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What's new in atopic eczema? An analysis of systematic reviews published in 2017. Part 1: treatment and prevention

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Summary

This review forms part of a series of annual updates that summarize the evidence base for atopic eczema (AE). It provides a summary of key findings from 25 systematic reviews that were published or indexed during 2017, and focuses on the treatment and prevention of AE. There is high-quality evidence to demonstrate that dupilumab is better than placebo for the treatment of AE, is not associated with a higher incidence of adverse effects and does not increase the risk of infection compared with placebo; however, comparison studies with other systemic treatments are necessary. Topical tofacitinib is a promising treatment for mild–moderate AE, but currently lacks sufficient evidence from well-designed randomized controlled trials (RCTs) comparing with other active treatments. Topical doxepin may be effective for pruritus in AE, but available studies have short follow-up periods and longer-term outcomes are needed. Bleach baths were no more effective than water baths alone at reducing AE severity. Topical antibiotics cannot be recommended for infected AE, owing to insufficient evidence of benefit. There is little comparison of different emollients in RCTs, but overall evidence indicates that they reduce AE severity, are steroid-sparing and lead to better outcomes in combination with topical corticosteroids (TCS) than TCS alone. No clear benefit was demonstrated for vitamin D/C/E supplementation in pregnancy for eczema prevention.

Background

This evidence update aims to highlight the outcomes of recent systematic reviews (SRs) published or indexed in 2017. This article is the first of a two-part series

and focuses on treatment and prevention of atopic eczema (AE). For epidemiology, aetiology and risk factors, see Part 2. Similar eczema evidence updates and the search strategy have previously been published.^{1,2} In this update, the quality of individual studies is summarized in Table 1.

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Drug therapies for atopic eczema

Dupilumab

Four SRs assessed dupilumab, a first-in-class biologic for the treatment of moderate–severe AE.^{3–6} Seven randomized controlled trials (RCTs) were common to all and three included an eighth,^{3,5,6} totalling 2705 participants.

Two SRs examining efficacy concluded dupilumab was effective.^{4,6} Meta-analysis demonstrated superior

Table 1 Details and assessment of quality of individual systematic reviews (abbreviations: PICO, patients, intervention, comparator, outcomes; RoB, risk of bias).

Author	Studies included				Number of participants	Funding/COI	Authors' conclusion	Quality of studies
	Objective of review	Total	On AE	Type of trials				
Fleming and Drucker (2018) ³	To determine the impact of dupilumab on rates of skin and other infections in patients with moderate-severe AE	8	8	RCTs	2706	Funding: none COI: declared, 1 author with COI	Dupilumab associated with a decreased incidence of skin infections and eczema herpeticum in adults with moderate-severe AE Dupilumab appears to significantly decrease the risk for skin infections and eczema herpeticum in adults with moderate-severe AE	PICO: yes Pre-published protocol: stated registered on PROSPERO Adherence to protocol: only 1 outcome amended Included study designs: RCTs only Literature search: PubMed only Grey literature: references checked; trial registries Duplicate study selection: yes Duplicate data extraction: no, only 1 reviewer Exclusions and justification: clear in a flow diagram RoB technique: yes, using the Cochrane RoB tool Meta-analysis: yes RoB comment: not sufficient Heterogeneity analysis: none Publication bias: no assessment PICO: no clear PICO Pre-published protocol: not stated Included study designs: RCTs only Literature search: multiple databases searched; English-language studies only. Grey literature: none Duplicate study selection/data extraction: not stated Exclusions and justification: not stated RoB technique: Begg funnel plot and Egger test done Meta-analysis: yes RoB comment: yes, sufficient analysis Heterogeneity analysis: yes, from 1 study Publication bias: Begg funnel and Egger test: unlikely impact
Han <i>et al.</i> (2017) ⁴	To evaluate the efficacy and safety of dupilumab	7	7	RCTs only	1965	Funding: National Natural Science Foundation of China No COI	Dupilumab was shown to be consistently more effective than placebo, with a trend of a dose-dependent effect, and had a placebo-like safety profile Combination of dupilumab with topical glucocorticoids seemed to improve the effects	

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Ou <i>et al.</i> (2018) ⁵	To assess the influence of dupilumab on adverse events in adults with moderate-severe AE	8	8	RCTs	1790	Funding: none COI: no statement found	Dupilumab moderately reduced the risk of skin infection and the exacerbation of AE, slightly increased the risk of headache, and moderately increased the risk of injection-site reaction and conjunctivitis, but had little effect on other infections in adults with moderate-severe AE	PICO: clear Pre-published protocol: not stated Included study designs: RCTs only Literature search: EMBASE, PubMed and Web of Science; English-language studies only. Grey literature: not mentioned Duplicate study selection/data extraction: yes Exclusions and justification: use of flow diagram RoB technique: Cochrane RoB tool used to assess bias Meta-analysis: none RoB comment: adequate assessment of study quality and outcomes Heterogeneity: Assessment of heterogeneity discussed Publication bias assessed using funnel plot

