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

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Potential 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

Key words: Eczema, atopic dermatitis, evidence-based medicine

Word count: 2611, 47 references and 3 figures

Structured abstract

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 randomised 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 continued use of oral antihistamines, oral or topical anti-staphylococcal treatments for infected eczema or probiotics for treating eczema. Non-pharmacological 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.

Introduction

Eczema (syn atopic eczema or atopic dermatitis) management is a partnership with a patient that involves 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 twelve 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 randomised 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? 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

(i) 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 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 randomised controlled trials, an increased risk of relapse was associated with inadequate control of eczema symptoms during initial therapy (fluticasone: risk ratio, 1.31 [95% 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 summarises 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 side 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 the eczema under the skin'.

(ii) Use more patient/carer education material, especially on 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) (MD = 8.67 better [95% CI 3.67, 13.67] at 12 months, with SCORAD MID 8.7 [14]). Improvements in Infants' Dermatology Quality of Life Index scores (MD = 1.50 [95% CI 0.33, 2.67] at 6 months) compared with the non-health 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].

(iii) 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.

(iv) 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 twenty years and act in an immunomodulatory capacity, inhibiting T 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 (Figure 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 safe 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].

(v) 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]; 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 to 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 to 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 (**Be**st systemic treatments for adults with **a**topi**c** eczema over the l**on**g 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

(i) 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 3,285 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 to 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.

(ii) Anti-staphylococcal treatments - unless systemically unwell

The management of overt secondary infection and colonisation 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 anti-staphylococcal treatments are often used in the management of eczema flares, including systemic and topical antibiotics (sometimes in combination with TCS). A Cochrane review of anti-staphylococcal treatments in children and adults with eczema included 41 studies and 1,753 participants [36]. In the treatment of both clinically infected and uninfected eczema, there was insufficient evidence to support the use of anti-staphylococcal 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 anti-staphylococcal 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].

(iii) 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 2,599 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 was 3.91 points lower [95%CI 5.86 to 1.96 points lower], GRADE low certainty evidence; MID 8.7); significant heterogeneity between studies was observed. A trial sequential analysis was conducted (Figure 3), indicating that future RCTs of probiotics are unlikely to change the conclusion that a 2-point difference in eczema symptoms (measured by SCORAD) between probiotic and no probiotic will be found.

(iv) Some 'non-pharmacological' interventions including silk clothing, water softeners and bath emollients

Various non-pharmacological 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 (MID 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 (≥200mg/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 to 108] at 12 weeks, 0.66 [95%CI -1.37 to 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]. 483 children were randomised 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 to 1.10] points higher [worse] than in the bath additives group, below the published minimal clinically important difference for POEM of 3 points). Together, these three large independent RCTs suggest no additional benefits with the use of silk clothing, water softeners and bath emollient additives.

(v) 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]. 1,394 newborns were randomised 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 non-significant increase in food allergy. A subsequent Cochrane prospectively planned individual patient meta-analysis that included 17 studies that randomised 5823 participants to emollients for eczema prevention found that emollient use in infancy did not change risk of eczema by one to two years of age (risk ratio (RR) 1.03, 95% confidence interval (CI) 0.81 to 1.31; moderate-certainty evidence; 3075 participants, 7 trials) nor time to onset of eczema (hazard ratio 0.86, 95% CI 0.65 to 1.14; moderate-certainty evidence; 3349 participants, 9 trials) [45]. Another study found that increased use of moisturisers 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

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 anti-staphylococcal agents should be stopped, though this may not easy to do when these practices have become deeply engrained

