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What's new in atopic eczema? An analysis of systematic reviews published in 2012 and 2013. Part 2. Treatment and prevention

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Summary

This review provides a summary of key findings from 22 systematic reviews on atopic eczema (AE) published over the 2-year period from January 2012 to 31 December 2013, focusing on prevention and treatment of AE. For an update of systematic reviews on the epidemiology, mechanisms of disease and methodological issues, see Part 1 of this update. Based on current systematic review evidence, the most promising intervention for the prevention of AE is the use of probiotics (and possibly prebiotics) during the late stages of pregnancy and early life. Exposure to household pets, especially dogs, may also be protective, but exclusive breastfeeding for up to 7 months does not confer benefit. The role of vitamin D in preventing AE is currently unclear. Very few of the systematic reviews provided additional evidence for the use of specific treatments for AE. Further research is required to establish the role of desensitization, Chinese herbal medicines, homeopathy and specialist clothing. Nevertheless, there is now clear evidence that evening primrose oil and borage oil are not effective for the treatment of AE. There have been no randomized controlled trials on the use of H1 anti-histamines as monotherapy for the treatment of AE.

Background

Atopic eczema (AE) is one of the 50 most prevalent diseases worldwide.[1] The aim of this evidence update is to highlight the key clinical and research implications from recent systematic reviews on the topic of AE.

This second part of the evidence-based update review summarizes the findings of 22 systematic reviews on AE that were published or indexed between January 2012 and 31 December 2013 (Fig. 1). This evidence-based update covers reviews of AE prevention (n = 10) and AE treatments (n = 12). Similar evidence updates on AE have been published previously, along with the details of the search methods used.[2,3]

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Treatment of atopic eczema

Desensitization (systemic immunotherapy) for treatment of atopic eczema

Systemic immunotherapy (SIT) has been suggested as a potential long-term treatment for sensitized patients with AE. Two reviews both concluded that SIT improves AE, although these should be interpreted with caution because of the heterogeneity of the included studies and possible methodological concerns.

The first review by Compalati *et al.*[4] included four studies published between 2006 and 2011. Two randomized controlled trials (RCTs) included 102 participants. One RCT compared house dust mite SIT with placebo, and one RCT compared two different house

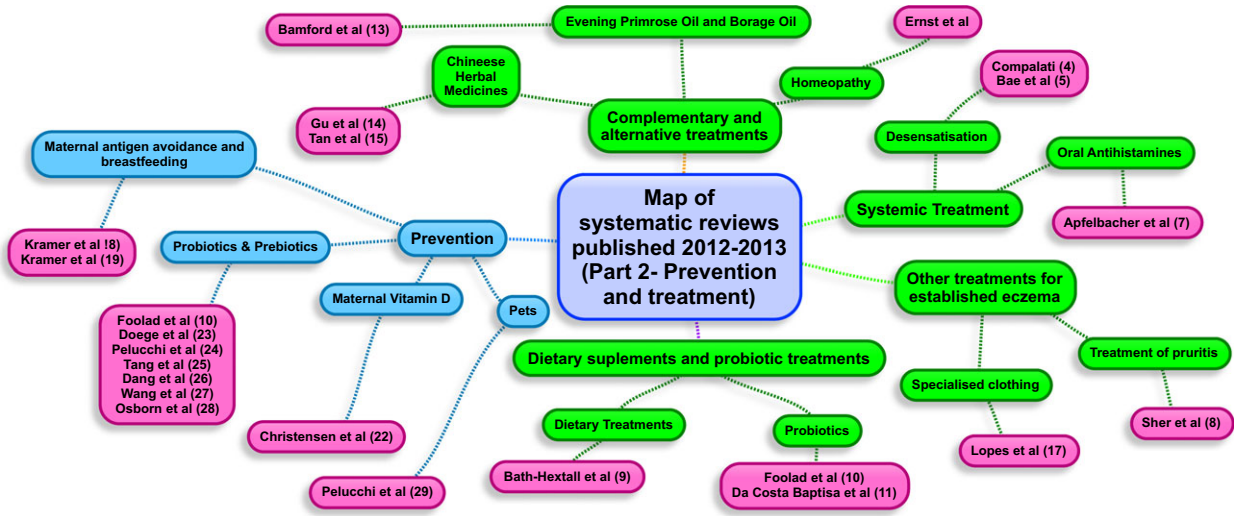

Figure 1 Map of systematic reviews published in 2012–2013 (part 2: prevention and treatment of atopic eczema).

dust mite SIT regimens. Two observational studies with 162 participants compared SIT with conventional therapy. Although all four studies reported an improvement in disease severity or symptoms, meta-analysis was not conducted because of the heterogeneity of the included studies.