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Xu <i>et al.</i> (2017) ⁶	To summarize efficacy, safety and influence of QoL of dupilumab treatment for moderate-severe AE in adults	7	7	Unclear	2705	Funding: National Natural Sciences Foundation of China No COI	Dupilumab is effective and safe for the treatment of moderate-severe atopic dermatitis in adults. This meta-analysis supports the role of dupilumab as a primary targeted biologic therapy in adult patients with moderate-severe atopic dermatitis	PICO: no clear comparator in the PICO question Pre-published protocol: not stated Adherence to protocol: NA Included study designs: RCTs only but not justified why Literature search: multiple databases; English-language studies only. Grey literature: not specified Duplicate study selection/data extraction: yes Exclusions and justification: clear in flow diagram Included studies description: yes RoB technique: Cochrane RoB tool used; also Egger test and Begg funnel plot Meta-analysis: yes RoB comment: Cochrane RoB tool used: clear assessment of individual studies Heterogeneity analysis: yes Publication bias: using Begg funnel and Egger test: unlikely impact

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Kostovic <i>et al.</i> ⁷ (2017) ⁷	To present updated data summary on the tofacitinib in the field of dermatology	43	2	Review articles, original research, case reports	74 (for AE)	Funding: no statement No COI	Authors concluded that results are promising for topical tofacitinib	PICO: not clear and not targeted to specific population or comparator Pre-published protocol: not stated Included study designs: all study types; language inclusion not specified Literature search: unclear what databases were included, and search strategy not provided. No details on article selection. Grey literature: not mentioned Exclusions and justification: no flow diagram RoB technique: not specified Meta-analysis: none RoB comment: in text, not sufficient Heterogeneity analysis: none Publication bias not assessed
Shreberk-Hassidim <i>et al.</i> ⁸ (2017) ⁸	To review systematically the available data on the use of JAK inhibitors in cutaneous diseases	134	1	All studies	69	Funding sources: none COI: 1 author has received speaker's honorarium from Pfizer	1 study described: a phase II study with topical vehicle vs. 2% tofacitinib. Showed a more significant reduction in area and severity of eczema; 81% reduction in EASI in tofacitinib group vs. 30% in vehicle group. Improvement in pruritus at 2 days	PICO: not clear, general review of JAK inhibitors in skin disease Pre-published protocol: not stated Included study designs: not clear Literature search: PubMed and clinicaltrials.gov. Grey literature: not mentioned Duplicate study selection/extraction: not stated Exclusions and justification: duplicates or irrelevant articles were excluded RoB technique: not specified Meta-analysis: none RoB comment: in text, not sufficient Heterogeneity analysis: none Publication bias not assessed

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Yu <i>et al.</i> (2018) ⁹	To review systematically the literature on efficacy and safety of systemic corticosteroid use (oral, IM and IV) in AE	52 reviews and 12 studies	52 reviews and 12 studies	SRs, treatment reviews and trials	Unclear	Funding: yes COI: numerous COIs with pharma companies	Evidence is not strong enough to determine optimal delivery or duration of systemic corticosteroids in AE Literature supports short-term use of short courses of oral corticosteroids (3 weeks) to interrupt acute flares, but rebound flaring is commonly observed after discontinuation	PICO: no comparator given Pre-published protocol: not specified Included study designs: yes, stated Literature search: multiple databases; English-language studies only. Grey literature: not mentioned Duplicate study selection/data extraction: no Exclusions and justification: yes in a flow diagram in the supplement Included studies description: yes, in table RoB technique: not formally done, but commented on Meta-analysis: none RoB comment: in text, but little assessment of RoB in individual studies/outcomes Heterogeneity analysis: none Publication bias not assessed

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Eskeland <i>et al.</i> (2017) ¹¹	To investigate the anti-inflammatory potential of antidepressants	28	5	3 RCTs for topical therapies; 1 case report and 1 observational for oral therapies	1252	Funding: partly supported by Lovisenberg Diagonale Hospital COI: none declared	Antidepressants may be useful in AE Good indications that topical doxepin is helpful for pruritus in AE	PICO: clear Pre-published protocol: not stated Included study designs: not clear Literature search: multiple databases. Grey literature: 'supplementary searches' performed Duplicate study selection/data extraction: no Exclusions and justification: not stated, no flow diagram RoB technique: yes; comment in discussion Meta-analysis: none RoB comment: not sufficiently assessed in the text for AE Heterogeneity analysis: none Publication bias: not assessed
Li <i>et al.</i> (2017) ¹²	To assess the nomenclature, prevalence, origins and effect on treatment adherence of TCS phobia in AE	16	16	Cross-sectional	Not specified	Funding: not specified COI: 1 consultant paid and performed research by numerous pharmaceutical companies	Prevalence of TCS fear ranged from 21% (CI 15.8–26.2%) to 83% (CI 81.9–85.5%) At least 1/5 of all the populations studied were affected by TCS phobia Top 2 concerns among studies were (i) skin thinning, and (ii) growth and development. Authors suggest identifying these concerns early and considering counselling	PICO: clear Pre-published protocol: not stated Included study designs: all study types excluding abstracts, reviews, case reports, case series Literature search: multiple databases. Grey literature: not specified Duplicate study selection/extraction: not stated Exclusions and justification: excluded. Non-eczema studies excluded. This was specifically justified RoB technique: not specified Meta-analysis: none RoB comment: in text, limited RoB assessment of studies or outcomes Heterogeneity analysis: none Publication bias not assessed

