Evidence-based management of eczema: five things that should be done more and five things that should be dropped

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Purpose of review
We provide readers with an evidence-informed opinion on current treatments for eczema (atopic dermatitis) with the intention of improving patient care. We suggest five treatment aspects that should be promoted and five that should be demoted. Evidence sources include key randomized controlled trials and systematic reviews.

Recent findings
Under-treatment of eczema can be countered by more aggressive use of topical therapies including the 'get control then keep control' regimen, and systemics for severe disease, supplemented with good patient education. Topical corticosteroids should be used once daily rather than twice daily. Topical calcineurin inhibitors are useful for sensitive sites. There is little evidence to support the continued use of oral antihistamines, oral or topical antistaphylococcal treatments for infected eczema or probiotics for treating eczema. Nonpharmacological treatments including silk clothing, ion-exchange water softeners and emollient bath additives have not been shown to benefit eczema patients. Despite promising pilot studies, large trials suggest that emollients from birth do not prevent eczema and may result in harms such as increased skin infections and food allergy.

Summary
New evidence-based insights on existing and newer treatments allow clinicians the opportunity to change their practice in a way that enhances patients' quality of life.

Keywords
atopic dermatitis, eczema, evidence-based medicine

INTRODUCTION

Eczema (syn atopic eczema or atopic dermatitis) management is a partnership with a patient that involves an explanation of the disease, management of acute flares and long-term control by adopting a holistic, patient-centred approach. Good communication is of paramount importance in order to ascertain how patients (and their families) cope with eczema and to provide education in order to negotiate evidence-based management approaches.

Over the last 12 years, the Centre of Evidence-Based Dermatology (CEBD) has conducted annual updates of systematic reviews related to various aspects of eczema management [1–3] with a focus on critical appraisal, in order to inform clinical practice. Topics include epidemiology [4], disease mechanisms [5], risk factors [6,7], prevention [8], topical [3] and systemic therapies [2]. We use this comprehensive resource of appraised systematic reviews as the main evidence source for this article, supplemented by key randomized controlled trials (RCTs).

Many longstanding practices in the clinical setting are ingrained, often with uncertain origins. Why are most topical corticosteroid (TCS) preparations advised to be applied twice daily? Why are topical antibiotics used in combination with TCS?

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Curr Opin Allergy Clin Immunol 2021, 21:386–393
DOI:10.1097/ACI.0000000000000750

KEY POINTS

- Eczema is often undertreated.
- Topical corticosteroids applied once daily should be used in moderate disease to induce remission and then maintain remission using a proactive approach.
- Severe eczema should be treated more aggressively with systemic agents.
- Good prescribing practice is not enough; patient education and information provision is key.
- Practices such as prescribing oral antihistamines, probiotics and antistaphylococcal agents should be stopped, though this may not easy to do when these practices have become deeply engrained.

Why are antihistamines used frequently if the itch of eczema is not caused by histamine? Although it is difficult to change longstanding well intentioned prescribing habits, as exemplified by the international 'Choosing wisely' campaign, it is important for clinicians and their patients to choose care that is supported by evidence and which is truly necessary [9]. By providing a focus on recent evidence-based findings in studies of eczema management that reflect the whole spectrum of disease severity, we herein present five interventions we wish to promote, and five interventions we wish to demote.

FIVE INTERVENTIONS TO PROMOTE

Induction of remission and maintenance of remission ('get control then keep control')

Skin diseases differ from other internal illnesses because of their visual nature. Because patients can see that the skin is inflamed, the inclination may be to stop topical treatment once the redness has reduced. This contrasts with the treatment of asymptomatic 'invisible' illnesses such as hypertension, where medication adherence is unaffected by symptoms or visible indicators. Eczema is due to a combination of a defective skin barrier and immune dysregulation, leading to cell-mediated cytokine-driven inflammation [10]. A systematic review has determined the effects of cessation of treatment when visible erythema or symptoms have settled by collating evidence on the nature of subclinical inflammation in eczema, the effect of treatment on subclinical inflammation and, importantly, how different treatment strategies affect long-term control [11]. Twenty-six studies were included and the skin biopsy findings in patients with subclinical eczema were reviewed. Across 14 randomized controlled trials, an increased risk of relapse was associated with inadequate control of eczema symptoms during initial therapy (fluticasone: risk ratio, 1.31 [95% confidence interval (CI) 1.02–1.68]; tacrolimus: risk ratio, 1.36 [95% CI 1.12–1.66]) [11]. The disparate approaches used to induce remission in these trials, ranging from less than 2 weeks to 16 weeks, highlighted the variations in the optimal duration of initial therapy [11], which will depend on the thickness and chronicity of eczematous skin changes.

