

What's new in atopic eczema? An analysis of systematic reviews published in 2007 and 2008. Part 2. Disease prevention and treatment

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Summary

This review summarizes clinically important findings from systematic reviews indexed in bibliographical databases between August 2007 and August 2008 that dealt with disease prevention (six reviews) and treatment of atopic eczema (seven reviews). Regarding disease prevention, two independent systematic reviews found some clinical trial evidence that ingestion of probiotics by mothers during pregnancy might reduce the incidence of subsequent eczema. Another review failed to find any clear benefit of prebiotics in eczema prevention. Although furry pets are often cited as causing allergic disease, a systematic review of observational studies found no evidence that exposure to cats or dogs at birth increases eczema risk. One very large review of studies of breastfeeding found some evidence of a protective effect on eczema risk, although all the studies were limited by their observational nature. A German group has attempted an overview of eczema prevention studies with a view to informing national guidelines. In terms of eczema treatment, two systematic reviews have confirmed the efficacy of topical tacrolimus ointment. Another review of 31 trials confirms the efficacy of topical pimecrolimus, although many of those trials were vehicle controlled, which limits their clinical utility. A review of 23 studies of desensitization therapy for allergic diseases found some evidence of benefit for eczema, which needs to be explored further. Despite the popularity of antistaphylococcal therapies for eczema, a Cochrane Review of 21 trials failed to show any clear benefit for any of the therapies for infected or clinically noninfected eczema. Another Cochrane Review dealt with dietary exclusions for people with eczema and found little evidence to support any dietary exclusion, apart from avoidance of eggs in infants with suspected egg allergy supported by evidence of sensitization. A review of 13 studies of probiotics for treating established eczema did not show convincing evidence of a clinically worthwhile benefit, an observation that has been substantiated in a subsequent Cochrane Review.

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A similar and more detailed review to the material published in this review appeared in the National Library for Health Skin Disorders Specialist Library's Annual Evidence Update in September 2008 (<http://www.library.nhs.uk/skin/Page.aspx?pagename=ECZEMANEW>) and explicit reference is given to that fuller version throughout. There are no copyright issues with using material from that source.

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Background

In part 1 of this two-part review, nine systematic reviews dealing with definitions, causes and consequences of atopic eczema (AE) were discussed. Those reviews were indexed in bibliographical databases between August 2007 and August 2008, and were included in the 2008 Annual Evidence Update on Atopic Eczema from the National Library for Health Skin Disorders Specialist Library (now NHS Evidence – skin disorders). In this second part, we summarize the clinical implications of systematic reviews that deal with the prevention (six reviews) and treatment (seven reviews) of AE that were indexed in the same period. The review builds on the systematic review evidence for eczema treatments presented in the 2007 Annual Evidence Update.¹ This review is not a detailed analysis of all the included systematic reviews, but a pointer to clinically relevant points, written with the busy clinician in mind. Readers interested in finding out more about a study are encouraged to read the full report and original papers cited in the 2008 Annual Evidence Update (<http://www.library.nhs.uk/skin/ViewResource.aspx?resID=292501&tabID=289&catID=8310>), where omitted citations and reasons for omission are given. The full methods for the search can be found elsewhere in the methods (<http://www.library.nhs.uk/skin/Page.aspx?pagename=ECZEMAMETH>). This review is restricted to systematic reviews simply because the results of single randomized controlled trials (RCTs) are often contradicted by subsequent trials.² Throughout the review, we will refer to the term 'eczema' to denote the phenotype of AE (syn. atopic dermatitis) in accordance with the World Allergy Organization nomenclature,³ and specifically comment on people who were truly atopic and for whom sensitization has been clearly documented.