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Chopra et al. (2017) ¹³	To determine the efficacy of bleach vs. water baths for decreasing AE severity	5	5	3 RCTs, 1 randomized crossover trial, 1 unblinded, single-arm, pilot study	116	Funding: none COI: none declared	Although bleach baths are effective in decreasing AE severity, they do not appear to be more effective than water baths alone. Future larger-scale, well-designed, RCTs are needed	PICO: clear Pre-published protocol: not stated Included study designs: any retrospective or prospective study Literature search: Numerous databases. Grey literature: unclear Duplicate study selection/data extraction: no RoB technique: no specific framework, commented on in the discussion Meta-analysis: none RoB comment: in discussion only Heterogeneity analysis: significant, adjusted for in the review Publication bias: not assessed
Van Zuuren et al. (2017) ¹⁵	To assess the effects of moisturizers for eczema	77	77	RCTs	6603	Funding: Cochrane COI: declared	Evidence for outcomes: low quality Overall results: most emollients have some beneficial effects Emollients + active treatment: better than active treatment alone No reliable evidence that 1 emollient is better than another	PICO: clear Pre-published protocol: yes Adherence to protocol: differences to protocol published online Included study designs: clear Literature search: multiple databases checked. Grey literature: unpublished data sought Duplicate study selection/data extraction: yes Exclusions and justification: yes RoB technique: using the GRADE proforma Meta-analysis: yes RoB comment: yes; sufficient, using GRADE Heterogeneity analysis: yes Publication bias assessed

Table 1 continued

Author	Objective of review	Studies included			Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE						
Lim <i>et al.</i> (2017) ¹⁶	To examine the published literature and generate helpful conclusions for clinicians faced with dietary questions for AE	43	43		All study types	Unclear	Funding: not stated COI: not stated	Authors state that there is some evidence to support the use of elimination diets in specific, preselected populations Level 1 evidence that exacerbation of AE due to food allergies established by robust and validated testing is a real phenomenon. They suggest that clinicians should target this	PICO: not specific Pre-published protocol: not stated Included study designs: most, including case studies Literature search: PubMed only; limited to MeSH terms; references checked; English-language studies only. Grey literature: not specified Duplicate study selection/data extraction: not clearly stated Exclusions and justification: clearly justified, no flow diagram RoB technique: not specified Meta-analysis: none RoB comment: not measured using a tool, but stated that there was a high RoB in certain studies Heterogeneity analysis: none Publication bias not assessed
Notay <i>et al.</i> (2017) ¹⁷	To identify evidence for use of supplementation with probiotics, prebiotics or synbiotics for prevention and treatment of dermatological diseases in adults	12	9		RCTs and prospective observational	269	Funding: none. COI: 1 author is a scientific advisor for Dermveda	Authors note limited evidence for use of probiotics and prebiotics in adults and therefore conclusions cannot be made Certain probiotic supplements and mixtures may be helpful	PICO: wide-ranging review on evidence for prevention and treatment of AE Pre-published protocol: not stated Included study designs: clear Literature search: multiple databases. Grey literature: not specified Duplicate study selection/data extraction: yes Exclusions and justification: clear in the text RoB technique: done well, using the Jadad score to look at study quality Meta-analysis: none RoB comment: Jadad score Heterogeneity analysis: none Publication bias not assessed

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Shi <i>et al.</i> (2017) ¹⁸	To evaluate the efficacy and safety of TCM	24	24	RCTs	1618	Funding: yes COI: none	SR did not provide the practical and beneficial results of TCM and related treatment for AE therapy	PICO: clear Pre-published protocol: not stated Included study designs: RCTs only Literature search: clear search strategy, multiple databases, no language restrictions. Grey literature: not stated Duplicate study selection/ extraction: yes 2 reviewers for title and abstract selection and data extraction Exclusions and justification: use of flow diagram RoB technique: RoB plot included; low risk of bias for most studies Heterogeneity analysis: performed, moderately high (65%). Sources analysed but not found Publication bias assessed with funnel plots: no evidence of bias

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Hashimoto <i>et al.</i> (2017) ¹⁹	To determine the efficacy of psychological and educational interventions	12	12	RCTs only	232	Funding: not reported COI: none	Authors state the data did not have sufficient power to provide evidence-based conclusions	PICO: no clear PICO Pre-published protocol: not stated Included study designs: RCT only, not stated why Literature search: included clinical trial databases; no language restrictions; journals manually checked; references reviewed. Grey literature: not mentioned Duplicate study selection: yes, 2 authors Exclusions and justification: Quasi-randomized studies only. RoB technique: Cochrane RoB bias tool Meta-analysis: none RoB comment: yes. Thorough description in text Heterogeneity analysis: yes Publication bias: no assessment