A more comprehensive review by Bae *et al.*[5] included a meta-analysis of 8 studies (8 RCTs with 385 participants) that compared allergen SIT with placebo control in patients with known sensitivity to house dust mite. The review reported improvement in AE severity for participants receiving SIT (RR = 5.35, 95% CI 1.61–17.77). Given the degree of heterogeneity between the included studies, and lack of prespecified outcomes of interest, this meta-analysis may have overestimated the treatment effect, making clinical interpretation difficult.[6] Desensitization therapy is not currently available on the National Health Service (NHS), and this intervention requires further evaluation in a large, pragmatic study before it can be recommended for wide-scale adoption.

Antihistamines

Apfelbacher *et al.*[7] published a Cochrane review of oral H1 antihistamines used as monotherapy for the treatment of AE. The authors were unable to identify any RCT meeting their eligibility criteria, as antihistamines were always used as adjuvant therapy in addition to existing AE treatments. As a result, there is currently no evidence to support or refute the efficacy or safety of oral H1 antihistamines used as monotherapy for AE. However, as antihistamines are rarely used as monotherapy for the treatment of AE, it is likely that a broader systematic review including trials of antihistamines used in combination with other AE treatments would be more clinically relevant.

Treatment of pruritus

A meta-analysis by Sher *et al.*[8] examined the role of topical and systemic therapies in relieving the pruritus associated with AE. Unfortunately, many of the studies were excluded from this systematic review because the authors were unable to collect separate data on pruritus. The review thus included heterogeneous studies, and the reported findings cannot be regarded as reliable.

Dietary supplements and probiotics

A Cochrane review by Bath-Hextall *et al.*[9] considered a wide variety of dietary treatments for AE. Probiotics, evening primrose oil and borage oil were excluded from the review, as these were covered in separate Cochrane reviews. In total, 11 RCTs were included, which used fish oil (3 RCTs with 2 RCTs pooled for analysis; 144 participants), vitamin D and vitamin E (2 RCTs; 52 participants), vitamin B6 (1 RCT; 50 participants), sea buckthorn oil (1 RCT; 78 participants), hempseed oil (1 RCT; 20 participants), sunflower oil (1 RCT; 48 participants), docosahexaenoic acid (DHA) (1 RCT; 53 participants), selenium (1 RCT; 60 participants) and zinc sulfate (1 RCT; 50 participants). Overall,

the authors found no convincing evidence of benefit for dietary supplements in AE. All of the studies were of low quality, and most were underpowered to detect even relatively moderate treatment benefits. However, pooled analysis of the two RCTs on fish oil found that this intervention produced significantly improvements, compared with placebo, on the impact on daily living and the area affected by AE at the end of treatment, as assessed by the physician.

Probiotics are thought to be beneficial in preventing AE in children (see above), but they have also been tested as a treatment for established AE. Two systematic reviews did not support the use of probiotics for the treatment of established AE.[10,11]

Evening primrose oil and borage oil

Evening primrose oil and borage oil have been consistently shown to be of little or no benefit for the treatment of AE.[12] A Cochrane review by Bamford *et al.*,[13] examining 27 RCTs (of which 11 were never published outside the pharmaceutical company) with a total of 1596 participants, confirmed this lack of effect. Both patients and doctors reported no significant clinical improvement in AE severity. For evening primrose oil, 19 RCTs were included [patient-reported global improvement in symptoms from baseline compared with placebo, mean difference (MD) −2.22, 95% CI −10.48 to 6.04; physician-reported global improvement in symptoms, MD −3.26, 95% CI −6.96 to 0.45]. Similarly, for borage oil, there have been eight RCTs (for which no meta-analysis of the included studies could be conducted because of the different ways in which studies were reported). The authors concluded that further studies of evening primrose oil and borage oil for the treatment of AE would be difficult to justify.

Chinese herbal medicines

Gu *et al.*[14] published an update of the 2004 Cochrane review on Chinese herbal medicine, which examined 28 RCTs with a total of 2306 participants. The review provided low-quality evidence that oral ingestion of Chinese herbs or Chinese herbal formulae could improve AE compared with placebo (physician rating of total effectiveness rate, RR = 2.09, 95% CI 1.32–3.32) or compared with other drugs (RR = 1.43, 95% CI 1.27–1.61). No convincing evidence supported the use of topical application of Chinese herbal medicine, whether used alone or in conjunction with oral ingestion of Chinese herbal formulas, in reducing the severity of AE in children or adults. The authors concluded that well-designed RCTs are still needed to evaluate the efficacy and safety of Chinese herbal formulas for patients with AE.