Disease prevention

Probiotics

Because clinicians only deal with people who already have eczema, the concept of disease prevention seems remote from the consulting room, unless the clinician is advising a mother of a child who already has eczema how she might prevent it from occurring in a subsequent child. One possible prevention strategy is ingestion of probiotics by the mother during pregnancy or ingestion of probiotics by infants. Probiotics are live bacteria that colonize the gut and may provide health benefit to the host. A systematic review by Lee *et al.*⁴

reviewed randomized controlled trials (RCTs) of probiotics for eczema prevention and treatment. The six prevention RCTs were higher in quality than the treatment RCTs, and a pooled analysis suggested a possible preventive benefit of probiotics, with a reduced relative risk of subsequent incidence of AE [relative risk (RR) 0.69, 95% CI 0.57–0.83]. The treatment effect was smallest in the largest study and two of the studies did not perform an intention to treat study, which is important given the high drop-out rates. On a similar theme, Osborn and Sinn⁵ performed a Cochrane Review on probiotics (mainly *Lactobacillus rhamnosus*) for prevention of atopic disease in infants at high risk of allergy born to atopic parents and found an overall reduction of eczema (five RCTs) by about 18% (RR = 0.82, 95% CI 0.70–0.95). When only those with proof of atopic sensitization were analysed, the results were no longer significant (RR = 0.80, 95% CI 0.62–1.02). Very few possible harmful effects were reported in these reviews. Probiotics may therefore have a place in preventing eczema, but which strain to use and for how long is still uncertain.

Prebiotics

In a separate Cochrane Review, Osborn and Sinn studied prebiotics for atopy prevention.⁶ Prebiotics are nondigestible foods that may help the host by stimulating growth of nonpathogenic 'good' bacteria in the colon. Sadly, only two studies evaluated eczema outcomes; one study suggested a possible benefit, but the other failed to find any benefit.

'Kick the cat'

Doctors often tell atopic families to get rid of furry pets, but a systematic review by Langan *et al.*⁷ found no evidence from a variety of observational studies (including cohort studies, which can separate cause from effect over time) to support the notion that having a cat or dog around at the time of birth does any harm. In fact, the authors found some evidence to suggest that dogs may have a protective effect, although such an effect became insignificant when adjusted for avoidance behaviour.

Breastfeeding

Much has been written on the possible benefits of breastfeeding, but if you want it all in one place, then look no further than the 2007 US Agency of Healthcare Research and Quality (AHRQ) review.⁸ It is a huge piece

of work that looked at all health outcomes, including eczema. The report suggests a possible protective effect of breastfeeding, but cautions the reader on the limited nature of the observational evidence, i.e. those who breastfeed may be influenced by the disease rather than *vice versa*.

Prevention guidelines

It is good that people are starting to think about the possibility of prevention. To take things further, a German group has formulated preliminary guidelines for preventing allergic diseases including eczema, and these guidelines included a systematic review of all eczema-prevention studies.⁹

Disease treatment

Topical tacrolimus

Two systematic reviews of topical tacrolimus by Yan *et al.*¹⁰ and Li *et al.*¹¹ showed that both 0.03% and 0.1% tacrolimus were better than 1% hydrocortisone acetate or 1% pimecrolimus. The reviews do not add much clinically useful information to a previous review published in the *BMJ*.¹²

Topical pimecrolimus

A Cochrane Review by Ashcroft *et al.*¹³ of 31 RCTs involving 8019 participants found plenty of evidence that pimecrolimus works better than vehicle cream for short-term control and preventing flares. Comparing against other eczema treatments, two studies suggested that pimecrolimus was 25% and 39% less effective than 0.1% triamcinolone acetonide and 0.1% betamethasone valerate, respectively. Topical pimecrolimus was also found to be around 42% less effective than 0.1% tacrolimus ointment, based on two trials involving 639 participants. Pimecrolimus was associated with more overall withdrawals and skin burning. None of the trials reported on key adverse effects such as the extent of skin thinning (which is supposed to give topical calcineurin inhibitors a significant advantage over topical corticosteroids). The exact role of topical pimecrolimus is still unclear. Although both topical tacrolimus and pimecrolimus are recommended by the National Institute for Health and Clinical Excellence¹⁴ to be used in those whose eczema is uncontrolled by topical corticosteroids, none of the studies included such people.

Desensitization therapy

Instead of trying to reduce ubiquitous allergens such as house dust, another approach is to attempt to desensitize people whose allergic disease is triggered by such factors. Bussmann *et al.*¹⁵ reviewed 23 studies on desensitization in allergic disease, four of which included eczema outcomes. When combined, the four small RCTs showed a significant benefit of desensitization therapy in eczema, but no estimate of the magnitude of benefit and its precision was provided. The largest benefit was seen in those with severe eczema and it should be noted that around one-fifth developed a severe exacerbation during therapy. Much larger pragmatic studies are now needed to assess the role of desensitization therapy (delivered by the sublingual or subcutaneous route) in carefully selected and defined patients with AE.

