2009 Annual Evidence Update on Atopic Eczema

Published: 14 September 2009

Welcome to the third Annual Evidence Update on Atopic Eczema produced by NHS Evidence - skin disorders, with the results of a search for new guidelines and systematic reviews published or indexed since the last Annual Evidence Update in September 2008. There is also a "what's new" analysis, discussing the new evidence and its implications for clinical practice.

2009 Annual Evidence Update on Atopic Eczema - Introduction

Introduction by Professor Hywel Williams (Clinical Lead) and Dr Douglas Grindlay (Information Specialist), NHS Evidence - skin disorders

Welcome
Welcome to the 2009 Annual Evidence Update on Atopic Eczema from NHS Evidence - skin disorders. This is a summary of important new evidence published or indexed since our 2008 Annual Evidence Update. Although NHS Evidence - skin disorders is aimed at healthcare professionals, we hope that many people with eczema, and also parents and carers, will also find some of the information of interest.

So what's in our Annual Evidence Update on Atopic Eczema?
The Annual Evidence Update searches for new evidence in the form of guidelines and systematic reviews. We use systematic reviews as our core evidence source for Annual Evidence Updates because of the well-known hazards in interpreting the results of single research studies (see, for example, Ioannidis 2005). The citations we found have been listed under relevant headings in our Results, with links to PubMed or free full text where available, should you wish to read more deeply. As usual, we have provided a commentary and guide for busy health care professionals on the new evidence and its potential implications for clinical practice in our "What's new?" commentary. We would like to express our thanks to Dr Jonathan Batchelor (Specialist Registrar and UK Dermatology Clinical Trials Network Fellow) for helping us to put the "What's new" section together this year.

Filling important research gaps
We hope you enjoy this Annual Evidence Update, but if you feel that important questions about atopic eczema have not been answered, please send these to us using our DUETs submission form so that we can consider including them in the atopic eczema topic of DUETs, the UK Database of Uncertainties about the Effects of Treatments. Documenting such uncertainties will help future researchers and funders to prioritise and fill those important gaps—and there are lots of important gaps to fill.

Hywel Williams and Douglas Grindlay, 14th September 2009

2009 Annual Evidence Update on Atopic Eczema - Results

A literature search was carried out to identify **new systematic reviews and guidelines** relating to atopic eczema (atopic dermatitis) that have been published or indexed since the 2008 Annual Evidence Update on Atopic Eczema.

The result of this search is the **2009 Annual Evidence Update on Atopic Eczema**.

Search period

January 2008 was set as the limit for earliest publication date in this year's searches, to allow for any delays in indexing of citations in the bibliographic databases used (which might mean the citations were not found in the searches for the previous Annual Evidence Update in August 2008).

All the searches were carried out for the last time on 18th August, 2009.

Sources Searched

The following sources were searched:

- Ovid MEDLINE (using SIGN MEDLINE systematic review filter)
- Ovid EMBASE (using SIGN EMBASE systematic review filter)
- PubMed (using PubMed Clinical Queries systematic review filter)
- Cochrane Library
- NHS Evidence - skin disorders

All citations found in the searches were hand searched by reading the titles and abstracts to identify systematic reviews and potential systematic reviews relevant to atopic eczema. For all potential systematic reviews where there was still some doubt, the full texts were then read to ensure that they were indeed systematic reviews.

The definition of a systematic review from the Glossary of Cochrane Collaboration Terms on the Cochrane Collaboration website was used:

“A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.”

Results

A total of 11 new systematic reviews judged of direct relevance to the topic of atopic eczema and its treatment were identified.

The citations for these systematic reviews are listed below, arranged by topic. Within each topic, the citations are presented in reverse chronological order, i.e. most recent first. Links to PubMed abstracts or free full text, where available, are provided.

Please note that the inclusion of citations in this list does not imply endorsement. NHS Evidence - skin disorders does not accept responsibility for the content or quality of included studies.

LIST OF NEW SYSTEMATIC REVIEWS ON ATOPIC ECZEMA AND ITS TREATMENT

UK Guidelines

No new UK guidelines identified.

Overseas guidelines

Werfel T, Erdmann S, Fuchs T, Henzgen M, Kleine-Tebbe J, Lepp U, Niggemann B, Raithel M, Reese I, Saloga J, Vieths S, Zuberbier T; German Society of Allergology and Clinical Immunology (DGAKI); Medical Association of German Allergologists (ADA); German Society of Pediatric Allergology.
Approach to suspected food allergy in atopic dermatitis. Guideline of the Task Force on Food Allergy of the German Society of Allergology and Clinical Immunology (DGAKI) and the Medical Association of German Allergologists (ADA) and the German Society of Pediatric Allergology (GPA).
Journal der Deutschen Dermatologischen Gesellschaft. 2009 Mar;7(3):265-71.
Link to PubMed abstract

(No indication of search methodology)

Causes

van den Oord RA, Sheikh A.
Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis.
BMJ. 2009 Jul 9;339:b2433.
Link to full text
Link to DARE abstract

Rodríguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, Irvine AD, Weidinger S.
Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease.
Journal of Allergy and Clinical Immunology. 2009 Jun;123(6):1361-70.e7.
Link to PubMed abstract

Willemsen R, Roseeuw D, Vanderlinden J.
Alexithymia and dermatology: the state of the art.
International Journal of Dermatology. 2008 Sep;47(9):903-10.
Link to PubMed abstract

Prevention

Oddy WH, Rosales F.
A systematic review of the importance of milk TGF-beta on immunological outcomes in the infant and young child.

Pediatric Allergy and Immunology. 2009 Jul 9. [Epub ahead of print]
Link to PubMed abstract

Anandan C, Nurmatov U, Sheikh A.
Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis.
Allergy. 2009 Jun;64(6):840-8.
Link to PubMed abstract
Link to DARE abstract

Yang YW, Tsai CL, Lu CY.
Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies.
British Journal of Dermatology. 2009;161:737-83. Epub 2009 Feb 23.
Link to PubMed abstract

Treatment – dietary exclusions

Bath-Hextall F, Delamere FM, Williams HC.
Dietary exclusions for improving established atopic eczema in adults and children: systematic review.
Allergy. 2009 Feb;64(2):258-64.
Link to PubMed abstract

(Based on Cochrane Review published in January 2008 and included in last year's AEU)

Treatment - probiotics

Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF, Tang ML.
Probiotics for the treatment of eczema: a systematic review.
Clinical and Experimental Allergy. 2009 Aug;39(8):1117-27. Epub 2009 Jul 1.
Link to PubMed abstract

(Based on Cochrane Review published in October 2008—see below)

Michail SK, Stolfi A, Johnson T, Onady GM.
Efficacy of probiotics in the treatment of pediatric atopic dermatitis: a meta-analysis of randomized controlled trials.
Annals of Allergy, Asthma & Immunology. 2008 Nov;101(5):508-16.
Link to PubMed abstract
Link to DARE abstract

Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF, Tang ML.
Probiotics for treating eczema.
Cochrane Database of Systematic Reviews. 2008 Oct 8;(4):CD006135.
Link to full text

Treatment - topical calcineurin inhibitors

El-Batawy MM, Bosseila MA, Mashaly HM, Hafez VS.
Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis.
Journal of Dermatological Science. 2009 May;54(2):76-87. Epub 2009 Mar 20.
Link to PubMed abstract
Link to DARE abstract

(Only PubMed searched)

EXCLUDED REFERENCES

Oddy WH.
The long-term effects of breastfeeding on asthma and atopic disease.
Advances in Experimental Medicine and Biology. 2009;639:237-51.
Link to PubMed abstract