Figure 1 summarizes the clinical implications of the findings of this systematic review, demonstrating the importance of initial treatment beyond the resolution of signs and symptoms in order to treat subclinical inflammation, reducing the risk of relapse and the overall quantity of topical treatment used. Of equal importance to inducing initial remission is the concept of then maintaining remission. Here, the strategy of applying topical anti-inflammatory preparations for two consecutive days (such as weekends) each week to keep the skin clear has been shown to drastically reduce subsequent flares (risk ratios [RRs[of 0.48 [95% CI 0.35–0.65] with fluticasone vs. vehicle; and 0.74 [95% CI 0.58–0.95] for tacrolimus versus vehicle) without increased risk of adverse effects [11]. This proactive [12] concept of induction of remission followed by maintenance of remission is common to many other diseases, such as treatment of cancer and rheumatoid arthritis. The concept is easily explained to patients by the phrase 'get control then keep control' and 'treating eczema under the skin'.

Use more patient/carer education material, especially in adequate quantities

Translating evidence-based findings into patient benefit relies on good patient and guardian/carer education. Two-way education is particularly pertinent in eczema management because, in most cases, eczema is a long-term chronic condition self-managed by patients in a community setting. Because eczema affects approximately 20% of children [13], the quality of life of patients and their families is also affected. Recent research on patient education for eczema has focused on children and their guardians; a meta-analysis of eight RCTs investigating the effect of education on eczema management including specially convened evening classes for parents and children, demonstrated that the health education groups had significant reductions of SCORing Atopic Dermatitis (SCORAD) (mean difference (MD) = 8.67 better [95% CI 3.67, 13.67] at 12 months, with SCORAD minimum clinically important difference (MCID) 8.7 [14]). Improvements in Infants'