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Ridd <i>et al.</i> (2017) ²⁰	To review evidence on self-management in AE in children, caregivers and adults with AE	20	20	RCTs	3028	Funding: none COI: none author funded by NIHR fellowship	Uncertainty about the benefit of educational interventions for AE—partly due to poor and limited evidence to base conclusions on Authors felt that internet-based and face-to-face approaches probably improve self-management and outcomes for patients, but the optimum means of delivering support in a cost-effective way not yet determined	PICO: clear Pre-published protocol: stated as registered on PROSPERO Adherence to protocol: yes, but not otherwise stated Included study designs: yes Literature search/grey literature: good literature search, including grey literature and all languages Duplicate study selection and data extraction: yes Exclusions and justification: yes, flow diagram Included studies description: tabulated and clear RoB technique: yes, Cochrane RoB tool Meta-analysis: none RoB comment: yes, sufficient Heterogeneity: none, not applicable Publication bias not assessed

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Jeon <i>et al.</i> (2017) ²¹	To review studies investigating the effect of AE on sleep in adults and provide an approach for clinicians caring for this population	39	39	Original studies, excluding case series and reports and commentaries	Unclear	Funding: none. COI: 1 author with relevant COIs	High prevalence of sleep disturbance experienced by adults with AE (33–87.1%), which can have significant impact on QoL. Pruritus and scratching appear to be large contributors Mixed outcomes regarding correlation of severity of SCORAD vs. sleep disturbance	PICO: not clear, just an assessment of studies related to sleep and eczema Pre-published protocol: not stated Included study designs: not clear Literature search: 2 databases (PubMed/EMBASE). Grey literature: not done Duplicate study selection: yes; 2 authors Exclusions and justification: no flow diagram. Case series and reports excluded RoB technique: not specified Meta-analysis: none RoB comment: in text, limited discussion of RoB of studies/outcomes Heterogeneity analysis: none Publication bias not assessed

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Barfield <i>et al.</i> (2017) ²²	To review the literature and critique evidence to understand better the use of emollient therapy in AE	10	10	9 RCTs 1 pilot cohort	Unclear: several thousand	Funding: none COI: none	Emollient therapy is effective for primary prevention in at-risk populations for AE Emollients have a steroid-sparing effect Authors felt a clinical tool is required to help carers select an emollient, how to apply it and how to educate parents for long-term management	PICO: none Pre-published protocol: not stated Included study designs: RCTs Literature search: 2005–2015, Numerous databases, English studies only. Search strategy not clear. Grey literature: unclear Exclusions and justification: explained, no flow diagram Duplicate study selection/data extraction: not stated RoB technique: in text discussion of some study limitations Meta-analysis: none RoB comment: insufficient discussion of strength of recommendations Heterogeneity analysis: none Publication bias: not assessed
Cooke <i>et al.</i> (2018) ²³	To identify important skin practices for baby skin in healthy term babies aged 0–6 months	26	26	16 RCTs, 3 nonrandomized studies, 1 mixed methods, 6 qualitative		Funding: Royal College of Midwives COI: 1 author is an advisor for J&J. One author has undertaken trial for J&J	No significant differences between tested wash products and water or tested baby wipes and water Some evidence that full body emollients may reduce the risk of AE in those predisposed	PICO: clear Pre-published protocol: registered on PROSPERO Included study designs: 2000 onwards. English only. All RCTs, quasi-controlled trials, non-controlled trials and non-randomized experimental studies Literature search: multiple databases. Grey literature: checked references, trials registries, abstracts Exclusions and justification: via flow diagram RoB technique: GRADE Meta-analysis: yes RoB comment: Cochrane RoB tool Heterogeneity analysis: adjusted for in the review Publication bias: not assessed

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Yepes-Núñez <i>et al.</i> (2018) ²⁴	Efficacy and safety of vitamin D supplementation compared with no supplementation in pregnant women, breastfeeding women, infants and children for the prevention of allergies	1 RCT and 4 nonrandomized trials	1 RCT	RCT	151	Funding: World Allergy Organization COI: 2 authors had financial COI from pharma companies	Limited information available addressing primary prevention of allergic diseases after vitamin D supplementation and its potential impact remains uncertain	PICO: clear Pre-published protocol: mentioned a priori Adherence to protocol: NA Included study designs: RCTs and non-randomized trials not justified Literature search: multiple databases. Grey literature: references checked, trials registers Duplicate study selection/data extraction: yes Exclusions and justification: clear RoB technique: GRADE used for each outcome Meta-analysis: yes RoB comment: yes; sufficient Heterogeneity analysis: yes Publication bias: Funnel plot with visual inspection if ≥ 10

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Szajewska and Honvath (2017) ²⁶	To update evidence on use of pHF by a single manufacturer (Nestlé) for reducing risk of eczema and allergy in infants at high risk	8	6	RCTs and quasi-randomized RCTs	Varied: see meta-analyses	Funding: Medical University of Warsaw COI: yes; specified conflicts	Authors concluded that this meta-analysis demonstrated that pHF compared with CMF reduces risks of eczema	PICO: clear Pre-published protocol: not stated Included study designs: RCTs only Literature search: Cochrane, EMBASE, MEDLINE. Grey literature: references reviewed; authors emailed Duplicate study selection and data extraction: yes Exclusions and justification: yes in flow diagram Included studies description: yes, tabulated RoB technique: using GRADE and Cochrane RoB tool Meta-analysis: yes RoB comment: yes; sufficient Heterogeneity: yes Publication bias not assessed because not enough studies