(Based on study first reported in 2004, so search is out of date)

Rao S, Srinivasjois R, Patole S.
Prebiotic supplementation in full-term neonates: a systematic review of randomized controlled trials.
Archives of Pediatrics & Adolescent Medicine. 2009;163(8):755-64.
Link to PubMed abstract

(Only mentions eczema as a possible marker of intolerance of prebiotics, rather than assessing the effect of prebiotics on established eczema)

2009 Annual Evidence Update on Atopic Eczema - Commentary

"What's new?" — a tour of the 2009 Annual Evidence Update on Atopic Eczema with the busy clinician in mind
Dr Jonathan Batchelor, Dermatology Registrar, Addenbrookes Hospital, Cambridge and Professor Hywel Williams, Clinical Lead for NHS Evidence - skin disorders and Co-ordinating Editor of the Cochrane Skin Group

Jonathan (left) and Hywel (right)

New guidelines from Germany - food allergy and eczema

No new UK guidelines on atopic eczema have been identified since the 2008 Annual Evidence Update on Atopic Eczema. The most recent UK guidance was that from NICE in December 2007 (Link to full text) and from the Royal College of Nursing in March 2008 (Link to full text, PDF file).

However, some new guidance has emerged from Germany by Werfel *et al*. (2009) (Link to PubMed abstract) on how to manage suspected food allergy in atopic dermatitis (syn. atopic eczema).

This guideline is essentially a consensus between members of the German Society of Allergology and Clinical Immunology, the Medical Association of German Allergologists and the German Society of Pediatric Allergology, and it is good to see different professionals who deal with atopic eczema patients working together like this. The authors rightly point out the need to correctly identify those who might benefit from elimination diets. They also emphasise the need to avoid unnecessary elimination diets in children who will not benefit, in order to avoid an excessive burden for parents and a risk of malnutrition in the children. The guideline emphasises the unreliability of history and allergy tests in predicting food allergy, and advocates the use of elimination diets before then conducting double blind placebo controlled food challenges to suspected foods in order to more accurately identify who would benefit from a dietary approach. Since eczematous reactions can develop slowly, they emphasise the importance of examining the skin on the day following the challenge rather than just looking for immediate or same-day reactions. The article provides a useful summary of the main types of food reactions in atopic eczema, the tests that can be used to explore suspected reactions further, and stepwise procedures for carrying out food challenges. It also provides some useful practical guidance on different scenarios and points out that results from provocation tests are only valid for 12-24 months in childhood. So, this guideline contains lots of useful information and guidance on a topic that is high on patients' agendas.

Our main criticism of the guideline is the lack of a clear link between quality of evidence and strength of recommendations. It is also unclear how the evidence was searched and collated – no methods are described, and in the heading entitled "Procedures in creating consensus" at the end of the article, we are simply given a list of 12 names of people who cited their own work in 13 out of the 32 references used to inform the guidance.

We have to confess that we do not use double blind placebo controlled food challenges in our eczema clinic, mainly because they are such a palaver for families and children, and they are very resource intensive. It is an area that is ripe for a cost-effectiveness study, comparing the results against simple advice based on history plus simple allergy tests. There is no doubt that food allergy

exists in childhood eczema, especially in the first year of life. It is also important to emphasise that, as we read later in this commentary in the section on dietary exclusions, there is no good evidence to support the use of elimination diets in unselected cases of eczema.

Causes - filaggrin (again) and alexithymia

The strong association between filaggrin gene mutations and atopic eczema was captured in a systematic review by Baurecht *et al*. (2007) (Link to PubMed abstract) that was included in the 2008 Annual Evidence Update on Atopic Eczema. Two new systematic reviews dealing with the role of filaggrin gene (FLG) mutations in allergic diseases have now appeared and feature in the results for this year's Annual Evidence Update. The first, by Rodríguez *et al*. (2009) (Link to PubMed abstract), looks at the strength of association between FLG mutations and eczema (24 studies) and asthma (17 studies). Rodríguez *et al*. confirm the strong and consistent association between FLG mutations and eczema in case-control and family studies (Odds Ratio [OR] 3.12; 95% Confidence Interval [CI] 2.57-3.79), and even stronger associations with dermatologist-diagnosed atopic eczema (OR 4.24; 95% CI 3.09-5.81) and severe to moderate cases (OR 5.16; 95% CI 3.92-6.80). Interestingly, 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). The review was very well reported and the results suggest that there may be a specific eczema plus asthma phenotype which is distinct from other forms of asthma.

The other systematic review by van den Oord and Sheikh (2009) (Link to full text) is quite similar, but it also includes data on allergic rhinitis and allergic sensitization as well as eczema and asthma. The review has been nicely summarized by the Database of Abstracts of Reviews of Effects or DARE (Link to DARE abstract). Like the Rodríguez *et al*. review, van den Oord and Sheikh did not find an 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) based on two case-control studies. Combined filaggrin gene defects increased risk of allergic sensitization, but the associations were not so strong, with and odds ratio of 1.57 (95% CI 1.20-2.07) based on two case-control studies and an odds ratio of 1.91 (95% CI 1.44-2.54) in five family studies, with results differing considerably between 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 those people with hay fever and asthma without eczema are studied, the association becomes even weaker or disappears.

The third systematic review dealing with eczema aetiology was something out of the ordinary, in that it explored the association between alexithymia and various skin disorders. Don't worry, we had to look up alexithymia too—it refers to people who have difficulty in experiencing, describing and expressing emotional responses. The review by Willemsen *et al*. (2008) (Link to PubMed abstract) gives a lot of background about the definition and measurement of alexithymia and how it may be associated with other diseases. The authors then go on to describe studies that have explored the possible association between alexithymia and various skin diseases. Although the authors tentatively conclude that preliminary data suggest that alexithymia is associated with atopic dermatitis, more detailed reading of the text reveals that this assertion is based on only one study in 1982 of three atopic dermatitis patients, one patient with nodular prurigo and one with excoriated acne, and six controls tested in a sleep laboratory. The most alexithymic characteristics were found in the three atopic patients, who had less time in rapid eye movement (REM) sleep and fewer movements during REM sleep. It was unclear to us what REM sleep has to do with alexithymia. It was also unclear whether alexithmia is a primary trait of atopic dermatitis or whether it is secondary to an uncomfortable, itchy skin disease. Apart from knowing a bit more about alexithymia, we were not impressed at the possible association with eczema, and we were left feeling a bit alexithymic about this review...

Prevention - breastfeeding

Preventing children from developing eczema continues to be debated in the literature. Last year, we reported a review of the effects of breastfeeding on maternal and infant health outcomes, carried out by Ip *et al*. (2007) for the US Agency of Healthcare Research and Quality (Link to full text (PDF file). That review was very large and looked at many health outcomes in both parents and children. The authors concluded that breastfeeding does not seem to prevent children of atopic parents from developing eczema.