Anti-staphylococcal interventions

There is no doubt that secondary infection is a common event in eczema, and that colonization without overt clinical infection may also play a role in driving eczematous inflammation through superantigens. Many interventions such as topical antibiotic/corticosteroid creams, antiseptic bath additives, and antibacterial clothing and soaps have therefore been developed and claimed to help those with eczema. Yet when the evidence based on 21 RCTs involving 1018 people with infected or uninfected eczema was examined in a Cochrane Review,¹⁶ there was no clear evidence for any clinical benefit of the interventions, despite their success in reducing *Staphylococcus aureus* numbers on the skin. Emergence of resistant bacterial strains is a further serious concern with interventions such as topical antibiotic/corticosteroid combination, and their continued use has to be questioned until better evidence of clinical benefit becomes apparent.

Exclusion diets

Dietary manipulation is commonplace in eczema families, yet according to a Cochrane Review,¹⁷ there is no good RCT evidence that either milk and egg exclusion (six studies), a few-foods diet (one RCT) or an elemental diet (two studies) helps eczema in unselected people. One study suggests that an egg-free diet may help infants with proven sensitivity to eggs.

Probiotics

The systematic review by Lee *et al.*⁴ on probiotics discussed earlier in relation to prevention also looked at the possible benefits in treating established eczema. Although very small differences using an objective method for scoring eczema were noted between the two groups that favoured probiotics, such a small effect is unlikely to be helpful in clinical practice. A Cochrane Review on the same topic has now been published,¹⁸ which concluded that probiotics are not an effective treatment for eczema on present evidence.

Clinical and research implications

The key clinical messages from this review are provided in the box below. The review has revealed some interesting new data on the possibility of preventing eczema by interventions such as probiotics. Getting rid of the cat or dog at birth of a child is not necessary if the aim is allergic disease prevention. Many of the eczema treatment studies are still poorly reported, but when considered together they suggest that we should not be using topical antibiotic/corticosteroid cream or probiotics for those with established disease. Similarly, unselected children with eczema do not need to be subjected to the ordeal of difficult dietary exclusions unless there is convincing evidence of food sensitivity. The exact role of topical tacrolimus and pimecrolimus is still unclear as although they have been recommended for people who are unresponsive or who are at high risk of skin thinning due to topical corticosteroids, none of the studies have been done in these groups. Desensitizing patients with eczema seems to be an interesting approach in people who are sensitive to ubiquitous allergens such as house dust mite, and is an approach that now needs to be addressed in a large, pragmatic clinical trial.

Learning points

- Two systematic reviews have suggested that the incidence of eczema may be reduced by 20–30% in children born to atopic parents if their mothers ingest probiotics during pregnancy.
- There is not enough evidence yet to comment on the possible benefit of foods that promote healthy gut bacteria (prebiotics) in preventing eczema.
- There is no evidence that owning a cat or dog before or at birth of a child increases the risk of the child developing eczema.

- It is still unclear whether breastfeeding prevents eczema, as studies suggesting such an effect were observational, making it difficult to distinguish cause from effect.
- Two systematic reviews have confirmed that topical tacrolimus is more effective than weak topical corticosteroids and topical pimecrolimus.
- Topical pimecrolimus is more effective than plain grease for short-term control or preventing flares, but less effective than potent topical corticosteroids or 0.1% tacrolimus. It is still unclear where topical pimecrolimus fits into eczema treatment.
- There is some evidence that subcutaneous desensitization may improve eczema symptoms in those who are sensitive to house dust mites, especially those with more severe disease. Larger studies are needed before they can be used in clinic.
- A Cochrane Review has concluded that there is no good evidence that interventions aimed at reducing staphylococci on the skin, such as topical antibiotics/corticosteroid combinations or antiseptic bath additives, have a clinically useful effect on eczema.
- There is no good evidence to suggest that unselected children with eczema benefit from exclusion diets, few-food diets or elemental diets. An egg-free diet may be helpful in infants who are sensitized to egg.
- There is no good evidence to suggest that probiotics are clinically helpful in people with established AE.

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