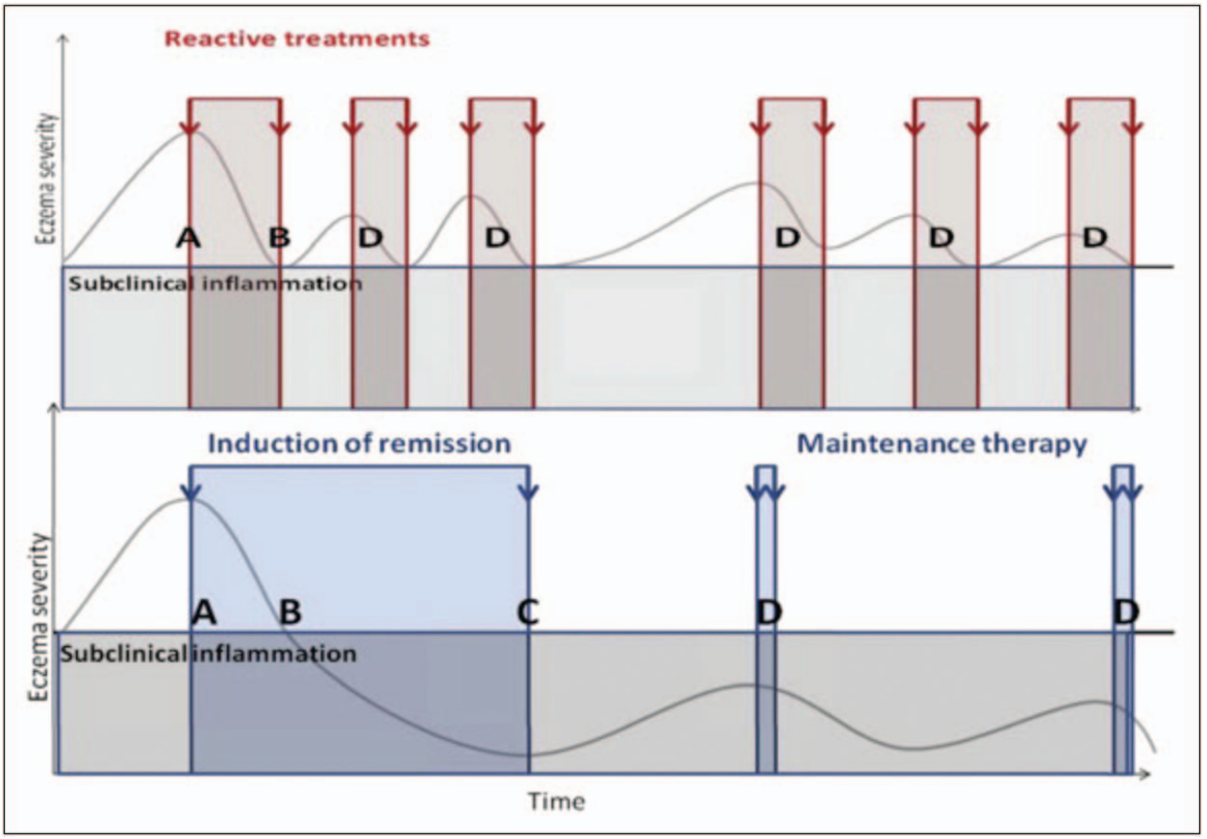

FIGURE 1. The concept of 'getting control then keeping control'; inducing remission of eczema with a prolonged burst of potent topical treatment followed by maintenance of remission flares with once weekly topical treatment used on weekends. Reproduced with permission from [11].

Dermatology Quality of Life Index scores (MD = 1.50 [95% CI 0.33, 2.67] at 6 months) compared with the nonhealthy education group also occurred [15].

Approaches to facilitate patient education have also been investigated. A systematic review of qualitative studies on the effect of written action plans for children with long-term conditions, including two studies on eczema and seven on asthma, highlighted that written instructions boost confidence in disease management, alleviate worry and promote feelings of responsibility amongst guardians and school teachers regarding the child's medical needs [16].

A recent systematic review of qualitative studies reporting views and experiences of managing eczema highlighted four main challenges, including perceived suboptimal information provision and hesitancy about eczema treatment [17▪]. Guidance from the National Institute for Health and Care Excellence (NICE) suggests that the primary cause of treatment failure is underuse of topical treatment [18]. Therefore, the second intervention we promote is the use of more educational materials, particularly related to adequate quantities of treatment, a challenge that is being addressed by an ongoing Eczema Care Online (ECO) programme in the UK [19].

Once daily topical corticosteroids is enough

Although TCSs are licensed for once to twice daily use [20], the majority are prescribed and applied twice daily [21]. A NICE systematic review [22] suggested no clinically useful benefit with twice daily compared with once daily use for potent corticosteroids [23] – a position that was reinforced in a further independent panoramic review of all eczema treatments [24]. Implementation of once daily use of TCSs is likely to have a variety of benefits including better adherence, reduced adverse effects and reduced costs.

Know when and where to use topical calcineurin inhibitors

Topical calcineurin inhibitors (TCIs), including tacrolimus and pimecrolimus, have been licensed for eczema management for almost 20 years and act in an immunomodulatory capacity, inhibiting T-