Table 1 continued

Author	Objective of review	Studies included			Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE						
Waidyatillake <i>et al.</i> (2018) ²⁷	To review the association between breast milk PUFAs and allergic disease	18	9 (10 publications)		11 cohort, 2 case-control, 2 cross-sectional studies	Not specified	Funding: not declared COI: none	Insufficient evidence to suggest a link between PUFA and AE	PICO: not clear Pre-published protocol: PROSPERO protocol published prospectively Adherence to protocol: not otherwise stated Included study designs: clear: RCT and observational studies included Literature search: multiple databases. Grey literature: not specified Duplicate study selection/data extraction: yes Exclusions and justification: yes, flow diagram used RoB technique: commented on but no specific tool used Meta-analysis: not done owing to heterogeneity RoB comment: confounding factors noted for each study, little comment on level of bias for each outcome Heterogeneity analysis: yes, significant Publication bias: not assessed but commented on

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Cuello-García (2018) ²⁸	To assess in pregnant women, breastfeeding mothers, infants the effect of prebiotics vs. no prebiotics on development of allergic diseases	22	6	6 RCTs	2030	Funding: World Allergy Organization COI: some authors had support or honoraria from companies relevant to allergy and nutrition	Prebiotics to infants: risk of developing eczema RR = 0.68 (0.40–1.15) No evidence of increased risk of AE Evidence for prebiotic supplement to reduce the risk of allergies is very uncertain	PICO: yes Pre-published protocol: not stated Included study designs: randomized trials with a minimum follow-up of 4 weeks Literature search/grey literature: contacted authors, abstracts, trials registries Duplicate study selection: 4 authors did the search separately Duplicate data extraction: 4 extracted with data Exclusions and justification: clear RoB technique: yes; in S1 supplement Meta-analysis: yes RoB comment: in discussion and use of Cochrane RoB tool Heterogeneity analysis: adjusted for in the review Publication bias: assessed

Table 1 continued

Author	Objective of review	Studies included		Type of trials	Number of participants	Funding/COI	Authors' conclusion	Quality of studies
		Total	On AE					
Huang <i>et al.</i> (2017) ²⁹	To evaluate the effects of probiotics used to treat AE in children	13	13	RCTs only	1070	Funding: China's National Basic Work of Science and Technology COI: None	Data suggested probiotic supplementation in children may provide benefit in those with AE; however, there is significant heterogeneity and further studies are necessary to provide additional evidence	PICO: clear Pre-published protocol: not stated Included study designs: RCTs only Literature search: references reviewed, English-only text Duplicate study selection and data extraction: yes Exclusions and justification: clear on flow chart RoB technique: performed and tabulated. Not clear if used a specific tool Funding: other column Meta-analysis: yes RoB comment: yes, 'minimal RoB' Heterogeneity analysis: yes, χ^2 -test showed heterogeneity Publication bias assessed with funnel plots; possible bias

AE, atopic eczema; COI, conflict of interest; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; IM, intramuscular; IV, intravenous; J&K, Johnson & Johnson; JAK, Janus kinase; NA, not available; NIHR, National Institute for Health Research; PUFA, polyunsaturated fatty acid; QoL, quality of life; pHF, partially hydrolysed formula; PICO, Patient, Intervention, Comparator, Outcome; PROSPERO, International Prospective Register of Systematic Reviews; RCT, randomized controlled trial; RoB, risk of bias; RR, relative risk; SCORAD, SCORing Atopic Dermatitis; SR, systematic review; TCM, traditional Chinese medicine; TCS, topical corticosteroid.

efficacy of dupilumab compared with placebo for clinical outcomes including Eczema Area and Severity Index (EASI), with a weighted mean difference of -10.56 (95% CI -11.37 to -9.15).⁶ An alternate weekly dose of dupilumab 300 mg achieved similar outcomes to weekly dosing⁶ but lower doses and decreased dosing frequencies were less effective.⁴ Efficacy up to 52 weeks was also demonstrated, showing similar outcomes to those seen at 16 weeks.⁶

While pooled analysis demonstrated similar numbers of adverse effects for both groups,⁶ conjunctivitis was more frequently observed for dupilumab⁵; as this association has not been seen in dupilumab-treated patients with asthma or chronic sinusitis, it appears to be AE-specific. Compared with placebo, patients on dupilumab were less likely to get skin infections^{3,5} and eczema herpeticum.³

Janus kinase inhibitors

Two SRs assessed dermatological use of Janus kinase (JAK) inhibitors. One phase II double-blind RCT of topical tofacitinib 2% (69 participants with mild–moderate AE) demonstrated benefit over placebo, with improvement in EASI, Physician's Global Assessment (PGA) and involved body surface area at 4 weeks.^{7,8} However, larger studies with topical corticosteroid (TCS) comparators are required.