A concurrent systematic review of oral Chinese herbal medicine by Tan *et al.*[15] examined 6 RCTs with a total of 432 participants in a meta-analysis. The meta-analysis of oral Chinese herbal medicine compared with placebo, using the data of three RCTs with a total of 134 participants, showed a significant difference in AE severity in favour of the intervention (erythema scores: standardized MD −0.76, 95% CI −1.05 to −0.47; surface damage scores: standard MD −1.08, 95% CI −1.59 to −0.56).

However, these results should be interpreted with caution given the limitations of the included studies. The requirement for standardization of ingredients and lack of availability within the NHS means that Chinese herbal medicine is currently not recommended for use in the UK. Two of the studies included in the meta-analysis by Tan were not included in the updated Cochrane review by Gu because the product used in these studies is no longer available.

Homeopathy

One systematic review by Ernst[16] included 2 non-randomized studies of homeopathy with a total of 253 participants, and 1 RCT with 24 participants. All the studies were methodologically weak, and no meta-analysis was possible. The review found no evidence of benefit from homeopathy for the treatment of AE.

Specialist textiles

Lopes *et al.*[17] conducted a systematic review and meta-analysis in which they examined the safety and effectiveness of functional textiles for AE, including silver-impregnated textiles, specialist silk clothing and ethylene vinyl alcohol fibre,[1] from 13 studies (8 RCTs and 5 observational studies) with a total of 372 participants. Although the included studies hinted at a possible benefit of functional textiles for the management of AE, the quality of the included studies means that the current evidence base is limited, and large-scale, independent studies are needed.

Prevention of atopic eczema

There have been 11 systematic reviews investigating the potential to prevent AE, demonstrating growing interest in this field.

Maternal antigen avoidance and breastfeeding

A Cochrane review by Kramer *et al.*[18] examined the combined evidence from 2 studies (334 pregnant women), and showed no protective effect of maternal food-antigen avoidance on the incidence of AE for women at high risk of AE, compared with placebo (RR = 1.01, 95% CI 0.57–1.79).

A second review by Kramer *et al.*[19] looked at the influence of breastfeeding on several health outcomes. Data on AE were provided by two large, observational studies (n = 3584) conducted in two countries. The review concluded that exclusive breastfeeding for 6–7 months conferred no protection against the development of AE at 5–7 years compared with exclusive breastfeeding for 3–4 months (RR = 0.86, 95% CI 0.47–1.58). These results support a previously published systematic review[20] and a large study based on ISAAC study data,[21] which showed a lack of evidence for a protective effect of exclusive breastfeeding on childhood eczema.

Maternal vitamin D intake

Three observational studies formed part of a subgroup analysis in a review by Christensen *et al.*[22] on the impact of vitamin D in pregnancy on extraskeletal health in children. The analysis (which was not pooled) provided inconclusive evidence as to the role of vitamin D in preventing AE. Of the 3 included studies, 1 study of 763 participants (mothers and children) showed that maternal vitamin D intake of ≥ 172 IU/day through food during pregnancy was associated with a 37% reduction in the odds of parental-reported AE in children aged 16–24 months (adjusted OR 0.63–95% CI 0.41–0.98). However, in the other 2 studies, comprising a total of 2109 participants, no association was found between vitamin D intake or 25 hydroxylated vitamin D dosage during pregnancy and AE at 9 months or 5 years of age.

Probiotics and prebiotics

Probiotics are viable microorganisms that may exert beneficial health effects on the host. Prebiotics are oligosaccharides that encourage the growth of these beneficial micro-organims. Prebiotics can be used alone or in combination with probiotics (symbiotics).

Six systematic reviews have examined the role of probiotics and/or prebiotics in the prevention of AE, with varying results.[10,23–27] Overall, there is now good evidence to suggest that probiotics are effective and safe in preventing AE, with a decreased risk of approximately 20%. Lactobacillius strains seemed to provide a stronger benefit compared with other bacterial strains.[23] However, uncertainty remains about how probiotics should be ideally delivered (to mothers before birth, to children after birth or both) and what exact strains should be used (single strain or mixed strains) There was some evidence in a Cochrane review by Osborn *et al.*[28] that a prebiotic supplement added to infant feeds may prevent AE. This meta-analysis of four studies found a significant reduction in AE risk of prebiotics compared with placebo (RR = 0.68, 95% CI 0.48–0.97).

Pet exposure

A meta-analysis by Pelucchi *et al.*[29] of 21 birth cohort studies involving 71 721 participants reported an approximately 30% decreased risk of AE for children who had exposure to dogs (RR = 0.72, 95% CI 0.61–0.85), whereas no association emerged with cat exposure (RR = 0.94, 95% CI 0.76–1.16). Moderate heterogeneity between studies was reported, and the results should therefore be interpreted with caution.

