

Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema (Review)

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[Intervention review]

Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema

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ABSTRACT

Background

Staphylococcus aureus can cause secondary infection in atopic eczema, and it may promote inflammation in eczema that does not look infected. Many antimicrobial products exist for eczema, but it is unclear if they work or if they promote bacterial resistance.

Objectives

To assess the effects of interventions to reduce *Staphylococcus aureus* for treating infected or uninfected atopic eczema.

Search strategy

We searched the Cochrane Skin Group Specialised Register (March 2008), the Cochrane Central Register of Controlled Trials (*Cochrane Library* Issue 1, 2008), MEDLINE (OVID) (from 2002 to March 2008), EMBASE (OVID) (from 2002 to March 2008), Ongoing trials registers (March 2008). References from trials and reviews were searched, pharmaceutical companies were contacted for unpublished trials. There were no language restrictions.

Selection criteria

Randomised controlled trials (RCTs) of people with atopic eczema who have been treated with a product intended to reduce *S. aureus* on the skin.

Data collection and analysis

Two people independently performed the study selection, data abstraction and quality assessment.

Main results

We included 21 studies (1018 participants) covering 7 treatment categories. Most studies were poorly reported and study differences limited pooling of results. Adverse effects were especially poorly reported, and only one study reported the emergence of resistant bacterial strains following oral antibiotics. Oral antibiotics were not associated with benefit in non-infected (2 trials, 66 participants) or infected eczema (1 trial, 33 participants). We did not find any benefit for antibacterial soaps (1 trial, 50 participants), or antibacterial

bath additives (2 trials, 41 participants), or topical antibiotics/antiseptics (4 studies, 95 participants). Adding antibiotics to topical corticosteroids reduced numbers of *Staphylococcus aureus* in 4 trials (302 participants), but there was no evidence of any clinical benefit in 9 trials involving 677 participants: betamethasone plus neomycin vs clobetasol (MD 1.2; 95% CI 0.25, 2.15), prednicarbate plus antimicrobial vs prednicarbate (RR 0.64; 95% CI 0.25, 1.68), or betamethasone valerate plus gentamicin vs betamethasone (RR 0.31; 95% CI 0.07, 1.35). One trial (30 participants) showed no significant improvement in eczema for those using silver textiles (RR 2.67; 95% CI 0.98, 7.22), despite using 10 times the amount of topical steroids.

Authors' conclusions

We failed to find clear evidence of benefit for antimicrobial interventions for people with atopic eczema, despite their widespread use. This does not necessarily mean they do not work because the studies were small and poorly reported. Further large studies with long-term outcomes and clearly defined participants are urgently required.

PLAIN LANGUAGE SUMMARY

Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema

Atopic eczema (atopic dermatitis or childhood eczema) is a big problem worldwide. The skin of people with atopic eczema often contains high numbers of a bacterium called *Staphylococcus aureus* (*S. aureus*).

Sometimes *S. aureus* results in an obvious secondary infection. Even when the eczema does not look infected *S. aureus* may still play a part in promoting skin inflammation. As a result, lots of eczema treatments have been developed to reduce *S. aureus*, including antibiotics taken by mouth, washing with antibacterial soaps or antibiotics combined with other eczema treatments. We undertook a systematic review on this topic as it is not clear which treatments offer any clinical benefit and because there is some concern that their widespread use may promote bacterial resistance.

Our review included 21 randomised controlled trials involving 1018 participants covering a range of anti-staphylococcal treatments: oral antibiotics (3 trials), antibacterial soaps (1 trial), topical steroids combined with antibacterials (10 trials), antibacterial bath additives (2 trials), topical antiseptic/antibiotics creams (4 trials) and silver impregnated textiles (1 trial). Generally, the quality of the reported studies was poor, and many were too small to identify important differences even if they existed. None of the trials showed any clear benefit in terms of short-term eczema control for any of the interventions tested, although several interventions were associated with decreased numbers of *S. aureus* on the skin. There was no clear evidence that widely used topical steroid/antibiotic combinations were any better than the topical steroids used alone. Adverse effects like irritation were especially poorly reported and only one study reported on the emergence of resistant bacterial strains in the group treated with oral antibiotics. Only one small inconclusive study evaluated people with clinically infected eczema.