This year, we found a systematic review by Yang *et al*. (2009) (Link to PubMed abstract) that focuses on whether breastfeeding protects children from developing eczema. The authors noted that a previous systematic review of breastfeeding and eczema carried out in 2001 by Gdalevich *et al*. [1]

had concluded that breastfeeding is protective against incident eczema in childhood, especially in families with a history of atopy. Yang *et al*. were keen to re-examine the evidence, given that several large birth cohort studies had been published since the 2001 review.
Yang *et al*. identified 21 English language prospective cohort studies studies involving 27 study populations, totalling 34,227 participants, mostly in developed countries. Mean duration of follow-up was 2.2 years. The studies compared exclusive breastfeeding for at least 3 months with either partial breastfeeding (15 studies) or formula feeding (6 studies). Onset of eczema was assessed by a doctor in only 14 studies; the other studies used self-reported symptoms or assessment by a health visitor. Importantly, no uniform diagnostic criteria were used to assess the onset of eczema and many studies used, in the opinion of the reviewers, rather 'lax' criteria. Ten studies adjusted for two or more potential confounders, such as parental education, pet-keeping, parental smoking and gestational age.
Breastfeeding was found to be associated with a slightly decreased risk of eczema (OR 0.89), but the 95% confidence interval crossed the value of 1 (95% CI 0.76-1.04). Given that the studies were quite different from each other, Yang *et al*. carried out restricted analyses of certain subgroups. Exclusive breastfeeding was found to be significantly protective (just) against eczema when compared to formula feeding (OR 0.70; 95% CI 0.50-0.99), but when compared to partial breastfeeding, the significance was lost. When only families with a history of atopy were explored, exclusive breastfeeding was associated with a slightly decreased risk of eczema in families with a history of atopy (OR 0.78; 95% CI 0.58-1.05) compared to those without (OR 0.93; 95% CI 0.60-1.45), although both risk estimates were non-significant since the confidence intervals crossed one. This decrease in risk disappeared after adjustment for potential confounders (OR 0.96; 95% CI 0.78-1.20). Suggestion of a protective effect of breastfeeding was also associated with assessment of the eczema by a doctor, as opposed to self-reported symptoms (OR 0.78; 95% CI 0.61-0.99). One particular study [2], the methodology of which has caused some controversy, was noted to be an 'outlier'. Omitting data from this study gave an overall OR of 0.94 (95% CI 0.81-1.08), compared to 0.89 when it was included. The only statistically significant result found to this point, for exclusive breastfeeding versus formula feeding, became non-significant when this study was omitted (OR 0.84; 95% CI 0.64-1.09).
Yang *et al*. concluded that 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. They suggested that further studies are needed, with standardised 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). So, 'breast is best' in many ways, but not, on current evidence, for preventing eczema.
Another systematic review by Oddy and Rosales (2009) (Link to PubMed abstract) focused on the possible link between transforming growth factor-beta (TGF-beta) levels in mothers' breast milk and the risk of their children developing atopic disease. Only three of the 12 studies included in the review assessed the development of eczema. Two were cohort studies and the other was a randomised controlled trial (RCT) included in both of the systematic reviews of probiotics for prevention of eczema found in the 2008 Annual Evidence Update on Atopic Eczema. This RCT, by Rautava *et al*. [3], suggested that TGF-beta2 levels were increased in the breast milk of mothers taking probiotics, and this significantly reduced the risk of their children developing eczema (OR 0.32; 95% CI 0.12-0.85). However, one of the cohort studies, which allowed for potential confounders, showed no link between TGF levels and eczema risk (OR 1.07; 95% CI 0.56-2.00). Although the subject of breast milk composition and its effects on the child's immune system and risk of atopy is an interesting one, the relationship between TGF levels in breast milk and development of eczema is unclear at this stage.

Prevention - omega 3 and omega 6 oils, beneficial fish oils or snake oil?
Dietary supplementation to prevent or treat eczema seems to be a recurring theme in these Annual Evidence Updates (see the section on probiotics later). Omega 3 and omega 6 oils are essential fatty acids found in foods such as oily fish and have attracted much interest because their derivatives are involved in various inflammatory and immunological processes, including atopic diseases.
Anandan *et al*. (2009) (Link to PubMed abstract) systematically reviewed the effectiveness of omega 3 and omega 6 oils for the primary prevention of sensitization and development of allergic diseases, including eczema. The well-reported review included both completed and ongoing studies investigating the effectiveness of omega 3 and 6 oil supplements in individuals with a high risk of developing atopic disease. Six studies were included in the review; four assessed omega 3 supplements (679 participants in total) and two assessed omega 6 (259 participants in total—much smaller numbers than in some of the other reviews discussed so far. Eczema incidence, assessed by a doctor, was reported in five of the studies, in three studies on omega 3 and in both of the omega 6

studies. Meta-analysis of the data from these studies showed a non-significant increased risk of developing eczema after omega 3 supplementation (Relative risk [RR] 1.10; 95% CI 0.78–1.54) and a non-significant decreased risk after omega 6 supplementation (RR 0.80; 95% CI 0.56–1.16). The review also found no statistically significant effect of omega 3 on development of asthma, allergic rhinitis, food allergy or sensitization to common allergens.
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 - dietary exclusions
The 2008 Cochrane Review by Bath-Hextall *et al*. on dietary exclusions for the treatment of established atopic eczema (Link to full text) was included in last year's Annual Evidence Update, and has now been summarised in a journal version by Bath-Hextall *et al*. (2009) (Link to PubMed abstract). In case you missed last year's Annual Evidence Update, the Cochrane Review of nine randomised controlled trials involving a total of 421 participants found little evidence to support the use of various exclusion diets in unselected people with atopic eczema. This may be because trial participants were not allergic to those substances in the first place, but many studies were also small and so may have lacked power to detect significant differences between diets. In addition, many studies in the review were poorly reported or were of too short a duration.

Treatment – probiotics
Probiotics are live microorganisms that may confer a health benefit to people when administered in adequate quantities. Probiotics have been thought to have a potential role in treatment of eczema based on the observation that gut bacteria are different in those with and without eczema [4]. It is suggested that probiotics may reduce intestinal inflammation and permeability and subsequent antigen presentation in gut lymphoid tissue [5] or have beneficial effects on gut flora and immune responses [6].
In the 2008 Annual Evidence Update on Atopic Eczema we included a systematic review of probiotics for the prevention of paediatric atopic eczema by Lee *et al*. (2008) (Link to PubMed abstract) which included 13 randomised controlled studies of probiotics for treating people who already had atopic eczema. The quality of the studies in that review was generally poor and only very small differences in SCORAD were noted between groups. Moreover, the methodology of the review has been questioned, both in a letter to the journal editor [7] and in the DARE commentary (Link to DARE abstract). Since the paper by Lee *et al*. (2008), a Cochrane Review on the same topic by Boyle and colleagues has been published, appearing in the the *Cochrane Database of Systematic Reviews* in October 2008 (Link to full text), with a summary version in *Clinical and Experimental Allergy* in August 2009 (Link to PubMed abstract). We also found a further systematic review in this area by Michail *et al*. (2008) (Link to PubMed abstract), which included the same studies as the Cochrane Review, minus one.
In the Cochrane Review, Boyle and colleagues (Link to full text) identified 12 randomised controlled trials examining the efficacy of probiotics for treating eczema, with a total of 781 participants, all of whom were children. Eleven of the studies used *Lactobacillus* species, either alone or in combination with other probiotics. Randomisation and concealment of treatment allocation were not described in nearly two-thirds of the studies. Blinding was generally not reported clearly and intention-to-treat analysis of outcome data performed in less than half of the studies. In other words, the quality of reporting of studies was generally quite poor, raising doubts about the validity of the results from some of the included studies.
Meta-analysis of data from five of the trials showed a 0.9 point reduction in eczema symptoms (as measured by SCORAD Part C) after probiotic treatment compared with placebo, but this was not statistically significant: the 95% CI was -2.84 to 1.04, consistent with an increase in symptoms in some individuals. Quality of life (QOL) data were available for only two studies. These could not be combined, but the individual studies showed no significant difference in QOL between participants receiving probiotics or placebo. Data from four studies that reported the need for other eczema treatment could not be pooled, but again the individual studies showed no significant difference between probiotics and placebo. All of the studies reported investigator-rated eczema severity. Meta-analysis of data from seven trials which measured severity with the SCORAD scale showed no significant difference in investigator rated eczema severity between probiotic treatments and placebo. Pre-defined subgroup analysis by eczema severity or presence of atopy did not identify a specific population in which probiotic treatment was effective. There was marked heterogeneity between studies, although the pooled results of three studies that used the same probiotic strain (*Lactobacillus rhamnosus* strain GG) showed an overall increase in eczema severity. Pooled results for all other

Lactobacillus strains showed an overall decrease in eczema severity. No significant adverse events were reported in the studies included in the review. Boyle and colleagues concluded that there is no good evidence at present to support the use of probiotics to treat existing eczema, although the heterogeneity brought about by different probiotic strains could still be consistent with a benefit when specific strains are used.