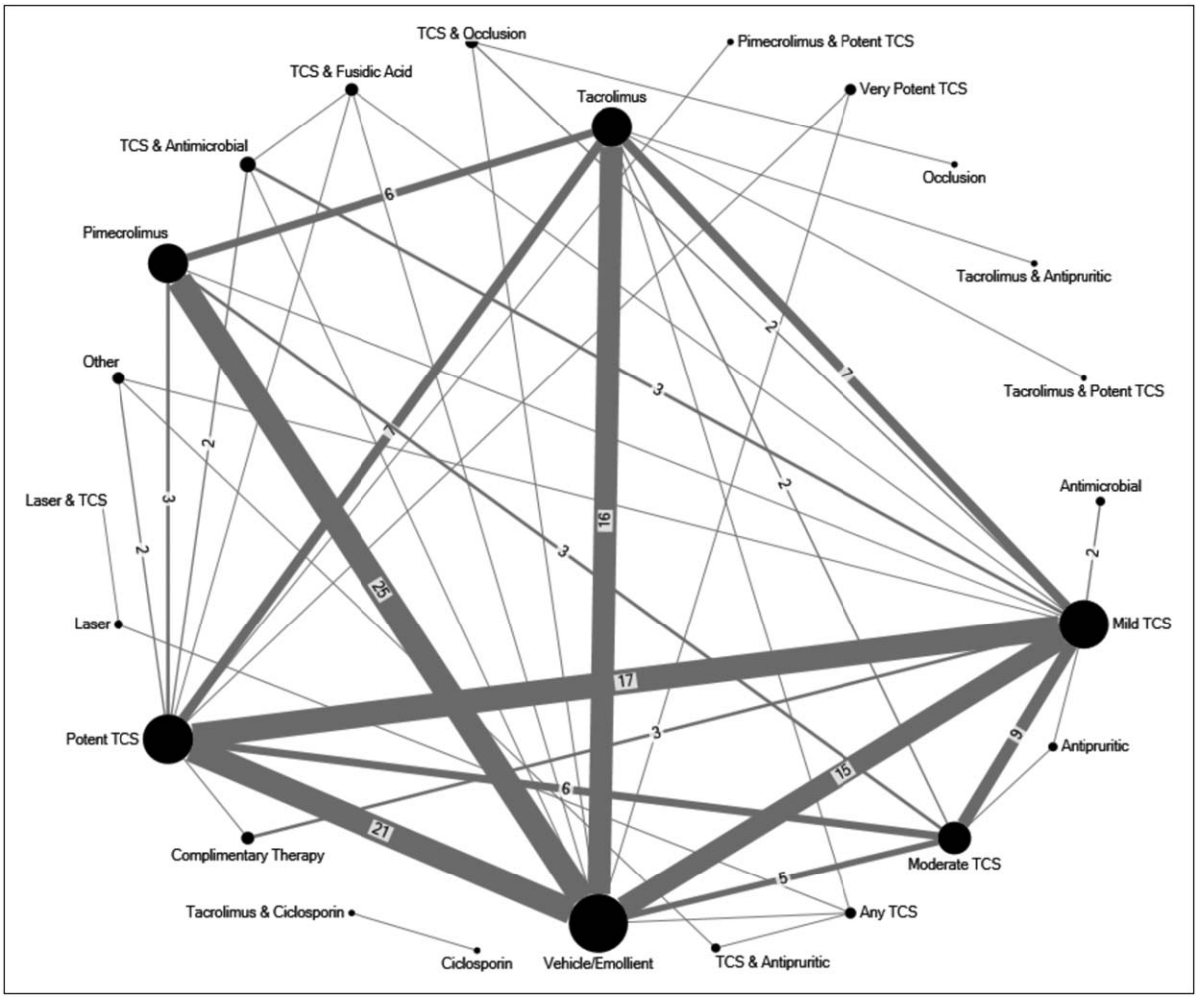

FIGURE 2. Network plot summarizing RCTs of eczema management with topical corticosteroids, tacrolimus or pimecrolimus, illustrating overuse of vehicle comparisons for new topical treatments. Reproduced with permission from [27].

cell proliferation and activation [25]. Though TCSs remain first line, there are specific clinical scenarios in which consideration of TCIs is indicated. As TCIs are not associated with skin atrophy with long-term use, they can be used safely for longer on sensitive sites such as the face. TCIs might also be used for TCS withdrawal syndrome – an uncommon rebound of skin inflammation that results from strong TCSs being used for too long on sensitive sites such as the face or genitalia [26]. Unfortunately, most TCIs have been mainly compared against vehicle rather than optimum active treatments with TCSs (Fig. 2) [27].

A meta-analysis comparing a range of TCSs of different potencies with TCIs identified similar efficacy between the two treatments and an increased risk of application site adverse effects with TCIs, namely skin burning and pruritus. No differences were identified with regards to skin atrophy, skin infections, severe adverse events or the requirement of treatment discontinuation [21]. The absence of clinically significant skin thinning when TCS are used appropriately supports their continued use as well tolerated and effective first-line treatment. Combination treatment approaches, such as applying TCSs once in the morning and TCIs once nightly, is sometimes also suggested, although there is little robust evidence to support this approach [24].

