authors (HN and SB or SS) with discrepancies resolved by consensus
133 or by an arbitrator (HCW, KST or FMD). Although primarily a scoping review, trial quality (specifically
134 randomisation, allocation concealment and blinding) was evaluated. This was done using Cochrane
135 collaboration's risk of bias assessment tool.¹⁵ The overall risk of bias for the included studies was summarised
136 according to defined criteria (Supplementary Table 1). Authors were not blinded to the identity of the RCT
137 authors, and a more detailed quality assessment (such as GRADE¹⁶) was unfeasible given the number of
138 included studies.

139 **Presentation of the results**

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

149

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

- 151 i) treatments for which there is reasonable *evidence of benefit*
- 152 ii) treatments for which there is reasonable evidence of *no-clinically useful benefit*
- 153 iii) treatments for which there is *insufficient evidence to inform clinical decision-making*
- 154 iv) treatments with an *absence of RCT evidence*.

155

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

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

163

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

168 **Results of the review**

169 **Summary of trials**

170 In addition to the 254 RCTs identified in the original 2000 scoping review, this updated includes an additional
171 287 new RCTs, making 541 RCTs in total covering 92 different interventions for treating AE. The number of
172 RCTs published according to broad treatment categories is shown (Figure 1), with further details provided in
173 Supplementary Figure 2.

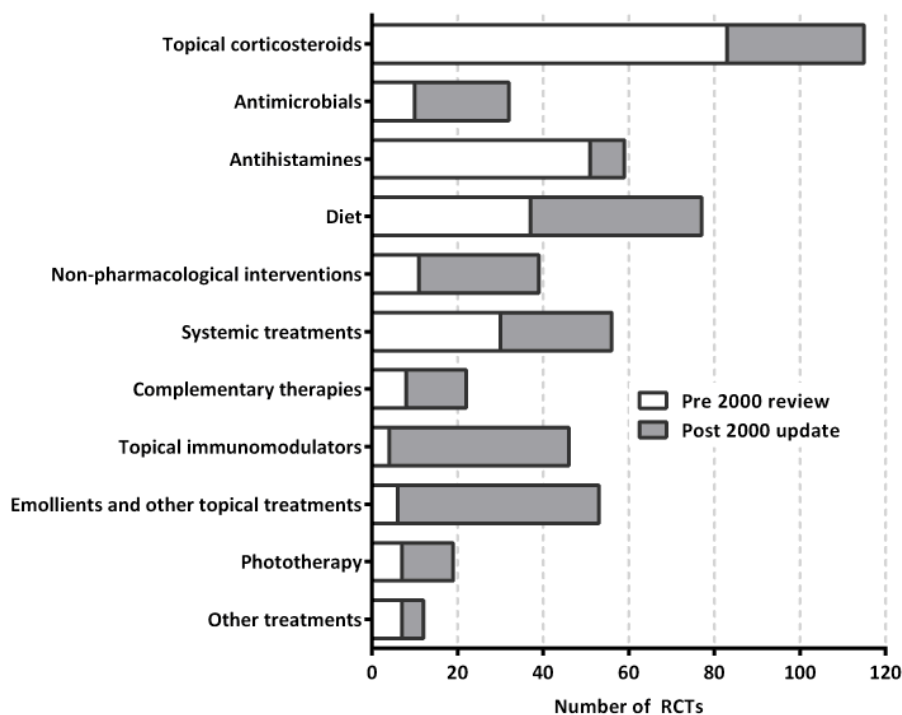
174

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

179 Reporting was generally poor, with “unclear” categories dominating the assessments: randomisation method
180 (2% high, 36% low and 62% unclear risk of bias), allocation concealment (3% high, 15% low and 82% unclear
181 risk of bias), and blinding or masking of the intervention (15% high, 28% low, 57% unclear risk of bias). Only
182 22/287 (8%) were considered to be at low risk of bias for all three quality criteria (randomisation, allocation
183 concealment and blinding). Overall agreement between the team members on the availability and quality of
184 the evidence, and the likelihood of clinically important effects was good.

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Figure 1: Number of included RCTs per treatment category

192 **Treatments with reasonable evidence of benefit**

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

200

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

203 **Treatments with evidence of no clinically useful benefit**

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

207 **Treatments which require more research**

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

211 **Treatments with an absence of RCT evidence**

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

217

218 Discussion

219 Main findings

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

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

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

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

244 Implications for research

245 There is a lack of AE treatment trials conducted in a primary care setting, where most patients are seen. The
246 research questions being investigated often fail to reflect the most pressing questions for clinicians and
247 patients. A recent James Lind Alliance Priority Setting Partnership³ identified the most important treatment
248 uncertainties as judged by patients and clinicians. When set in the context of the updated evidence base from
249 the review, the following areas identified from the Priority Setting Partnership seem to be most pressing:

250

251 **Priority areas with no current RCT evidence**

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

- 254 • Which should be applied first when treating AE – emollients or topical corticosteroids?
255