The review by Michail and colleagues (Link to PubMed abstract) identified 11 randomised controlled trials of 678 children all of which were included in the Cochrane Review. The authors were able to obtain raw data, including SCORAD values, for 10 of the included studies (more than the Cochrane authors were able to obtain). Using a funnel plot technique [8], the authors did not detect any publication bias in the included studies, although the authors acknowledge that the small number of included studies will have given the test less power to detect any potential bias.

The authors reported a statistically significant difference favouring probiotics compared with placebo in reducing SCORAD (mean change from baseline -3.01; 95% CI -5.36, 0.66). However, they point out that the 3-point SCORAD reduction in favour of probiotics is probably of limited clinical significance. 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 [9] with the total SCORAD scores (A+B+C) from other studies. Subgroup analysis according to duration of probiotic therapy, type of probiotic strain and age of participants showed no significant differences between probiotic and placebo groups. Analysis according to baseline severity of eczema suggested that improvement in SCORAD for children with moderately severe disease was significantly greater than for those with only mild disease. There was a non-significant trend for probiotics to be more effective in IgE-sensitized children. Despite Michail and colleagues finding some statistically significant results in favour of probiotics, the magnitude of those benefits, if true, is very small and unlikely to be clinically useful.

In conclusion, neither of these systematic reviews provides any clear evidence of significant clinical benefit for probiotics in patients with established eczema. It will still be interesting to look for the results of further trials examining the effect of specific probiotic strains, but for the time being perhaps the Yakult can stay in the 'fridge as far as eczema is concerned!

Treatment – Topical calcineurin inhibitors

In the 2008 Annual Evidence Update on Atopic Eczema we found two systematic reviews on topical tacrolimus for eczema by Li *et al*. (2007) (No PubMed abstract) and Yan *et al*. (2008) (Link to PubMed abstract), neither of which added much to a previous review by Ashcroft and colleagues [10]. Last year we also found a Cochrane systematic review of pimecrolimus by Ashcroft *et al*. (2007) (Link to full text).

This year, our search found yet another systematic review on the use of topical calcineurin inhibitors in the treatment of atopic eczema, by El-Batawy *et al*. (2009) (Link to PubMed abstract). El-Batawy *et al*. evaluated 19 randomised controlled trials (10 for tacrolimus and 9 for pimecrolimus), involving 7,378 participants, which is less than the number of trials and participants included in the Cochrane Review of pimecrolimus alone. All of the trials of pimecrolimus in the review by El-Batawy and colleagues were the same as those included in the previous Cochrane Review, except one small trial involving 34 participants. The tacrolimus trials were all the same as those in the review by Ashcroft *et al*. [10], with the exception of one new vehicle-controlled trial and one with active comparators. Only trials reported in English, French or German were included in the El-Batawy review and the outcomes of interest were decided retrospectively, after all included trials had been selected, which raises the possibility of bias. However, the authors did go to the trouble of recalculating outcomes on an intention-to-treat basis if the trials had not reported the data in this way. As in the systematic reviews mentioned last year, many of the trials used placebo controls rather than active comparators, which are of little use for informing clinical practice since they do not compare the new treatment to existing standard therapy, i.e. topical corticosteroids.

As with the previous reviews, El-Batawy and colleagues concluded that, unsurprisingly, both tacrolimus and pimecrolimus were more effective than placebo. Pimecrolimus was found to be less effective than potent topical corticosteroids but there was evidence that it reduces the number of eczema flares and has a steroid-sparing effect. However, this does not add anything to what we already know 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. The authors claim in their conclusion that 'In contrast to [the review by Ashcroft *et al*.] we aimed to include RCTs on infants', but their included trials differ by only three, none of which were

on infants. Finally, this review did not address one of the most important outcomes: long-term safety. In conclusion, this new systematic review has not really provided any new useful information on topical calcineurin inhibitors.

Summary points

- History and allergy tests are not very reliable predictors of food allergy.
- Double blind placebo controlled food challenges to suspected foods, with assessment of eczematous reactions the following day, may be more accurate in identifying which patients would benefit from dietary modification but are difficult to organise and perform.
- There is a strong and consistent association between FLG mutations and development of eczema. The associations between FLG mutations and atopic sensitization, rhinitis and asthma are weaker than eczema, especially if those who also have eczema are removed.
- We are unconvinced of a possible association between alexithymia and eczema.
- 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 is probably unlikely to play an important a 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 atopic eczema. The same applies to few foods or elemental diets. An egg-free diet may be helpful in those who are sensitised to egg.
- There is still little evidence to suggest a clinically useful benefit from using probiotics in patients with established eczema.
- One systematic review evaluating topical calcineurin inhibitors for eczema looks at more or less the same trials and comes to almost exactly the same conclusions as previous systematic reviews.
- There are no new systematic review data available regarding the long-term safety of topical calcineurin inhibitors for eczema.

Acknowledgement
We would like to thank Dr Bob Boyle for his insightful comments on the systematic reviews of probiotics in eczema, and Dr Douglas Grindlay for carrying out the searches and editing the text.

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2009 Annual Evidence Update on Atopic Eczema - DUETs uncertainties update

UK DUETs uncertainties update
Dr Douglas Grindlay, Information Specialist, NHS Evidence - skin disorders

Introduction

NHS Evidence – skin disorders is involved in collecting and collating uncertainties about the effects of treatments for skin disorders, to be added to the UK Database of Uncertainties about the Effects of Treatments (DUETs).
DUETs has been established to publish treatment uncertainties that cannot currently be answered reliably by referring to up-to-date systematic reviews of existing research evidence. These uncertainties can then be used to inform future research.
DUETs draws on three main sources to identify uncertainties about the effects of treatments:

- Patients', carers' and clinicians' questions about the effects of treatments;
- Research recommendations in reports of systematic reviews and clinical guidelines;
- Ongoing research, both systematic reviews in preparation and new 'primary' studies.

Please note that DUETs is a work in process. If you have identified any uncertainties on atopic eczema treatments or other skin disorders—clinical questions that are not answered by existing systematic reviews—then do please let us know. You can contact us via our DUETs feedback form.
This DUETs uncertainties update discusses the implications of the new systematic reviews found in the 2009 Annual Evidence Update on Atopic Eczema for the collection of uncertainties about atopic eczema that has already been added to UK DUETs.
Please click here to view the updated UK DUETs module on atopic eczema.

Update on treatment uncertainties on atopic eczema

DUETs uncertainty: Probiotics for treating established atopic eczema
The 2008 Annual Evidence Update on Atopic Eczema included a systematic review by Lee *et al.* (2008) on probiotics for prevention and treatment of paediatric atopic eczema (Link to PubMed abstract) which concluded “meta-analyses of 6 prevention and 4 treatment clinical trials indicate that current evidence favors the use of probiotics for prevention but not for treatment.” However, there were several methodological deficiencies with this review, as pointed out by a subsequent letter to the editor of the journal (Link to PubMed abstract) and the recent DARE abstract (Link to full text).