Treat severe eczema more aggressively

People with severe eczema are probably undertreated [28]. For the treatment of moderate to severe eczema, several effective systemic therapies are available, including ciclosporin, methotrexate and dupilumab – the latter being a biologic treatment that inhibits interleukin (IL)-4 and IL-13 signalling. Many more new treatments are in the development pipeline, including oral selective Janus Kinase (JAK) inhibitors, such as baricitinib [29] and abrocitinib [30], and other biologic treatments, including

nemolizumab, lebrikizumab and tralokinumab [2]. Although systemic steroids have been commonly used in the management of eczema, a systematic review of 64 studies suggests that they are associated with severe rebound and should not be used in eczema treatment [31].

A Cochrane network meta-analysis of systemic treatments for eczema published in 2020 included 74 RCTs; 70 were available for quantitative synthesis and 29 systemic immunosuppressive agents were assessed [32▪]. Analyses identified that dupilumab demonstrated the most robust efficacy data across all biological treatments for eczema (achieving 75% improvement in Eczema Area and Severity Index [EASI75]; a range of follow-up between 4 weeks and 16 weeks, Dupilumab vs. placebo in 8 RCTs ($n = 1978$), RR 3.04 [95% CI 2.51–3.69], RD 37.6% [95% CI 27.8–49.6]), and that no new serious adverse event concerns were identified; however, this conclusion was based on short-term (2–16 weeks) follow-up data. Most trials (65%) were placebo-controlled and, therefore, it was challenging to rank efficacy and safety against conventional treatments such as methotrexate used at adequate doses. To address the deliberate avoidance of active comparator studies common to most new drugs, a platform trial by the UK Dermatology Clinical Trials Network (UKDCTN) called BEACON (Best systemic treatments for adults with atopic eczema over the long term) is planned to compare oral ciclosporin, subcutaneous methotrexate and dupilumab in the management of eczema in adults. Additional biologics will be added and less effective treatment arms will be dropped using an adaptive design, as evidence accrues. Treatment with systemic agents should be considered more readily for patients with severe eczema, tailoring the therapeutic and safety profiles to the individual patient.

FIVE INTERVENTIONS TO DEMOTE

Oral H1 antihistamines

Oral antihistamines are commonly prescribed in addition to topical treatments to alleviate itch in eczema. The sedating effects of first-generation antihistamines are sometimes used to manage the sleep disturbances in eczema due to itching, particularly in children [33]. A Cochrane review investigating oral H1 antihistamines as an 'add-on' treatment in adults and children with eczema collated evidence from 25 RCTs and 3285 participants [34]. Though antihistamines were assessed as being safe, no consistent evidence was found to indicate that H1 antihistamines, including cetirizine and loratadine, were more effective when compared to placebo. Though fexofenadine showed a small improvement in patient-rated pruritus (MD 0.25 [95% CI 0.43–0.07] point improvement on a scale of 0–8), no significant difference in the quantity of treatment used to prevent flares of eczema was found. There is little evidence, therefore, to continue the routine use of oral antihistamines in eczema management, perhaps with the exception of those with concomitant urticarial lesions and allergic rhinitis/hay fever with associated periorbital eczema.

Antistaphylococcal treatments: unless systemically unwell

The management of overt secondary infection and colonization of the skin by *Staphylococcus aureus* in eczema is a contentious topic, with high variation in practice between clinicians and in primary versus secondary care settings. *S. aureus* is rarely found on healthy skin (in <5%) and is identified in approximately 70% of eczematous skin lesions [35]. Various antistaphylococcal treatments are often used in the management of eczema flares, including systemic and topical antibiotics (sometimes in combination with TCS). A Cochrane review of antistaphylococcal treatments in children and adults with eczema included 41 studies and 1753 participants [36]. In the treatment of both clinically infected and uninfected eczema, there was insufficient evidence to support the use of antistaphylococcal treatments. Apart from a high quality recent pivotal trial [37], the evidence was generally poor and studies were quite heterogeneous, limiting the ability to pool results. Given the serious concerns that overuse of antibiotics will contribute to antimicrobial resistance and the absence of evidence of benefit in eczema, the use of antistaphylococcal treatments should be demoted in routine clinical practice, unless a patient is systemically unwell [37], a position that is supported by recent guidance from the UK National Institute for Health and Care Excellence [38▪].