Care should be taken in interpreting the above studies as failure to show benefit in a series of small, poorly reported studies does not mean that the anti-staphylococcal interventions could not be helpful in eczema. It is clinical common sense to treat overtly infected eczema with oral antibiotics, and that practice should continue until good evidence suggests otherwise. However, given that none of the other studies showed clear clinical benefit for anti-staphylococcal interventions in non-infected eczema, their continued use should be questioned in such situations. More studies should be done to look at the long-term possible benefits and harms of such interventions in preventing flares of atopic eczema.

BACKGROUND

Description of the condition

Atopic eczema (syn: atopic dermatitis) is a chronic, relapsing, intensely itchy, inflammatory skin disease, which involves the skin creases such as the folds of the elbows or behind the knees (Williams 1994). Symptoms usually appear below the age of 2 years and around 60% of cases will be clear by early adolescence, although some will relapse or continue into adult life. The prevalence of atopic eczema varies considerably from one country to another, and also within countries (Williams 1999). In the UK there has been a steady increase in prevalence, and the condition now affects around 15% of schoolchildren (Kay 1994; Neame 1995; Emerson 1997) and 1 to 2% of adults.

The cause of atopic eczema is unknown but evidence suggests a role for both genetic and environmental factors in determining both the occurrence and the severity of disease (Williams 1992)

Staphylococcus aureus and atopic eczema

An association between *S. aureus* and atopic eczema has been recognized for many years. It has been demonstrated that *S. aureus* can be isolated from 90% of atopic eczema skin lesions (Leyden 1974) and the density of *S. aureus* tends to increase with the clinical severity (Williams 1990). In contrast, *S. aureus* is rarely found on healthy skin (<5%), and it is less common to have severe colonisation or infection in other skin diseases, so atopic eczema does appear to be a special case. However, whilst this association is well recognized, the role of *S. aureus* in causing atopic eczema or making it worse, as opposed to simply colonising the skin, is still under debate.

Clinically infected atopic eczema

At one end of the spectrum there is undoubtedly a clinical condition of 'infected atopic eczema' manifest by oozing, crusting and presence of pus spots overlying the areas of pre-existing eczema. This corresponds with heavy growth of bacteria in the laboratory on swabs taken from the affected areas, usually of *S. aureus*, but there are also reports of beta haemolytic streptococci being isolated either alone or in combination with *S. aureus*. In this situation

the overt infection responds to antibiotic treatment, although the atopic eczema itself may not. Clinical infection is a major problem for some atopic eczema sufferers (David 1986).

S. aureus and non-clinically infected atopic eczema: coloniser or pathogen?

In atopic eczema that is not overtly clinically infected, the role of *S. aureus* is much less clear. It may be that *S. aureus* simply colonises the skin, taking advantage of a favourable environment for growth. This is supported by the fact that treatment of the underlying atopic eczema with topical steroid alone drastically reduces the number of colonies of *S. aureus* (Stalder 1994).

However, several possible mechanisms for a pathogenic role have also been suggested. There may be a direct chemical irritation or a non-specific reaction of the protein A component of the bacterium with immune cells (White 1985). Great interest has been shown in possible mechanisms involving superantigens (McFadden 1993). The superantigen theory proposes that *S. aureus* exacerbates or maintains skin inflammation in atopic eczema by secreting a group of toxins, which are capable of stimulating large populations of T-lymphocytes distant from the eczematous site, giving rise to widespread activation of existing lesions. Several lines of investigation support a role for superantigens in atopic eczema (Leung 2000). First, it has been shown that such toxins can be produced by *S. aureus* isolated from atopic eczema patients, and that in these patients a T-lymphocyte expansion consistent with superantigen stimulation has occurred. Second, most atopic eczema sufferers make specific IgE antibodies directed against superantigen toxins found on their skin. Third, a correlation has been found between the presence of these antibodies and the severity of the eczema. Finally, the application of one specific superantigen to the skin has been shown to induce skin changes of erythema and thickening of the skin (Strange 1996).