Now, in the 2009 Annual Evidence Update on Atopic Eczema, we have found two more systematic reviews on the use of probiotics to treat established atopic eczema. The Cochrane Review by Boyle *et al.* published in October 2008 (Link to full text) concluded:
"The data suggest that probiotics are not an effective treatment for eczema symptoms and are not effective at overall control of eczema. This conclusion is based on analysis of small numbers of participants, and a significant benefit cannot be confidently excluded. However analysis of composite severity score (SCORAD) data suggests that any reduction in eczema severity from probiotic treatment is likely to be modest (less than 7.45 points on the total SCORAD score) and therefore unlikely to be clinically significant."
Boyle *et al.* (2008) recommended that further research was needed, stating:
"Further probiotic eczema treatment studies would help to clarify whether specific probiotic strains have a greater effect on eczema severity and symptoms than the strains studied to date, and might evaluate their efficacy in adolescent/adult populations."
The second new systematic review by Michail *et al.* was published in November 2008 (Link to PubMed abstract). This systematic review concluded:
"Data from this meta-analysis suggest a modest role for probiotics in pediatric AD [atopic eczema]. The effect is seen in moderately severe rather than mild disease."
However, the differences reported by Michail *et al.* (2008) would be of very limited clinical significance, and derive from a different interpretation of some of the data than in the Cochrane Review.
Conclusion: While the Cochrane Review suggests that on existing evidence probiotics are not an effective treatment for established atopic eczema, the need to investigate the effects of specific probiotic strains and the differing conclusions of the other two reviews suggest that there is still sufficient uncertainty to support the retention of probiotics for treating established atopic eczema as an uncertainty in DUETS.

DUETs uncertainty: Are topical tacrolimus and pimecrolimus for atopic eczema safe or can they cause lymphoma or skin cancer?
DUETs uncertainty: Long-term safety of pimecrolimus and tacrolimus for atopic eczema
A new systematic review by El-Batawy *et al.* (2009) (Link to PubMed abstract) reviewed topical calcineurin inhibitors in atopic eczema but did not consider the side effects and safety of these drugs as an outcome, and in fact excluded studies reporting safety outcomes only.
Conclusion: Pimecrolimus and tacrolimus have not been used for long enough to gauge their long-term safety, so this remains an uncertainty.

DUETs uncertainty: Topical pimecrolimus compared to mild corticosteroids for atopic eczema
This uncertainty was highlighted in the Cochrane Review on topical pimecrolimus for eczema by Ashcroft *et al.* (2007) (Link to full text). The new systematic review by El-Batawy *et al.* (2009) (Link to PubMed abstract) found no studies comparing topical pimecrolimus with mild corticosteroids (such as 1% hydrocortisone) used alone.
Conclusion: The efficacy of topical pimecrolimus compared to mild corticosteroids for atopic eczema remains an uncertainty.

DUETs uncertainty: Will breast feeding reduce the chances of a baby developing atopic eczema?
DUETs uncertainty: Exclusive breast-feeding for preventing atopic eczema in infants at high risk for the development of atopy
A new systematic review and meta-analysis by Yang *et al.* (2009) (Link to PubMed abstract) reported:
"This meta-analysis found no strong evidence suggesting that exclusive breastfeeding for at least 3 months was associated with a decreased risk of AD [atopic dermatitis]" and "We did not find a significant protective effect of breastfeeding in the study population with a positive family history of atopy."
However, Yang *et al.* pointed out various deficiencies in the available evidence, including significant variability in design and reporting between observational studies that addressed the association between breastfeeding and atopic eczema. They concluded:
"More studies with standardized and deliberate methodology or a pooling project might be required for further systematic review."
Conclusion: In the light of the variation in existing studies and the recommendation that further studies of improved and standardised design are needed, the role of breast-feeding in preventing atopic eczema remains an uncertainty.

New DUETs uncertainty: Omega 3 and omega 6 fatty acids for prevention of atopic eczema

This uncertainty does not appear to have been addressed by previous systematic reviews, and so has not up to now been added to DUETs as an uncertainty. A new systematic review by Anandan *et al.* (2009) on omega 3 and 6 oils for primary prevention of allergic disease (Link to PubMed abstract) concluded:

"Contrary to the evidence from basic science and epidemiological studies, our systematic review and meta-analysis suggests that supplementation with omega 3 and omega 6 oils is probably unlikely to play an important role as a strategy for the primary prevention of sensitization or allergic disease."

The pooled data for risk of developing atopic eczema showed non-significant effects on relative risk compared to placebo for both omega 3 and omega 6 oils. However, the number of studies was small (three for omega 3 and two for omega 6 fatty acids) and the 95% confidence intervals for the pooled relative risk values were quite large.

Anandan *et al.* recommended:

"Future trials should seek to build on the findings of this systematic review and meta-analysis and in so doing ensure that they study the impact of these interventions on mechanistic, clinical and health services endpoints."

Conclusion: There is sufficient uncertainty about the preventive effect of omega 3 and omega 6 fatty acids for atopic eczema to add these as an uncertainty to the DUETs database.

Systematic reviews on atopic eczema - INDEX PAGE

This is the index page for a **mapping by topic of systematic reviews on atopic eczema** published from 2000 onwards (the date of the HTA monograph *Systematic review of treatments for atopic eczema*).

The systematic reviews are those found in the searches for the Skin Disorders Specialist Library's Annual Evidence Updates on Atopic eczema for 2007, 2008, 2009 and 2010.

Index of main topic headings:

- **Systematic reviews on atopic eczema - Epidemiology**
- This is a mapping by topic of **systematic reviews on the epidemiology of atopic eczema** that have been published from 2000 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Atopic Eczema. The links given are to the PubMed abstract or free full text where available.
- Please see also the full version of the 2007 NICE Clinical Guideline "Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years". This includes a systematic review of the diagnosis (Chapter 3), assessment of severity, psychological and psychosocial wellbeing and quality of life (Chapter 4), epidemiology (Chapter 5) and identification and management of trigger factors (Chapter 6) in atopic eczema in this age group.
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Aetiology	2009	Meta-analysis of genome-wide linkage studies of atopic dermatitis
	2009	Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systemati review and meta-analysis
	2009	Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disea
	2007	Toward a major risk factor for atopic eczema: meta-analysis of filaggrin polymorphism data
	2005	Atopic dermatitis and the 'hygiene hypothesis': too clean to be true?
	2004	How atopic is atopic dermatitis?
Risk factors	2010	Is there a rural/urban gradient in the prevalence of eczema? A systematic review
	2008	Caesarean delivery and risk of atopy and allergic disease: meta-analyses
	2008	A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis
	2006	What causes worsening of eczema? A systematic review
	2004	No epidemiological evidence for infant vaccinations to cause allergic disease
Co-morbidities	2010	Allergy and risk of glioma: a meta-analysis
	2010	Association between allergies and multiple sclerosis: a systematic review and meta-analysis
	2010	Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review
	2010	The association between atopy and childhood/adolescent leukemia: a meta-analysis
	2008	Alexithymia and dermatology: the state of the art
	2007	Atopy and risk of brain tumors: a meta-analysis