Probiotics

Probiotics are orally ingested live microorganisms that are purported to benefit people with active eczema. An updated Cochrane review of RCTs on this topic published in 2018 included 39 RCTs of 2599 participants [39]. The review found little evidence to support the use of probiotics in eczema, with little to no difference in quality-of-life outcomes (SMD 0.03 worse [95% CI 0.36 better to 0.42 worse], GRADE low certainty evidence) and in investigator-rated disease severity scores (MD total SCORAD score in the intervention groups

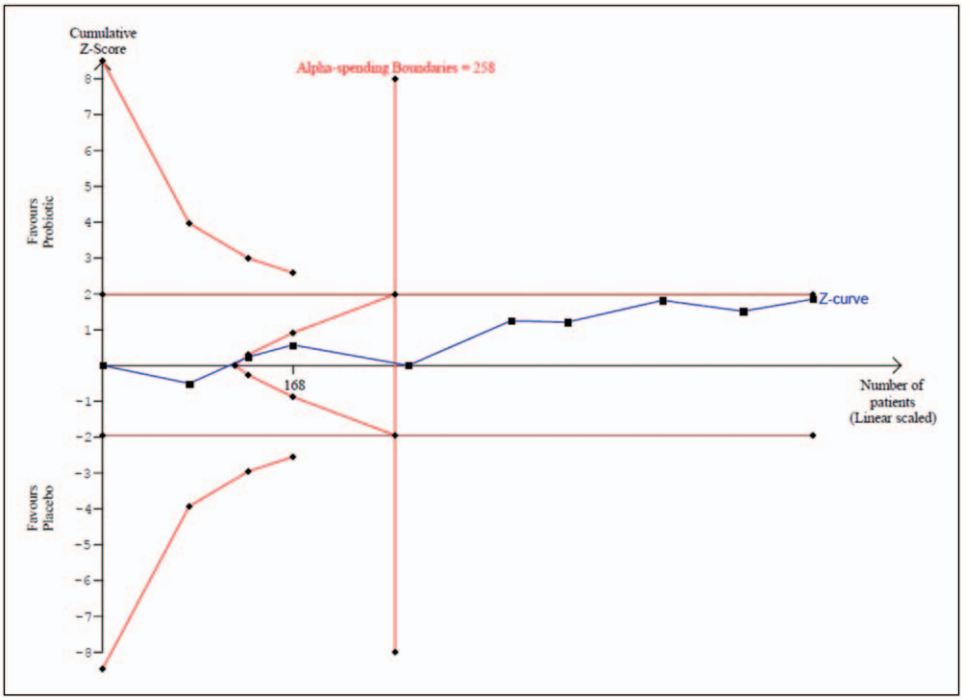

FIGURE 3. Trial sequential analysis: for a minimum difference of −2 points difference in eczema symptoms (SCORAD part C; range 0–20) between probiotics and no probiotics (90% power). Blue *z*-curve of meta-analysis shows that optimal heterogeneity-adjusted information size has been reached. Reproduced with permission from [39].

was 3.91 points lower [95% CI 5.86–1.96 points lower], GRADE low certainty evidence; MCID 8.7); significant heterogeneity between studies was observed. A trial sequential analysis was conducted (Fig. 3), indicating that future RCTs of probiotics are unlikely to change the conclusion that a two-point difference in eczema symptoms (measured by SCORAD) between probiotic and no probiotic will be found.

Some 'nonpharmacological' interventions including silk clothing, water softeners and bath emollients

Various nonpharmacological interventions are also often considered for eczema management, some of which have been investigated in trial settings. The role of silk clothing was tested in children with moderate to severe eczema in an observer-blind RCT (the CLOTHES trial) [40]. Silk garments were worn for 6 months in the intervention group and both groups received usual standard care. The primary outcome measure was the Eczema Area and Severity Index (EASI) score (MCID 6.6 [14]). Results failed to show any additional improvement with wearing silk garments (EASI score averaged over all follow-up visits adjusted for baseline EASI score, age, and centre: adjusted ratio of geometric means 0.95 [95%CI 0.85 to 1.07; this 95%CI is equivalent to a difference of −1.5 to 0.5 in the original EASI units, which is not clinically important).