Conclusion

Once again, this evidence-based update has highlighted the need for larger and better-quality trials that can answer some of the many unanswered questions in the management of patients with AE. Better-quality trials and transparent reporting of trial data are urgently needed if research money is to be spent wisely and efficiently.[17] It is disappointing to find so many systematic reviews that have been unable to reach clinical conclusions because of variability of AE trials in terms of design, timing of outcome assessment, choice of outcomes and lack of basic methods to avoid bias.

It is also salutatory that many of the systematic reviews that have been published over the past 2 years fail to address questions of importance to patients and clinicians. A James Lind Alliance eczema priority-setting partnership published in 2012 outlined 14 key priority areas for future research into the treatment of AE.[18] Only one of these priority areas (the role of diet in the management of AE) has been covered by systematic reviews published in the past 2 years. Future systematic reviews should focus on these priority areas, so that new research evidence can be summarized within the context of an up-to-date systematic review.

In order to avoid duplication of effort, we would also recommend that researchers consult systematic review registries for ongoing systematic reviews (PROSPERO http://www.crd.york.ac.uk/PROSPERO/; last accessed 14 March 2014). For an easily accessible list of published AE systematic reviews please consult the 'map of systematic reviews for AE' on the Centre of Evidence Based Dermatology website (http://www.nottingham.ac.uk/research/groups/cebd/resources/index.aspx; last accessed 14 April 2014)[19] or search the Global Resource for Eczema Trials (GREAT) database (http://www.greatdatabase.org.uk/).[20]

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Learning points

- There is no evidence to suggest that exclusive breastfeeding for up to 7 months reduces the risk of developing AE in infants compared with a shorter breastfeeding period.
- The role of vitamin D in preventing AE is currently unclear.
- There is now good evidence to suggest that probiotics are effective and safe in preventing AE, with a decreased risk of approximately 20%; however, uncertainty remains about the optimal methods of use.
- Prebiotics may be effective in reducing the risk of developing AE.
- Household pets (especially dogs) may have a protective effect in preventing the development of AE in infants
- There is some limited evidence in support of systemic immunotherapy (desensitization) for patients sensitized to house dust mite, but further research is required prior to implementation in the NHS.
- There have been no randomized controlled trials on the use of H1 anti-histamines as monotherapy for the treatment of AE.
- There is little or no evidence to support the use of specific dietary supplements for treatment of AE, including evening primrose oil and borage oil (no more new studies are needed), fish oil, vitamin D and vitamin E, vitamin B6, sea buckthorn oil, hempseed oil, sunflower oil, DHA, selenium or zinc sulfate.
- There is no evidence to support the use of homeopathy for the treatment of AE.
- There is some evidence to support the use of Chinese herbal medicine for AE, but the quality of the trial evidence and lack of availability within the NHS precludes its use.
- There is limited evidence to support the use of specialist textiles and clothing for the management of AE, and larger, independent studies are needed.

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CPD questions

Learning objective

To demonstrate knowledge of the findings of recent systematic reviews on atopic eczema (AE).

Question 1

Which one of the following has a protective effect against development of atopic eczema (AE) in children?

a) Maternal food-antigen avoidance.
b) Exclusive breastfeeding for 6–7 months compared with exclusive breastfeeding for 3–4 months.
c) Exposure to cats.
d) Prevention of exposure to dogs.
e) Probiotics.

Question 2

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

a) Two recent systematic reviews have concluded that systemic immunotherapy does not improve AE.
b) Desensitization therapy for AE is currently available on the NHS.
c) Antihistamines are almost always used as an adjuvant therapy with existing AE treatments.
d) A recent meta-analysis found clear evidence that some topical therapies relieve the pruritus associated with AE.
e) A recent meta-analysis found clear evidence that some systemic therapies relieve the pruritus associated with AE.

Question 3

A recent Cochrane review has found some evidence of effectiveness of which dietary treatment for atopic eczema (AE)?

a) Vitamin D.
b) Sea buckthorn oil.
c) Vitamin B6.
d) Selenium.
e) Fish oil.

Question 4

Recent systematic reviews have found some evidence of effectiveness for which treatment for atopic eczema (AE)?

a) Borage oil.
b) Probiotics.
c) Evening primrose oil.
d) Topical application of Chinese herbal medicine.
e) Oral Chinese herbal medicine.

Question 5

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

a) Probiotics are oligosaccharides that encourage the growth of beneficial micro-organisms.
b) Prebiotics should not be used in combination with probiotics.
c) There is some evidence that a prebiotic supplement may help prevent AE.
d) There is no evidence that Lactobacilli strains are more effective than other bacterial strains in preventing AE.
e) Mixed strains of probiotics are preferable to single strains.

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 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.