	2007	Risk of developing asthma in young children with atopic eczema: A systematic review
Diagnosis	2008	Diagnostic criteria for atopic dermatitis: a systematic review
	2006	What is meant by a "flare" in atopic dermatitis? A systematic review and proposal
Severity & outcome measures	2007	What are the best outcome measurements for atopic eczema? A systematic review
	2003	Measuring atopic dermatitis severity in randomized controlled clinical trials: what exactly are we measuring?
	2000	Outcome measures of disease severity in atopic eczema
Disease impact	2008	The socioeconomic impact of atopic dermatitis in the United States: a systematic review
	2008	Sleep disruptions in parents of children and adolescents with chronic illnesses: prevalence, causes and consequences
	2008	A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis
	2003	Treatment of atopic dermatitis and impact on quality of life: a review with emphasis on topical non corticosteroids

- **Systematic reviews on atopic eczema - Prevention**
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- This is a mapping by topic of **systematic reviews on the prevention of atopic eczema** that have been published from 2000 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Atopic Eczema. The links given are to the PubMed abstract or free full text where available.
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Maternal dietary exclusions	2010	Diagnosing and managing common food allergies: a systematic review
	2010	Prevalence, natural history, diagnosis, and treatment of food allergy: a systematic review of the evidence
	2008	Systematic review and evidence-based consensus guideline on prevention of allergy and atopic eczema of the German Network on Allergy Prevention (ABAP)
	2006	Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treati atopic disease in the child *(Cochrane Review)*
	2000	Systematic review of treatments for atopic eczema
Breastfeeding	2010	Diagnosing and managing common food allergies: a systematic review
	2010	Prevalence, natural history, diagnosis, and treatment of food allergy: a systematic review of the evidence
	2009	Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies
	2009	The long-term effects of breastfeeding on asthma and atopic disease
	2009	A systematic review of the importance of milk TGF-beta on immunological outcomes in the infant and young child
	2008	Systematic review and evidence-based consensus guideline on prevention of allergy and atopic eczema of the German Network on Allergy Prevention (ABAP)
	2007	Breastfeeding and maternal and infant health outcomes in developed countries
	2004	The optimal duration of exclusive breastfeeding: a systematic review
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2002	Optimal duration of exclusive breastfeeding *(Cochrane Review)*
	2001	Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies
Formulas	2010	Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis
	2010	Partially hydrolyzed 100% whey protein infant formula and atopic dermatitis risk reduction: a systematic review of the literature
	2010	Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases
	2008	Systematic review and evidence-based consensus guideline on prevention of allergy and atopic eczema of the German Network on Allergy Prevention (ABAP)
	2007	The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review
	2006	Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants *(Cochrane Review)*

	2006	Soy formula for prevention of allergy and food intolerance in infants *(Cochrane Review)*
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
Weaning	2008	Systematic review and evidence-based consensus guideline on prevention of allergy and atopic eczema of the German Network on Allergy Prevention (ABAP)
	2006	Systematic review of the relationship between early introduction of solid foods to infants and the development of allergic disease
	2004	The optimal duration of exclusive breastfeeding: a systematic review
	2002	Optimal duration of exclusive breastfeeding *(Cochrane Review)*
Diet	2010	Diagnosing and managing common food allergies: a systematic review
	2010	Prevalence, natural history, diagnosis, and treatment of food allergy: a systematic review of the evidence
	2010	Nutrition-related health effects of organic foods: a systematic review
	2010	Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omeg 3 fatty acids: a systematic review
	2009	Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysi
	2008	Systematic review and evidence-based consensus guideline on prevention of allergy and atopic eczema of the German Network on Allergy Prevention (ABAP)
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
Probiotics	2008	Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis
	2007	Probiotics in infants for prevention of allergic disease and food hypersensitivity *(Cochrane Revie*
	2005	Probiotics for atopic diseases
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
Prebiotics	2007	Prebiotics in infants for prevention of allergic disease and food hypersensitivity *(Cochrane Revie*
Pets	2008	Systematic review and evidence-based consensus guideline on prevention of allergy and atopic eczema of the German Network on Allergy Prevention (ABAP)
	2007	The role of furry pets in eczema: a systematic review
Avoidance of other aeroallergens	2008	Systematic review and evidence-based consensus guideline on prevention of allergy and atopic eczema of the German Network on Allergy Prevention (ABAP)
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report

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- **Systematic reviews on atopic eczema - Topical treatments**
- This is a mapping by topic of **systematic reviews on topical treatments for atopic eczema** that have been published from 2000 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Atopic Eczema. The links given are to the PubMed abstract or free full text where available.
- Please see also the full version of the 2007 NICE Clinical Guideline "Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years". This includes a systematic review of emollients (Section 7.1), topical corticosteroids (Section 7.2), topical calcineurin inhibitors (Section 7.3), dry bandages and medicated dressings, including wet wrap therapy (Section 7.4), antihistamines and other pruritics (Section 7.5) and treatment for associated infections (Section 7.6) in atopic eczema in this age group.
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Emollients	2009	Should we use bath emollients for atopic eczema?
	2007	A systematic review of the safety of topical therapies for atopic dermatitis
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Occlusive therapies	2010	Occlusive therapy in atopic dermatitis: overview
	2006	Efficacy and safety of 'wet-wrap' dressings as an intervention treatment in children with severe and/or refractory atopic dermatitis: a critical review of the literature
Topical corticosteroids	2007	Established corticosteroid creams should be applied only once daily in patients with atopic eczema
	2007	A systematic review of the safety of topical therapies for atopic dermatitis
	2005	Topical corticosteroids for atopic eczema: clinical and cost effectiveness of once-daily vs. more

		frequent use
	2004	Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation
	2003	Eumovate (clobetasone butyrate 0.05%) cream: A review of clinical efficacy and safety
	2003	Treatment of atopic dermatitis and impact on quality of life: a review with emphasis on topical non corticosteroids
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Coal tar	2007	A systematic review of the safety of topical therapies for atopic dermatitis
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Topical doxepin	2007	A systematic review of the safety of topical therapies for atopic dermatitis
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Pimecrolimus	2010	Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: a met analysis of randomized clinical trials
	2009	Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis
	2007	Topical pimecrolimus for eczema *(Cochrane Review)*
	2007	A systematic review of the safety of topical therapies for atopic dermatitis
	2006	Review of pimecrolimus cream 1% for the treatment of mild to moderate atopic dermatitis
	2005	Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatiti meta-analysis of randomised controlled trials
	2005	The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation
	2004	Topical calcineurin inhibitors in the treatment of atopic dermatitis: a meta-analysis of current evidence
	2003	Treatment of atopic dermatitis and impact on quality of life: a review with emphasis on topical non corticosteroids
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Tacrolimus	2010	Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: a met analysis of randomized clinical trials
	2010	An approach to pruritus in atopic dermatitis: a critical systematic review of the tacrolimus ointmen literature
	2009	Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis
	2008	Meta-analysis of tacrolimus ointment for atopic dermatitis in pediatric patients
	2007	A systematic review of the safety of topical therapies for atopic dermatitis
	2007	Efficacy and tolerability of topical tacrolimus in the treatment of atopic dermatitis: a systematic review of randomized controlled trials (Li *et al.*, *Journal of Clinical Dermatology* 2007; 36: 757-60)
	2005	Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatiti meta-analysis of randomised controlled trials
	2005	The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation
	2004	Topical calcineurin inhibitors in the treatment of atopic dermatitis: a meta-analysis of current evidence
	2003	Treatment of atopic dermatitis and impact on quality of life: a review with emphasis on topical non corticosteroids
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Cipamfylline cream	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
Topical ciclisporin	2000	Systematic review of treatments for atopic eczema
Lithium succinate ointment	2000	Systematic review of treatments for atopic eczema
Topical disodium cromoglycate	2000	Systematic review of treatments for atopic eczema
Nedocromil sodium cream	2000	Systematic review of treatments for atopic eczema
Topical tiacrilast	2000	Systematic review of treatments for atopic eczema