The SWET trial investigated whether the installation of an ion-exchange water softener in the home of children who live in hard water areas (≥200 mg/l calcium carbonate) can improve eczema [41]. This observer-blind RCT of 336 children with moderate-to-severe eczema identified no additional benefit in the intervention group (Six Area, Sign Sign Atopic Dermatitis severity score [range 0–108] at 12 weeks, 0.66 [95% CI −1.37–2.69]); both groups continued usual standard care without reported differences in topical anti-inflammatory use.

The BATHE trial was a multicentre pragmatic parallel group RCT conducted to determine the effect of emollient bath additives in the treatment of childhood eczema [42▪]. Four hundred eighty-three children were randomized to either standard care (which included direct application of emollients and TCSs) or standard care plus the use of bath additives regularly for 12 months. The primary outcome measure was the Patient Orientated Eczema Measure (POEM) score, which was measured weekly for 16 weeks. No clinically important or statistically significant differences were observed between groups (after controlling for baseline severity and confounders (ethnicity, topical corticosteroid use, soap substitute use) and allowing for

clustering of participants within centres and responses within participants over time, POEM scores in the no bath additives group were 0.41 [95% CI −0.27–1.10] points higher [worse] than in the bath additives group, below the published minimal clinically important difference for POEM of three points). Together, these three large independent RCTs suggest no additional benefits with the use of silk clothing, water softeners and bath emollient additives.

Emollients for eczema prevention

The Barrier Enhancement for Eczema Prevention (BEEP) trial sought to investigate whether daily emollient use in term infants at high risk of developing eczema (having at least one first degree relative with clinically diagnosed eczema, asthma or hayfever) could reduce the risk of developing eczema by the age of 2 years [43]. 1394 newborns were randomized and adherence in both groups was high. Daily emollient use did not prevent eczema in these high-risk infants, a result that was replicated in a similar Scandinavian study of 2397 high-risk children [44]. These studies also suggested that emollients were associated with a small increased risk of skin infections and a nonsignificant increase in food allergy. A subsequent Cochrane prospectively planned individual patient meta-analysis that included 17 studies that randomized 5823 participants to emollients for eczema prevention found that emollient use in infancy did not change the risk of eczema by 1–2 years of age (RR 1.03, 95% CI 0.81–1.31; moderate-certainty evidence; 3075 participants, seven trials) nor time to onset of eczema (hazard ratio 0.86, 95% CI 0.65–1.14; moderate-certainty evidence; 3349 participants, nine trials) [45▪▪]. Another study found that increased use of moisturizers in infancy may promote food allergies, with each additional weekly application associated with an adjusted odds ratio of 1.20 (95% CI 1.13–1.27) for developing food allergy [46▪].

CONCLUSION

We have suggested five interventions for eczema that should be promoted and five that should be demoted based on results of robust evidence. We also highlight some limitations of current RCT evidence including lack of common outcome measures and too many placebo-controlled trials that make it difficult for doctors to compare new treatments. There is a clear need for platform studies such as BEACON that test new treatments against active comparators on a level playing field. We also highlight research waste, for example, by continuing to test the effect of probiotics for active eczema or conducting more and more systematic reviews that seek to answer the same questions [47].

Existing guidelines have generally improved in their systematic approach to searching and appraising evidence, but they give rise to different recommendations. For example, once daily use of TCSs is recommended by NICE [48], whereas twice daily use is recommended in American [49] and Japanese [50] guidelines. European guidelines [51] are silent on TCS frequency. With regards to oral antihistamines, some guidelines recommend them as adjuvant therapy [50], whereas others highlight their lack of efficacy [51] or only recommend their use in specific settings, such as treating eczema associated with disturbed sleep [48,49]. Ideally, living guidelines [52▪] are needed alongside living network meta-analyses in order to provide up-to-date best evidence.

Acknowledgements

The authors would like to thank Dr Derek Chu for helpful and detailed editorial comments

Financial support and sponsorship

None.

Conflicts of interest

Hywel Williams is chief investigator of the Barrier Enhancement for Eczema Prevention (BEEP) study funded by the UK National Institute for Health Research Health Technology Assessment Programme.

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- ▪▪ of outstanding interest

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Special interest as it suggests a major rethink about how evidence should form part of an ecosystem with living guidelines.