

What's new in atopic eczema? An analysis of systematic reviews published in 2008 and 2009

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Summary

This review summarizes clinically important findings from nine systematic reviews of the causes, treatment and prevention of atopic eczema (AE) published between August 2008 and August 2009. Two systematic reviews concluded that there is a strong and consistent association between filaggrin (*FLG*) mutations and development of eczema. The associations between *FLG* mutations and atopic sensitization, rhinitis and asthma are weaker than between *FLG* mutations and eczema, especially if those who also have eczema are excluded. The relationship between transforming growth factor levels in breast milk and eczema development is still unclear. A further systematic review found no strong evidence of a protective effect of exclusive breastfeeding for at least 3 months against eczema, even in those with a positive family history of atopy. Based on a systematic review and meta-analysis of six randomized controlled trials, supplementation with omega-3 and omega-6 oils is unlikely to play an important role in the primary prevention of eczema or allergic diseases in general. There is little evidence to support dietary restrictions of certain foods in unselected children with AE. There is also little evidence to suggest a clinically useful benefit from using probiotics in patients with established eczema. A systematic review of topical pimecrolimus and tacrolimus added little additional information to previous reviews, and did not provide any new data on long-term safety. Both of these drugs work in AE, and may reduce flares and usage of topical corticosteroids; however, there is still uncertainty about how they compare with topical corticosteroids.

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Background

This review summarizes nine systematic reviews dealing with the causes, treatment and prevention of atopic eczema (AE) that were indexed in bibliographic databases between August 2008 and August 2009, and were included in the 2009 Annual Evidence Update on Atopic Eczema from NHS Evidence – Skin Disorders. This review aims to pick out clinically important points with the busy clinician in mind. Readers are encouraged to read the full report and original papers cited in the 2009 Annual Evidence Update,¹ where the methods and omitted citations are given. This review considers systematic reviews only, as they are generally considered to be the most reliable evidence source, whereas

the results of single randomized controlled trials (RCTs) are often contradicted by subsequent trials.² Similar reviews covering the 2007 and 2008 Annual Evidence Updates have been published previously in this journal.^{3–5}

Filaggrin mutations and atopic eczema

Two new systematic reviews deal with filaggrin gene (*FLG*) mutations in allergic diseases. A well reported systematic review by Rodríguez *et al.*⁶ confirmed the strong and consistent association between *FLG* mutations and eczema in 24 case-control and family studies (OR = 3.12; 95% CI 2.57–3.79), and even stronger associations with dermatologist-diagnosed AE (OR = 4.24; 95% CI 3.09–5.81) and severe to moderate cases of AE (OR 5.16; 95% CI 3.92–6.80). They found a weaker association with asthma (OR = 1.48; 95% CI 1.32–1.66) and no association when those who had asthma without eczema were analysed alone (OR = 1.11; 95% CI 0.88–1.41), suggesting a specific 'asthma plus eczema' phenotype that is distinct from other forms of asthma.

Another systematic review by van den Oord and Sheikh⁷ also found no association between *FLG* mutations and asthma without eczema. They found an increased risk of allergic rhinitis with eczema (OR = 2.84; 95% CI 2.08–3.88) and rhinitis without eczema (OR = 1.78; 95% CI 1.16–2.73) in two case-control studies. Combined filaggrin gene defects increased the risk of allergic sensitization, but the associations were not so strong, with an OR of 1.57 (95% CI 1.20–2.07) across two case-control studies and an OR of 1.91 (95% CI 1.44–2.54) across five family studies, with results differing considerably between the studies.

Overall, these two systematic reviews add new information about the possible role of filaggrin gene mutations in sensitization, rhinitis and asthma. All associations seem to be much weaker than for eczema, and when only those people with hay fever and asthma without eczema are analysed, the association becomes even weaker or disappears.