256 **Priority areas with limited RCT evidence**

- 257 • What is the best and safest way of using topical corticosteroids for AE?
258 • What is the long-term safety of applying topical steroids to the skin for AE?
259 • Which emollient is the most effective and safe in treating AE?
260 • What is the best psychological treatment for itching/scratching in AE?
261 • What are the best and safest 'natural' products to apply to the skin?
262 • How much does avoidance of irritants and allergens help people with AE?
263 • What is the role of diet in treating AE (exclusion diets and nutritional supplements)
264 • Which is more effective in the management of AE: education programmes, GP care, nurse-led care, dermatology-led
265 care of multi-disciplinary teams?
266 • Which is safer and more effective in treating AE: topical corticosteroids or calcineurin inhibitors (especially for
267 proactive flare prevention)?
268 • How effective are interventions to reduce skin infections in the management of AE?
269 • What is the best and safest way of using drugs that suppress the immune system (particularly in children)
270

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

276 **Methodological research**

277 One of the most pressing concerns identified by this review is the continued preponderance of small, poorly
278 reported and poorly conducted trials. Greater efforts to work collaboratively to conduct large, well designed
279 studies that address important questions, can only be of benefit to patients and healthcare providers.
280

281 Similarly, the ability to combine study results in meta-analysis continues to be hampered by the wide variation
282 in outcome measures used. The move towards using the same core outcome sets as encouraged by the
283 Harmonising Outcome Measures for Eczema (HOME) initiative¹⁸⁻²⁰ (www.homeforeczema.org) are likely to be
284 beneficial for future clinical interpretation and evidence syntheses.

285 **Strengths and limitations of the review**

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

292

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

298

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

303

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

309 **Conclusion**

310 The number of RCTs for AE has increased substantially since the year 2000⁴ yet most are still small, poorly
311 reported, and do not address questions of clinical importance to patients and healthcare professionals

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

316

317

318

319 **Table and figure legends**

320 Figure 1: Number of included RCTs per treatment category

321

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

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

324 Table 3: Treatments which require more research

325

326 Supplementary Figure 1: Search strategy used to identify trials

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

328

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	Ersrer 2014 ¹⁰⁶ Number of included studies:10 Meta-analysis: not done

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

330 * Please note, 3 studies were included within one paper

331

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

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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

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	<i>Not applicable</i>
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	Oral treatments	Other types of treatment
<p>Calcineurin Inhibitors Pimecrolimus (Elidel®) Tacrolimus (Protopic®)</p> <p>Corticosteroids Alclometasone dipropionate (Aclovate®) Betamethasone (Betnovate®) Clobetasol propionate (Dermovate®) Clobetasone butyrate (Eumovate®) Desonide hydrogel (Desonate®) Desoximetasone (Topicort®) Fluocinolone acetonide (Derma-Smoother/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)</p> <p>Corticosteroids with Antibiotics/Antifungals Fusidic acid and betamethasone-17-valerate (Fucicort®) Hydrocortisone and miconazole (Daktacort®) Triamcinolone acetonide and tetracycline</p> <p>Antibiotics/antifungals Ciclopirox olamine (Batrafen®) Fusidic acid (Fucidin®) Mupirocin (Bactroban®)</p> <p>Bathing-related Eucalyptus and oat extract mixture bath additive Sodium hypochlorite (bleach) bath additive Triclosan (Safeguard®) soap bar</p> <p>Emollients (unbranded) Farnesol and xylitol-containing Furfuryl palmitate-containing Glycerine-containing Triclosan-containing leave-on emollient Urea-containing</p> <p>Emollients (branded) A-Derma® Albolene® Aquaphor® Atopiclair™ Axera™ Canoderm® Cetaphil™ EpiCeram® Eucerin® Exomega milk® Hyaltopic™ Lipiderm® Miglyol® Mimyx™ Restoraderm® Stelatopia® Tefirax®</p> <p>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</p>	<p>Immunosuppressants Azathioprine Ciclosporin (Neoral®) Methotrexate Mycophenolate sodium Prednisolone</p> <p>Antihistamines Cetirizine (Zirtek®) Chlorpheniramine (Piriton®) Epinastine hydrochloride Fexofenadine (Telfast®) Ketotifen fumarate (Zaditen®) Loratidine (Clarityn®) Olopatadine hydrochloride</p> <p>Antifungals Itraconazole Ketoconazole (Nizoral®)</p> <p>Other Oral Anapso® Chinese herbal medicine (various) Hochu-ekki-to Naltrexone Montelukast (Singulair®) Pimecrolimus Tandospirone citrate</p> <p>Dietary Borage oil Evening primrose oil Fish oil Hempseed oil Milk replacements Prebiotics Probiotics Synbiotics Vitamin D2 and D3 Vitamin E</p>	<p>Immunoglobulins Intravenous immunoglobulin Mepolizumab (intravenous) Omalizumab (subcutaneous)</p> <p>Phototherapy Full spectrum light therapy Ultraviolet-A Ultraviolet-B</p> <p>Clothing Ethylene-vinyl alcohol (Mediele®) Silk (Dermasilk®) Silver filaments (Padycare®) Silver coated (X-Static®) Tourmaline coated</p> <p>Interaction-based Additional visits to healthcare professionals Educational E-health portal Psychological Support groups</p> <p>Complementary Acupuncture Acupressure Aromatherapy and massage Hypnotherapy Progressive muscle relaxation</p> <p>Environmental Balneotherapy House dust mite reduction Ion-exchange water softeners Visiting a different climate</p>

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