References

1. Williams H, Grindlay D: **What's new in atopic eczema? An analysis of the clinical significance of systematic reviews on atopic eczema published in 2006 and 2007**. *Clinical and Experimental Dermatology: Clinical dermatology* 2008, **33**:685-688.
2. Olabi B, Worboys S, Garland T, Grindlay D, Rogers N, Harman K: **What's new in atopic eczema? An analysis of systematic reviews published in 2018. Part 2: systemic therapies**. *Clinical and Experimental Dermatology* 2020.
3. Tasker F, Brown A, Grindlay D, Rogers N, Harman K: **What's new in atopic eczema? An analysis of systematic reviews published in 2018. Part 1: prevention and topical therapies**. *Clinical and Experimental Dermatology* 2020.
4. Davies E, Rogers N, Lloyd-Lavery A, Grindlay D, Thomas K: **What's new in atopic eczema? An analysis of systematic reviews published in 2015. Part 1: epidemiology and methodology**. *Clinical and Experimental Dermatology* 2018, **43**:375-379.
5. Madhok V, Futamura M, Thomas K, Barbarot S: **What's new in atopic eczema? An analysis of systematic reviews published in 2012 and 2013. Part 1. Epidemiology, mechanisms of disease and methodological issues**. *Clinical and Experimental Dermatology* 2015, **40**:238-242.
6. Lloyd-Lavery A, Solman L, Grindlay D, Rogers N, Thomas K, Harman K: **What's new in atopic eczema? An analysis of systematic reviews published in 2016. Part 2: Epidemiology, aetiology and risk factors**. *Clinical and experimental dermatology* 2019, **44**:370-375.
7. Hatfield S, Rogers N, Lloyd-Lavery A, Grindlay D, Barnett R, Thomas K: **What's new in atopic eczema? An analysis of systematic reviews published in 2014. Part 1. Epidemiology, risk factors and outcomes**. *Clinical and experimental dermatology* 2016, **41**:843-846.
8. Williams H, Grindlay D: **What's new in atopic eczema? An analysis of systematic reviews published in 2007 and 2008. Part 2. Disease prevention and treatment**. *Clinical and experimental dermatology* 2010, **35**:223-227.
9. ABIM_Foundation: **Choosing Wisely**. Edited by; 2020. vol 2020.]
10. Nakahara T, Kido-Nakahara M, Tsuji G, Furue M: **Basics and recent advances in the pathophysiology of atopic dermatitis**. *The Journal of dermatology* 2020.

11. Tang TS, Bieber T, Williams HC: **Are the concepts of induction of remission and treatment of subclinical inflammation in atopic dermatitis clinically useful?** *Journal of allergy and clinical immunology* 2014, **133**:1615-1625. e1611.
12. Wollenberg A, Ehmann LM: **Long term treatment concepts and proactive therapy for atopic eczema**. *Ann Dermatol* 2012, **24**:253-260.
13. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, Group IPTS: **Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three**. *Journal of Allergy and Clinical Immunology* 2009, **124**:1251-1258. e1223.
14. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J: **EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference**. *Allergy* 2012, **67**:99-106.
15. Li Y, Han T, Li W, Li Y, Guo X, Zheng L: **Efficacy of health education on treatment of children with atopic dermatitis: a meta-analysis of randomized controlled trials**. *Archives of Dermatological Research* 2020:1-11.
16. Waldecker A, Malpass A, King A, Ridd MJ: **Written action plans for children with long-term conditions: A systematic review and synthesis of qualitative data**. *Health Expectations* 2018, **21**:585-596.
17. Teasdale E, Muller I, Sivyer K, Ghio D, Greenwell K, Wilczynska S, Roberts A, Ridd MJ, Francis N, Yardley L: **Views and experiences of managing eczema: systematic review and thematic synthesis of qualitative studies**. *British Journal of Dermatology* 2020.
18. NICE: **Clinical guideline [CG57] Atopic eczema in under 12s: diagnosis and management**.
19. ECO: **Eczema Care Online**. Edited by; 2020. vol 2020.]
20. BNF: **British National Formulary: National Institute for Health and Care Excellence**. Edited by; 2020.
21. Broeders JA, Ali UA, Fischer G: **Systematic review and meta-analysis of randomized clinical trials (RCTs) comparing topical calcineurin inhibitors with topical corticosteroids for atopic dermatitis: A 15-year experience**. *Journal of the American Academy of Dermatology* 2016, **75**:410-419. e413.
22. Green C, Colquitt J, Kirby J, Davidson P: **Topical corticosteroids for atopic eczema: clinical and cost effectiveness of once-daily vs. more frequent use**. *British Journal of Dermatology* 2005, **152**:130-141.