Systemic corticosteroids

Yu *et al.*⁹ reviewed the use of systemic corticosteroids (SCS) in AE. The authors reported a lack of good-quality studies, although there was evidence that SCS do provide some benefit, particularly in providing rapid relief from intractable itch. A single RCT compared SCS with ciclosporin, finding ciclosporin to be more effective at achieving stable remission (6/17 ciclosporin; 1/27 with prednisolone).¹⁰ Owing to a paucity of evidence, no recommendations could be made on specific indications or dosing, although the general consensus is to limit to short courses.

Antidepressants

Eskeland *et al.*¹¹ reviewed the benefits of antidepressants in skin disorders. Two RCTs (619 participants) demonstrated benefit of topical doxepin 5% over vehicle for relief of pruritus in AE. However, the follow-up was short (7 and 8 days) and the SR did not report on the study quality. No studies assessing tricyclic antidepressants or selective serotonin reuptake inhibitors in

AE were identified. One open-label study assessing bupropion, an oral antidepressant, found improvement in 6 of 10 patients with AE. However, discontinuation led to relapse.

Topical corticosteroids

Li *et al.*¹² reviewed the nomenclature, prevalence, origins and effect on treatment adherence of TCS phobia in AE (16 cross-sectional studies with 6242 participants, in Asia, Europe and North America). There was wide variation in how TCS phobia was defined and assessed; however, there was a high prevalence of TCS fear across different populations, ranging from 21% to 83.7%, with higher rates of nonadherence in those with TCS phobia. The top two concerns were skin thinning and impact on growth and development.

Bleach baths

Bleach baths are purported to be an inexpensive method for reducing the colonization density of cutaneous *Staphylococcus aureus*, which has been correlated with AE severity. An SR assessing bleach baths for AE treatment¹³ identified four RCTs. Pooled analysis of 4-week outcomes demonstrated no additional benefit of bleach baths for AE severity nor any reduction in *S. aureus* density compared with water baths alone.

Topical antibiotics

Tran and Wright¹⁴ reviewed the use of topical antibiotics. They concluded from two SRs and one additional RCT that use of topical antibiotics combined with TCS in infected AE did not elicit statistically significant improvements in AE compared to TCS alone. Similarly, one RCT demonstrated that topical fusidic acid in combination with topical tacrolimus provided no additional benefit for infected AE. Although many of the RCTs had significant limitations, with potential for bias, the authors concluded that there was currently not enough evidence to recommend topical antibiotic use for infected eczema.

Emollients

Four SRs were found assessing emollients in AE, although three related to a single Cochrane review by van Zuuren *et al.*¹⁵ This included a large number of studies (77 RCTs, 6603 participants), but many had a high risk of bias. Six studies evaluated emollients compared with no emollient, of which three assessed

efficacy using SCORing Atopic Dermatitis (SCORAD) and two studies permitted continued use of moderate to strong TCS. The studies showed a statistically significant benefit of emollients [$n = 276$; mean difference (MD) -2.42 ; 95% CI -4.55 to -0.28] although failing to meet what was considered a minimal clinically important difference (8.7). Use of emollients vs. no emollients led to fewer flares [2 studies, 87 participants; relative risk (RR) = 0.40, 95% CI 0.23–0.70], a prolonged time to flares (median: 180 days vs. 30) and reduced use of TCS (2 studies, $n = 222$; MD -9.30 g over 6–8 weeks, 95% CI -15.3 to -3.27). Topical active treatment combined with emollient was better than active treatment alone in reducing disease severity scores [3 studies, $n = 192$; standardized mean difference (SMD) -0.87 , 95% CI -1.17 to -0.57] and flares (1 study, $n = 105$, RR = 0.43, 95% CI 0.2–0.93). There was no reliable evidence that one emollient was better than another.

Dietary treatments in eczema

Elimination diets

Lim *et al.*¹⁶ reviewed the benefit of elimination diets in AE across 43 papers. In unselected children with AE, they found mixed results, and were unable to draw conclusions regarding egg and cow's milk elimination diets. Whilst some lower-quality studies suggested some benefit, higher-quality studies with less risk of bias did not demonstrate any benefit of dietary exclusions.

For participants preselected based on confirmed food allergies, one RCT and a prospective controlled trial demonstrated significant AE improvement following exclusion diets for proven egg and cow's milk allergies based on positive radioallergosorbent test and double-blind placebo-controlled food challenges.

For general elimination diets, or more extreme versions, e.g. six-food and elemental diets, there were no high-quality studies.

Notay *et al.*¹⁷ looked at the benefit of probiotic, prebiotic and synbiotic supplementation for AE treatment. Nine studies evaluated probiotics; however, as the studies had small sample sizes and investigated different supplements, the results could not be pooled.