Platelet-activating factor antagonist	2000	Systematic review of treatments for atopic eczema
Salbutamol ointment	2000	Systematic review of treatments for atopic eczema
Topical antibiotics & antiseptics	2010	Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane review
	2008	Interventions to reduce Staphylococcus aureus in the management of atopic eczema *(Cochrane Review)*
	2007	A systematic review of the safety of topical therapies for atopic dermatitis
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Topical antibiotic-corticosteroid combinations	2010	Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane review
	2008	Interventions to reduce Staphylococcus aureus in the management of atopic eczema *(Cochrane Review)*
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
Antibacterial bath additives	2010	Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane review
	2008	Interventions to reduce Staphylococcus aureus in the management of atopic eczema *(Cochrane Review)*
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Silver textiles	2010	Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane review
	2008	Interventions to reduce Staphylococcus aureus in the management of atopic eczema *(Cochrane Review)*

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- **Systematic reviews on atopic eczema - Systemic treatments**
- This is a mapping by topic of **systematic reviews on systemic treatments for atopic eczema** that have been published from 2000 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Atopic Eczema. The links given are to the PubMed abstract or free full text where available.
- Please see also the full version of the 2007 NICE Clinical Guideline "Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years". This includes a systematic review of antihistamines and other pruritics (Section 7.5), treatment for associated infections (Section 7.6), and other systemic treatments (Section 7.8) in atopic eczema in this age group.
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Oral ciclosporin	2007	Cyclosporin in the treatment of patients with atopic eczema - a systematic review and meta-analys
	2007	Systemic treatment of severe atopic eczema: a systematic review
	2003	Treatment of atopic dermatitis and impact on quality of life: a review with emphasis on topical non corticosteroids
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Oral antihistamines	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Azathioprine	2007	Systemic treatment of severe atopic eczema: a systematic review
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
Methotrexate	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
Mycophenolate mofetile	2007	Systemic treatment of severe atopic eczema: a systematic review
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
Interferon-	2007	Systemic treatment of severe atopic eczema: a systematic review

gamma		
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Intravenous immunoglobulin	2007	Systemic treatment of severe atopic eczema: a systematic review
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Systemic corticosteroids	2007	Systemic treatment of severe atopic eczema: a systematic review
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
TNF inhibitors	2007	Systemic treatment of severe atopic eczema: a systematic review
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
Leukotriene inhibitors	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
Oral sodium cromoglycate	2000	Systematic review of treatments for atopic eczema
Oral nedocromil sodium	2000	Systematic review of treatments for atopic eczema
Ketotifen	2000	Systematic review of treatments for atopic eczema
Levamisole	2000	Systematic review of treatments for atopic eczema
Thymic extracts and derivatives	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Nitrazepan	2000	Systematic review of treatments for atopic eczema
Ranitidine	2000	Systematic review of treatments for atopic eczema
Theophylline	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Oral salbutamol	2000	Systematic review of treatments for atopic eczema
Oral papaverine	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Oral suplatast tosilate	2000	Systematic review of treatments for atopic eczema
Desensitisation therapy	2006	Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis?
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Allergen–antibody complexes of house dust mite	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Oral antibiotics	2010	Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane review
	2008	Interventions to reduce Staphylococcus aureus in the management of atopic eczema *(Cochrane Review)*
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema

Systematic reviews on atopic eczema - Phototherapy

This is a mapping by topic of **systematic reviews on phototherapy for atopic eczema** that have been published from 2000 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Atopic Eczema. The links given are to the PubMed abstract or free full text where available.

Please see also the full version of the 2007 NICE Clinical Guideline "Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years". This includes a systematic review of phototherapy in atopic eczema in this age group (Section 7.8).

Broadband UVA	2007	Phototherapy in the management of atopic dermatitis: a systematic review

	2000	Systematic review of treatments for atopic eczema
UVA1	2007	Phototherapy in the management of atopic dermatitis: a systematic review
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
Combined UVAB	2007	Phototherapy in the management of atopic dermatitis: a systematic review
	2003	Treatment of atopic dermatitis and impact on quality of life: a review with emphasis on topical non corticosteroids
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Narrowband UVB	2007	Phototherapy in the management of atopic dermatitis: a systematic review
	2005	Narrowband UVB phototherapy in skin conditions beyond psoriasis
	2003	Treatment of atopic dermatitis and impact on quality of life: a review with emphasis on topical non corticosteroids
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
PUVA	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report

Systematic reviews on atopic eczema - Dietary treatments for established eczema

This is a mapping by topic of **systematic reviews on dietary treatments for established atopic eczema** that have been published from 2000 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Atopic Eczema. The links given are to the PubMed abstract or free full text where available.

Please see also the full version of the 2007 NICE Clinical Guideline "Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years". This includes a systematic review of management of trigger factors, including dietary exclusions and modifications, in atopic eczema in this age group (Section 6.3).

Probiotics	2009	Probiotics for the treatment of eczema: a systematic review
	2008	Efficacy of probiotics in the treatment of pediatric atopic dermatitis: a meta-analysis of randomized controlled trials
	2008	Probiotics for treating eczema (Cochrane Review)
	2008	Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis
Dietary supplements	2004	Oral essential fatty acid supplementation in atopic dermatitis-a meta-analysis of placebo-controlled trials
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Dietary restrictions	2010	Diagnosing and managing common food allergies: a systematic review
	2010	Prevalence, natural history, diagnosis, and treatment of food allergy: a systematic review of the evidence
	2009	Dietary exclusions for improving established atopic eczema in adults and children: systematic revie
	2008	Dietary exclusions for established atopic eczema (Cochrane Review)
	2006	What causes worsening of eczema? A systematic review
	2004	Dietary treatment of childhood atopic eczema/dermatitis syndrome (AEDS)
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema

- **Systematic reviews on atopic eczema - Psychological and educational interventions**
- This is a mapping by topic of **systematic reviews on psychological and educational interventions for atopic eczema** that have been published from 2000 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Atopic Eczema. The links given are to the PubMed abstract or free full text where available.

- Please see also the full version of the 2007 NICE Clinical Guideline "Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years". This includes a systematic review of behavioural therapies (Section 7.10), education (Section 8.1) and adherence to therapy (Section 8.2) in atopic eczema in this age group.

Psychological interventions	2007	Psychological and educational interventions for atopic eczema in children *(Cochrane Review)*
	2007	The effects of psychological intervention on atopic dermatitis. A systematic review and meta-analy
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Educational interventions	2007	Psychological and educational interventions for atopic eczema in children *(Cochrane Review)*
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Nurse-led clinics	2006	Nurse-led clinics reduce severity of childhood atopic eczema: a review of the literature

- **Systematic reviews on atopic eczema - Complementary and alternative therapies**
- This is a mapping by topic of **systematic reviews on complementary and alternative therapies for atopic eczema** that have been published from 2000 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Atopic Eczema. The links given are to the PubMed abstract or free full text where available.
- Please see also the full version of the 2007 NICE Clinical Guideline "Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years". This includes a systematic review of complementary therapies in atopic eczema in this age group (Section 7.9).
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Chinese herbal medicine	2007	Systemic treatment of severe atopic eczema: a systematic review
	2005	Chinese herbal medicine for atopic eczema *(Cochrane Review)*
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Evening primrose oil	2006	A meta-analysis of randomized, placebo-controlled clinical trials of Efamol evening primrose oil in atopic eczema. Where do we go from here in light of more recent discoveries?
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Borage oil	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Homeopathy	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Massage	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Hypnotherapy & biofeedback	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2002	Complementary/alternative medicine in dermatology: evidence-assessed efficacy of two diseases and two treatments
	2000	Systematic review of treatments for atopic eczema
Bioresonance	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema

Systematic reviews on atopic eczema - Other interventions for established eczema

This is a mapping by topic of **systematic reviews on other (mainly physical) interventions for established atopic eczema** that have been published from 2000 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Atopic Eczema. The links given are to the PubMed abstract or free full text where available.