23. **Frequency of application of topical corticosteroids for atopic eczema. Technology appraisal guidance [TA81]**. Edited by. UK: National Institute for Health and Care Excellence; 2004.
24. Nankervis H, Thomas KS, Delamere FM, Barbarot S, Rogers NK, Williams HC: **Scoping systematic review of treatments for eczema**. *Programme Grants for Applied Research* 2016, **4**.
25. Hong C-h, Gooderham M, Bissonnette R: **Evidence Review of Topical Calcineurin Inhibitors for the Treatment of Adult Atopic Dermatitis**. *Journal of cutaneous medicine and surgery* 2019, **23**:5S-10S.
26. Hajar T, Leshem YA, Hanifin JM, Nedorost ST, Lio PA, Paller AS, Block J, Simpson EL: **A systematic review of topical corticosteroid withdrawal ("steroid addiction") in patients with atopic dermatitis and other dermatoses**. *Journal of the American Academy of Dermatology* 2015, **72**:541-549. e542.
27. Wilkes SR, Nankervis H, Tavernier E, Maruani A, Williams HC: **How clinically relevant are treatment comparisons of topical calcineurin inhibitor trials for atopic eczema?** *Journal of Investigative Dermatology* 2016, **136**:1944-1949.
28. Gisondi P, Girolomoni G: **Undertreatment in adult patients with moderate-to-severe atopic dermatitis and other chronic inflammatory skin diseases**. *Journal of the European Academy of Dermatology and Venereology* 2020, **34**:2168-2169.
29. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T, Kaszuba A, Kolodsick J, Yang FE, Gamalo M: **Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial**. *JAMA dermatology* 2020.
30. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, Bieber T, Thyssen JP, Yosipovitch G, Flohr C: **Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial**. *The Lancet* 2020, **396**:255-266.
31. Sherry HY, Drucker AM, Lebwohl M, Silverberg JI: **A systematic review of the safety and efficacy of systemic corticosteroids in atopic dermatitis**. *Journal of the American Academy of Dermatology* 2018, **78**:733-740. e711.
32. Sawangjit R, Dilokthornsakul P, Lloyd-Lavery A, Lai NM, Dellavalle R, Chaiyakunapruk N: **Systemic treatments for eczema: a network meta-analysis**. *Cochrane Database of Systematic Reviews* 2020.

33. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, Chamlin SL, Cooper KD, Feldman SR, Hanifin JM: **Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents**. *Journal of the American Academy of Dermatology* 2014, **71**:327-349.

34. Matterne U, Böhmer MM, Weisshaar E, Jupiter A, Carter B, Apfelbacher CJ: **Oral H1 antihistamines as 'add-on'therapy to topical treatment for eczema**. *Cochrane Database of Systematic Reviews* 2019.

35. Totté J, Van Der Feltz W, Hennekam M, van Belkum A, Van Zuuren E, Pasmans S: **Prevalence and odds of Staphylococcus aureus carriage in atopic dermatitis: a systematic review and meta-analysis**. *British Journal of Dermatology* 2016, **175**:687-695.

36. George SM, Karanovic S, Harrison DA, Rani A, Birnie AJ, Bath-Hextall FJ, Ravenscroft JC, Williams HC: **Interventions to reduce Staphylococcus aureus in the management of eczema**. *Cochrane Database of Systematic Reviews* 2019.

37. Francis NA, Ridd MJ, Thomas-Jones E, Butler CC, Hood K, Shepherd V, Marwick CA, Huang C, Longo M, Wootton M: **Oral and topical antibiotics for clinically infected eczema in children: a pragmatic randomized controlled trial in ambulatory care**. *The Annals of Family Medicine* 2017, **15**:124-130.