Complementary and alternative medicines

Shi *et al.*¹⁸ evaluated the efficacy of Chinese and allied alternative medicines for AE in 24 relevant, albeit heterogeneous, RCTs (1618 participants). Four meta-

analyses were performed for the following outcomes: 'clinical effectiveness' (RR = 1.10, 95% CI 0.99–1.21); SCORAD (SMD = 0.89, 95% CI 0–0.24 to 2.02); EASI (SMD = 3.22, 95% CI 0.41–6.03, $P = 0.02$) and symptom score reducing index (SMD = -0.36 , 95% CI -1.16 to 0.45). While the meta-analysis of EASI scores demonstrated significant benefit, only two studies were included. The authors concluded that any benefits of Chinese medicine vs. placebo or Western medicines for AE could not be confirmed.

Psychological interventions and self-help

Hashimoto *et al.*¹⁹ reviewed the efficacy of psychological and educational interventions for AE. The 12 RCTs (232 participants) identified were mostly small, with a high or unclear risk of bias. For combined outcomes of education and psychological intervention, meta-analysis of three trials for AE severity each using a different outcome measure [Patient-Oriented Eczema Measure (POEM), EASI and SCORAD], did not demonstrate benefit (SMD = -0.29 , 95% CI -0.64 to 0.07). The authors concluded that insufficient high-quality evidence exists to assess these types of intervention.

Ridd *et al.*²⁰ reviewed self-management strategies in AE and identified 20 RCTs (3028 participants). Of these, 13 studies were face-to-face education, 5 were online and 2 were written action plans. High risk of bias in individual studies negated meta-analyses and the authors commented on reporting being generally poor. While there was some evidence these interventions may be beneficial, the best strategy to support self-management in a clinically and cost-effective way remains unclear.

Jeon *et al.*²¹ reviewed the effect of AE on sleep, identifying 39 studies. They noted a high prevalence of sleep disturbance (33–87.1%), with pruritus and scratching identified as major causes. The authors concluded that pruritus management should be the primary focus for treatment. Although the SR did not report the strength of evidence for each recommendation, there was some evidence to support the following therapies to improve sleep: emollients (and addition of chlorhexidine-soaked dressings), TCS, melatonin (in children), blue-light therapy, methotrexate, azathioprine and dupilumab. There was some evidence to support sedating antihistamines, but the quality of evidence was weak. The use of benzodiazepines to aid sleep could not be recommended: sleep duration increased, but sleep architecture was disrupted, and scratching was unaffected.

Prevention of atopic eczema

Skin-care practices in babies

Barfield *et al.*²² examined emollients for childhood AE, including nine RCTs and one pilot cohort study. Four assessed the benefit of primary prevention in neonates, while six examined steroid-sparing capacity, most with short follow-up, up to 6 weeks. Although no meta-analysis was performed, the authors concluded that emollients have a steroid-sparing effect and may be helpful for primary prevention of AE.

Cooke *et al.*²³ reviewed skin care practices in babies 0–6 months with a focus on biophysical skin parameters, and AE as a secondary outcome. The only analyses with strong evidence were for Johnson's Top-to-Toe wash[®], which was demonstrated to be no different to water alone for a variety of outcomes, including transepidermal water loss, hydration and surface pH (3 RCTs, 362 babies). There was some evidence from four RCTs that emollients improve skin hydration at 4 and 8 weeks, with reduced incidence of AE at 26 weeks in two RCTs. The authors concluded that more studies with longer follow-up are required to determine the impact of regular emollient use on AE development.

Vitamin supplementation in pregnancy

Yepes-Núñez *et al.*²⁴ reviewed the effect of vitamin D supplementation on primary allergy prevention in pregnant women, breastfeeding mothers and infants. Only one study, with pregnant mothers (151 subjects, 3-year follow-up), was relevant, and this showed no significant effect on AE incidence.

Vahdaninia *et al.*²⁵ reviewed the effect of vitamin supplementation on allergic outcomes. Three RCTs were found with AE as an outcome (two for vitamin D and one study for combined vitamins C and E). Meta-analysis could not be performed because of study heterogeneity. None of the studies demonstrated any benefit of vitamin supplementation on AE incidence.

Nutrition and formula products on primary prevention of atopic eczema

Szajewska and Horvath²⁶ reviewed the evidence for a partially hydrolysed whey formula (Nestlé) vs. cow's milk formulas on primary prevention of AE. The six RCTs identified had a significant risk of bias. In the intention-to-treat meta-analysis, a significant beneficial effect on cumulative incidence was seen at 0 to 5–6 years (2 RCTs, $n = 938$, $RR = 0.83$, 95% CI

0.69–0.99) but not at the other five time points tested. For incidence at specified time points, hydrolysed formula reduced the risk of AE at 1 year (four RCTs, $n = 724$, $RR = 0.68$, 95% CI 0.48–0.98), but not 2, 3 or 6–7 years. Although there was some suggestion of benefit, the findings were not conclusive, and the quality of evidence was low to moderate.

Waidyatillake *et al.*²⁷ reviewed the association between breast milk polyunsaturated fats (PUFAs), which have immunomodulatory properties. Of the nine studies assessing AE incidence, the majority did not show a relationship between PUFA levels in breast milk and the risk of AE.