Please see also the full version of the 2007 NICE Clinical Guideline "Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years". This includes a systematic review of management of trigger factors in atopic eczema in this age group (Section 6.3).

House dust mite reduction	2006	What causes worsening of eczema? A systematic review
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Pet removal	2007	The role of furry pets in eczema: a systematic review
Avoidance of other aeroallergens	2006	What causes worsening of eczema? A systematic review
Avoidance of detergent enzymes	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema
Water softeners	2000	Systematic review of treatments for atopic eczema
Specialised clothing	2010	Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane review
	2009	A case report and critical appraisal of the literature on the use of DermaSilk in children with atopic dermatitis
	2008	Interventions to reduce Staphylococcus aureus in the management of atopic eczema *(Cochrane Review)*
	2003	AAD Guidelines of Care for Atopic Dermatitis: Technical Report
	2000	Systematic review of treatments for atopic eczema

Link to National Eczema Week (National Eczema Society)

2009 Annual Evidence Update on Atopic Eczema - Methodology

A literature search was carried out to identify new guidelines and systematic reviews relating to atopic eczema (atopic dermatitis) that have been published or indexed since the 2008 Annual Evidence Update on Atopic Eczema. The results are the **2009 Annual Evidence Update on Atopic Eczema** from NHS Evidence - skin disorders.
This webpage describes the search strategies used and the criteria for inclusion in the Annual Evidence Update.

Search period

The search for the 2009 Annual Evidence Update on Atopic Eczema was for citations published or indexed in 2008 or 2009 and not included in the 2008 Annual Evidence Update.
January 2008 was set as the limit for earliest publication date in most of the searches, to allow for any delays in indexing of citations in the bibliographic databases used (which might mean the citations were not found in the searches for the previous Annual Evidence Update in August 2008).
In the case of PubMed, the search was refined by searching for records *indexed* in the PubMed database in 2008 and 2009 (using the "edat" command), which would find any citations published before 2008 but indexed late and hence not found in last year's search.
All the searches were carried out for the last time on 18th August, 2009.

Sources Searched

The following sources were searched:
Ovid MEDLINE (using SIGN MEDLINE systematic review filter)
Ovid EMBASE (using SIGN EMBASE systematic review filter)
PubMed (using PubMed Clinical Queries systematic review filter)

Cochrane Library
NHS Evidence - skin disorders

The search of PubMed was carried out as an insurance to ensure that no systematic reviews were missed using MEDLINE and EMBASE, especially as PubMed tends to be more up to date than and so is better for finding new citations.
The search of the Cochrane Library was also carried out as an insurance, to find relevant citations in the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment Database. The intention was to confirm that nothing of relevance was missed in the searches of MEDLINE, EMBASE and PubMed.
The search of NHS Evidence - skin disorders was to find new guidelines and also gave a confirmatory search for new Cochrane Reviews and DARE abstracts.

Systematic review filters
The SIGN systematic review filters developed for Ovid implementations of MEDLINE and EMBASE were used as they provide a reasonable balance between specificity and sensitivity. Details of the SIGN systematic review filters can be found on the following webpage:
http://www.sign.ac.uk/methodology/filters.html

Details of the PubMed Clinical Queries systematic review filter and its validation can be found via the following links:
http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html
http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_sources.html

Search Strategies

The search terms were chosen to find citatations that used either "atopic eczema", "atopic dermatitis" or "neurodermatitis" as the disease name.

SIGN MEDLINE systematic review filter
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations & Ovid MEDLINE
1. Meta-Analysis/
2. meta analy$.tw.
3. metaanaly$.tw.
4. meta analysis.pt.
5. (systematic adj (review$1 or overview$1)).tw.
6. exp Review Literature/
7. or/1-6
8. cochrane.ab.
9. embase.ab.
10. (psychlit or psyclit).ab.
11. (psychinfo or psycinfo).ab.
12. (cinahl or cinhal).ab.
13. science citation index.ab.
14. bids.ab.
15. cancerlit.ab.
16. or/8-15
17. reference list$.ab.
18. bibliograph$.ab.
19. hand-search$.ab.
20. relevant journals.ab.
21. manual search$.ab.
22. or/17-21
23. selection criteria.ab.
24. data extraction.ab.
25. 23 or 24
26. review.pt.
27. 25 and 26

28. comment.pt.
29. letter.pt.
30. editorial.pt.
31. animal/
32. human/
33. 31 not (31 and 32)
34. or/28-30,33
35. 7 or 16 or 22 or 27
36. 35 not 34
37. atopic.mp. [mp=ti, ot, ab, nm, hw]
38. dermatitis.mp. [mp=ti, ot, ab, nm, hw]
39. 37 and 38
40. eczema.mp. [mp=ti, ot, ab, nm, hw]
41. neurodermatitis.mp. [mp=ti, ot, ab, nm, hw]
42. 39 or 40 or 41
43. 36 and 42
44. limit 43 to yr="2008 - 2009"

SIGN EMBASE systematic review filter
Ovid EMBASE
1. exp Meta Analysis/
2. ((meta adj analy$) or metaanalys$).tw.
3. (systematic adj (review$1 or overview$1)).tw.
4. or/1-3
5. cancerlit.ab.
6. cochrane.ab.
7. embase.ab.
8. (psychlit or psyclit).ab.
9. (psychinfo or psycinfo).ab.
10. (cinahl or cinhal).ab.
11. science citation index.ab.
12. bids.ab.
13. or/5-12
14. reference lists.ab.
15. bibliograph$.ab.
16. hand-search$.ab.
17. manual search$.ab.
18. relevant journals.ab.
19. or/14-18
20. data extraction.ab.
21. selection criteria.ab.
22. 20 or 21
23. review.pt.
24. 22 and 23
25. letter.pt.
26. editorial.pt.
27. animal/
28. human/
29. 27 not (27 and 28)
30. or/25-26,29
31. 4 or 13 or 19 or 24
32. 31 not 30
33. atopic.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
34. dermatitis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
35. 33 and 34
36. eczema.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
37. neurodermatitis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original

title, device manufacturer, drug manufacturer name]
38. 35 or 36 or 37
39. 38 and 32
40. limit 39 to yr="2008 - 2009"

PubMed using Clinical Queries systematic review filter
((eczema) OR (atopic AND dermatitis) OR (neurodermatitis)) AND 2008 : 2009[edat] AND systematic[sb]

Cochrane Library and NHS Evidence - skin disorders
eczema OR dermatitis OR neurodermatitis

Identification of systematic reviews

All citations found in the searches were hand searched by reading the titles and abstracts to identify systematic reviews and potential systematic reviews relevant to atopic eczema. A particularly careful analysis of the methods was made to identify citations with a systematic review methodology. For all potential systematic reviews where there was still some doubt, the full texts were then read to ensure that they were indeed systematic reviews.
To determine systematic reviews, the definition of a systematic review from the Glossary of Cochrane Collaboration Terms on the Cochrane Collaboration website was used:
“A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.”
The final decision on whether a citation was a systematic review and relevant to atopic eczema was made by Professor Hywel Williams, Clinical Lead for NHS Evidence - Skin Disorders and Co-ordinating Editor of the Cochrane Skin Group.