Transforming growth factor- β levels in breast milk and risk of atopic eczema

A systematic review by Oddy and Rosales⁸ looked at a possible link between levels of transforming growth factor (TGF)- β in breast milk and the risk of those children developing atopic disease. Only 3 of the 12 included studies had eczema outcomes. One was an RCT, which suggested that TGF- β 2 levels were

increased in breast milk of mothers taking probiotics, and that the likelihood of their children developing eczema was reduced (OR = 0.32; 95% CI 0.12–0.85). Of the two cohort studies, only one allowed for potential confounders and found no link between TGF levels and eczema risk (OR = 1.07; 95% CI 0.56–2.00). With so few studies looking at eczema, the relationship between TGF levels in breast milk and eczema development is still unclear at present.

Prevention of atopic eczema

Breastfeeding

A systematic review by Yang *et al.*⁹ explored whether breastfeeding protects children from developing eczema. Based on 27 studies involving 34 227 participants, the authors failed to find a significant difference in the risk of developing eczema (OR = 0.89; 95% CI 0.76–1.04). Exclusive breastfeeding was (just) significantly protective against eczema compared with formula feeding (OR = 0.70; 95% CI 0.50–0.99), but not compared with partial breastfeeding. When exclusively breastfed children with a family history of atopy and those without were compared, there was no significant difference in the risk of eczema between the two groups. The review concluded that there is no strong evidence that exclusive breastfeeding for at least 3 months protects against eczema, even in those with a positive family history. Further studies were recommended, with standardized methodology including controls for potential confounding and reverse causation (continuation of exclusive breastfeeding when a child develops eczema, due to public awareness of the benefits of breastfeeding). Thus, 'breast is best' in many ways, but not, on current evidence, for preventing eczema.

Omega-3 and -6 oils: are fish oils just another snake oil?

Omega-3 and omega-6 oils contain essential fatty acids involved in various inflammatory and immunological processes, including atopic diseases. Anandan *et al.*¹⁰ reviewed the effectiveness of omega-3 and omega-6 oils for the primary prevention of sensitization and development of allergic diseases, including eczema. This well-reported review included four studies assessing omega-3 supplements (679 participants) and two assessing omega-6 (259 participants). Meta-analysis of data from these studies found a nonsignificant increased risk of developing eczema after omega-3 supplementation [relative risk (RR) = 1.10; 95% CI 0.78–1.54] and a nonsignificant decreased risk after omega-6

supplementation (RR = 0.80; 95% CI 0.56–1.16). No significant effect of omega-3 on development of asthma, allergic rhinitis, food allergy or sensitization to common allergens was found. Given the uncertainty of the estimates in the studies performed to date, it is too early to say whether fish oils are useful or useless for prevention of eczema.

Treatment of atopic eczema

Dietary exclusions

A Cochrane Review of dietary exclusions for the treatment of established AE by Bath-Hextall *et al.*^{11,12} included 9 RCTs (421 participants) that found little evidence to support the use of exclusion diets in unselected people with AE. This may be because trial participants were not allergic to those substances in the first place, but many studies were also small and may have lacked power to detect significant differences between diets. Many studies in the review were poorly reported or were of too short a duration for meaningful results.

Probiotics

Probiotics are live microorganisms that may confer a health benefit. They are thought to have a possible role in eczema treatment, based on the observation that gut bacteria are different in those with and without eczema,¹³ and on the theory that probiotics may reduce intestinal inflammation and permeability and subsequent antigen presentation in gut lymphoid tissue,¹⁴ or have beneficial effects on gut flora and immune responses.¹⁵

A Cochrane Review of probiotics for the treatment of eczema by Boyle *et al.*^{16,17} included 12 RCTs (781 children). Eleven studies used *Lactobacillus* species, alone or in combination with other probiotics. Details of randomization, blinding and intention-to-treat (ITT) analyses were generally poorly reported, raising doubts about the validity of the results. Meta-analysis of data from five of the trials found a 0.9 point reduction in the modified Scoring Atopic Dermatitis (SCORAD) after probiotic treatment compared with placebo, but this was not significant (95% CI –2.84 to 1.04). Quality of life (QOL) data were available for only two studies. These could not be combined, but the individual studies reported no significant difference in QOL between participants receiving probiotics or placebo. Pre-defined subgroup analysis by eczema severity or presence of atopy did not identify a specific population in which

probiotic treatment was effective. No significant adverse events were reported.