Cuello-García *et al.*²⁸ assessed the effect of prebiotic supplementation in pregnant women, breastfeeding mothers and infants on the incidence of allergic diseases. No studies were found for breastfeeding or pregnant mothers. Six RCTs were relevant to AE in infants (2030 participants). Contrary to the 2013 Cochrane review on this topic, which concluded there was some evidence that prebiotic supplementation of infant feeds may prevent AE, the authors excluded studies with pre-term infants. No significant benefit was demonstrated in the combined meta-analysis ($RR: 0.68$, 95% CI 0.40–1.15); however, the quality of evidence was low. Huang *et al.*²⁹ reviewed the benefit of probiotic supplementation in children with AE. Thirteen RCTs were identified (1070 participants). While the meta-analysis demonstrated an overall benefit in terms of lower SCORAD values compared with controls, the authors noted significant heterogeneity between studies, individual study limitations and potential publication bias; therefore, concluding that better powered studies are necessary using standardized measurements.

Conclusions

Although there were some excellent examples of SR reporting and methodology, the issue of low-quality reporting and vague search strategies, single author abstract selection/review, and the lack of protocol registration on PROSPERO (the International Prospective Register of Systematic Reviews) for many studies still persists. Most SRs did not assess quality of outcomes using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE), a framework used in Cochrane reviews. This framework helps clinicians to understand the quality of evidence for individual outcomes, whether figures derived through pooled meta-analysis can be trusted, and whether further and more robust evidence is still necessary. This helps to better inform research priorities for the future.

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Learning points

- Strong evidence from eight RCTs demonstrates the benefit of dupilumab for treatment of AE up to 52 weeks compared with placebo.
- Dupilumab is not associated with an increased number of adverse effects compared with placebo and there is no increased risk of infection; however, conjunctivitis is seen more commonly with patients with AE treated with dupilumab, but not those treated for other atopic diseases.
- TCS phobia is common across multiple populations, with the greatest fears being skin thinning and the possible effect on growth and development.
- Bleach baths are no better than water baths for reducing the severity of AE and the density of *S. aureus* on the skin.
- There is insufficient evidence for the use of topical antibiotics in infected AE.
- Evidence from 77 RCTs demonstrates the benefit of emollients in the treatment of AE with or without TCS. Little evidence exists to demonstrate the benefit of one emollient over another.
- Primary prevention of AE using regular emollient therapy shows promising results based on current evidence, which should be further elucidated by the Barrier Enhancement for Eczema Prevention (BEEP) study outcomes.
- Although little evidence exists for using dietary exclusion in the general management of AE, the strongest evidence is demonstrated in preselected patients with a proven food allergy on formal testing.

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CPD questions

Learning objectives

To demonstrate up-to-date knowledge of prevention and treatment of atopic eczema.

Question 1

Which of the following is seen more commonly in patients treated with dupilumab for atopic eczema compared with placebo?

- (a) Bacterial skin infections.
- (b) Flares of eczema herpeticum.
- (c) Conjunctivitis.
- (d) Hepatitis.
- (e) Urticaria.

Question 2

Based on the available evidence, which of the following therapies can be recommended to improve sleep in atopic eczema?

- (a) Nonsedating antihistamines.
- (b) Oral benzodiazepines.
- (c) Emollients.
- (d) Red-light therapy.

- (e) Oral Janus kinase inhibitors.

Question 3

Which of the following statements regarding the use of topical antibiotics in infected atopic eczema is true?

- (a) Topical fusidic acid is more effective than placebo.
- (b) There is not enough evidence to recommend any topical antibiotic.
- (c) Topical mupirocin is more effective compared with placebo.
- (d) Topical erythromycin is more effective compared with placebo.
- (e) Topical tetracyclines are more effective compared with placebo.

Question 4

Which of the following regarding emollients in atopic eczema (AE) is true?

- (a) Emollients do not reduce the number of AE flares when used in combination with topical corticosteroids (TCS).
- (b) Oatmeal-containing emollients are the type of emollient with the highest-quality evidence,

indicating they are most effective in the management of AE.

- (c) Urea-containing emollients have strong evidence of benefit over standard emollients for AE.
- (d) Emollient use in addition to TCS reduces the number of AE flares.
- (e) There is high-quality evidence comparing the benefit of different types of emollient.

Question 5

Which of the following statements about primary prevention of atopic eczema (AE) is true?

- (a) There is at least moderate evidence that vitamin D supplementation in pregnancy reduces the incidence of AE in at-risk babies.
- (b) There is at least moderate evidence that partially hydrolysed formulas reduce AE incidence compared with cow's milk formula at 2, 3 and 6–7 years.
- (c) There is a clear relationship between breast milk polyunsaturated fatty acid levels and AE incidence.
- (d) There is at least moderate evidence that probiotic supplementation in infants can reduce the incidence of AE.
- (e) There is some evidence that the use of emollients for primary prevention of AE in at-risk individuals may provide benefit.

Instructions for answering questions

This learning activity is freely available online at <http://www.wileyhealthlearning.com/ced>.

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
- Reflect on the article
- Register or login online at <http://www.wileyhealthlearning.com/ced> and answer the CPD questions
- Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

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