38. **Secondary bacterial infection of eczema and other common skin conditions: antimicrobial prescribing. NICE guideline [NG190]**. Edited by: National Institute for Health and Care Excellence; 2021.

39. Makrgeorgou A, Leonardi-Bee J, Bath-Hextall FJ, Murrell DF, Tang ML, Roberts A, Boyle RJ: **Probiotics for treating eczema**. *Cochrane Database of Systematic Reviews* 2018.

40. Thomas KS, Bradshaw LE, Sach TH, Batchelor JM, Lawton S, Harrison EF, Haines RH, Ahmed A, Williams HC, Dean T: **Silk garments plus standard care compared with standard care for treating eczema in children: A randomised, controlled, observer-blind, pragmatic trial (CLOTHES Trial)**. *PLoS medicine* 2017, **14**:e1002280.

41. Thomas KS, Dean T, O'Leary C, Sach TH, Koller K, Frost A, Williams HC, Team ST: **A randomised controlled trial of ion-exchange water softeners for the treatment of eczema in children**. *PLoS Med* 2011, **8**:e1000395.

42. Santer M, Ridd MJ, Francis NA, Stuart B, Rumsby K, Chorozoglou M, Becque T, Roberts A, Liddiard L, Nollett C: **Emollient bath additives for the treatment of childhood eczema (BATHE): multicentre pragmatic parallel group randomised controlled trial of clinical and cost effectiveness**. *bmj* 2018, **361**.
43. Chalmers JR, Haines RH, Bradshaw LE, Montgomery AA, Thomas KS, Brown SJ, Ridd MJ, Lawton S, Simpson EL, Cork MJ: **Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial**. *The Lancet* 2020, **395**:962-972.
44. Skjerven HO, Rehbinder EM, Vettukattil R, LeBlanc M, Granum B, Haugen G, Hedlin G, Landrø L, Marsland BJ, Rudi K: **Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial**. *The Lancet* 2020, **395**:951-961.
45. Kelleher MM, Cro S, Cornelius V, Lodrup Carlsen KC, Skjerven HO, Rehbinder EM, Lowe AJ, Dissanayake E, Shimojo N, Yonezawa K, et al.: **Skin care interventions in infants for preventing eczema and food allergy**. *Cochrane Database Syst Rev* 2021, **2**:CD013534.
46. Perkin MR, Logan K, Marrs T, Radulovic S, Craven J, Boyle RJ, Chalmers JR, Williams HC, Versteeg SA, van Ree R, et al.: **Association of frequent moisturizer use in early infancy with the development of food allergy**. *J Allergy Clin Immunol* 2021, **147**:967-976 e961.
47. Ioannidis JP: **The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses**. *The Milbank Quarterly* 2016, **94**:485-514.
48. NICE: **Eczema - atopic**. Edited by; 2020. vol 2020.]
49. AAD: **Atopic Dermatitis Clinical Guideline**. Edited by; 2020. vol 2020.]
50. Katoh N, Ohya Y, Ikeda M, Ebihara T, Katayama I, Saeki H, Shimojo N, Tanaka A, Nakahara T, Nagao M: **Clinical practice guidelines for the management of atopic dermatitis 2018**. *The Journal of Dermatology* 2019, **46**:1053-1101.
51. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, Gieler U, Girolomoni G, Lau S, Muraro A: **Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II**. *Journal of the European Academy of Dermatology and Venereology* 2018, **32**:850-878.

52. Ravaud P, Créquit P, Williams HC, Meerpohl J, Craig JC, Boutron I: **Future of evidence ecosystem series: 3. From an evidence synthesis ecosystem to an evidence ecosystem**. *Journal of Clinical Epidemiology* 2020.

Figure legends

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].

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

Figure 3: Trial sequential analysis: for a minimum difference of -2 points difference in eczema symptoms (SCORAD part C; range 0-20) between probiotic 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].