Another systematic review by Michail *et al.*¹⁸ included the same studies as the Cochrane Review, apart from one. The authors were able to obtain raw data, including SCORAD values, for 10 of the studies (fewer than those obtained by the Cochrane authors). They reported a significant difference favouring probiotics compared with placebo in reducing SCORAD (mean change from baseline –3.01; 95% CI –5.36 to 0.66). However, a SCORAD reduction of only three points is probably not clinically significant. Slightly different and possibly suboptimal methods of meta-analysis were used in this review. In particular, in one meta-analysis, the authors included data from one study that recorded only SCORAD A + B components¹⁹ and compared them with the total SCORAD scores (A + B + C) from other studies. Subgroup analysis according to duration of probiotic treatment, type of probiotic strain and age of participants revealed no significant differences between probiotic and placebo groups. There was a nonsignificant trend for probiotics to be more effective in children with demonstrable IgE reactivity.

In summary, neither review provides any clear evidence of significant clinical benefit for probiotics in patients with established eczema. However, it is still possible that specific strains of some probiotics could be useful.

Tacrolimus and pimecrolimus

This year we found yet another systematic review on topical calcineurin inhibitors and AE, by El-Batawy *et al.*,²⁰ which evaluated 19 RCTs (10 for tacrolimus, 9 for pimecrolimus) involving 7378 participants. All of the pimecrolimus trials in the review were the same as those included in a previous Cochrane review by Ashcroft *et al.*²¹ except for one small trial involving 34 participants. The tacrolimus trials were all the same as those in another review by Ashcroft *et al.*,²² with the exception of one new vehicle-controlled trial and one with active comparators. Outcomes of interest were decided by the reviewers retrospectively, raising the possibility of bias, although they did go to the trouble of recalculating outcomes on an ITT basis if the trials had not reported the data in this way. Many of the trials used placebo controls, which are of little use for informing clinical practice because they do not compare the new treatment to existing standard treatment, i.e. topical corticosteroids. The authors concluded that both tacrolimus and pimecrolimus were more effective than placebo, and that pimecrolimus was less effective than

potent topical corticosteroids but reduced the number of eczema flares and has a steroid-sparing effect. This does not add anything to what is already known about pimecrolimus from previous reviews, probably because they evaluated the same trials. With respect to tacrolimus, the authors' conclusions were much the same as in previous reviews as well, although they did find one new trial that found 0.1% tacrolimus to be superior to a combined regimen of 0.1% hydrocortisone butyrate and 1% hydrocortisone acetate in patients with moderate to severe eczema. This review also did not address one of the most important outcomes: long-term safety.

Learning points

- There is a strong and consistent association between filaggrin (*FLG*) mutations and development of eczema. The associations between *FLG* mutations and atopic sensitization, rhinitis and asthma are weaker than for eczema, especially if those who also have eczema are excluded.
- The relationship between TGF levels in breast milk and eczema development is still unclear.
- There is no strong evidence of a protective effect of exclusive breastfeeding for at least 3 months against eczema, even in those with a positive family history of atopy.
- Supplementation with omega-3 and omega-6 oils seems unlikely to play an important role in the primary prevention of eczema or allergic diseases in general.
- There is little evidence to support dietary restrictions of certain foods in unselected children with AE.
- There is still little evidence to suggest a clinically useful benefit from using probiotics in patients with established eczema.
- A review of topical pimecrolimus and tacrolimus has added little additional information to previous reviews and did not provide any new data on long-term safety. Both drugs work, and may reduce flares and usage of topical corticosteroids. However, there is still uncertainty about how they compare with topical corticosteroids.

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