Description of the intervention

As a consequence of such findings, it is not surprising that a number of products with anti-staphylococcal properties have been developed for the treatment of atopic eczema, both clinically infected and uninfected, ranging from antibacterial soaps, impregnated clothing, to additives to bath oils and topical corticosteroids.

Possible concern about anti-staphylococcal treatment in atopic eczema

Quite apart from the fundamental question of whether anti-staphylococcal therapies work in atopic eczema, there are special concerns about their routine use in non-clinically infected eczema. For the individual patient, irritant and allergic contact dermatitis can occur from topically applied antiseptics or antibiotic containing preparations. The potential for development of bacterial resistance to antibiotics, which may be needed for systemic treatment of serious infections in the community, is also important. A recent

increase in the prevalence of fusidic acid resistant *S. aureus* has been observed in several areas of the UK (Reed 1999; Ravenscroft 2000; Simpson-Dent 2000; Brown 2002). In Harrogate, UK fusidic acid resistance has been shown to be associated with intensive local use of oral and topical fusidic acid containing preparations such as those marketed for use in eczema (Ravenscroft 2000). Such widespread use may limit the use of fusidic acid combination therapies for the treatment of more serious diseases including staphylococcal bone and joint infections and systemic methicillin-resistant *S. aureus* (MRSA) infections.

Why it is important to do this review

There is a plausible theoretical rationale for use of anti-staphylococcal agents. Yet existing evidence to support clinical benefit of anti-staphylococcal agents appears to be conflicting. There are concerns regarding adverse event issues, e.g. contact and irritant dermatitis, and promoting wider drug resistance in the community. Despite these concerns, anti-staphylococcal products are widely marketed and used by the clinical community.

OBJECTIVES

To assess the effects of interventions to reduce *S. aureus* for treating atopic eczema.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, including cross-over trials and randomised within-patient trials.

Types of participants

Anyone who has been diagnosed with atopic eczema by a medical practitioner. We regarded diagnostic criteria such as the Hanifin and Rajka definition (Hanifin 1980) or the UK modification (Williams 1994) as acceptable, as was diagnosis of atopic eczema by a dermatologist using the terms 'atopic eczema' or 'atopic dermatitis'. We only accepted the term 'eczema' when referring to children. Any other terms, such as 'Besnier's Prurigo' or 'Neurodermatitis,' had to have additional descriptive evidence of atopic eczema in the flexures before inclusion. It was noted whether the participants were described as 'clinically infected' or otherwise.

Types of interventions

(1) Oral antibiotics known to be active against *staphylococcus*.

- (2) Antibacterial soaps
- (3) Topical steroid plus antibiotic and antifungal agent
- (4) Antibacterial bath additives
- (5) Topical antiseptic/antibiotic.
- (6) Combination of antibiotics or antiseptics with other drugs such as corticosteroids.
- (7) Silver impregnated textiles

We accepted as comparators no treatment, vehicle only, or another active compound, e.g. topical steroid/antibiotic combination compared against the same topical steroid without the antibiotic.

Types of outcome measures

Primary outcomes

- (a) Global degree of improvement in symptoms or signs, or both, as rated by the patient or medical practitioner, i.e. percentage with good or excellent improvement. We included both short-term (less than or equal to a month) improvement and long-term (more than one month) benefit.
- (b) Improvement in Quality of Life questionnaires.

Secondary outcomes

- (a) Severe adverse events, i.e. severe enough to require withdrawal of treatment, including severe skin irritation.
- (b) Minor patient reported adverse events. This included mild skin irritation not sufficient to require cessation of treatment.
- (c) Emergence of antibiotic resistant micro-organisms. Only *S. aureus* was considered, and we only included studies if swab data before and after the intervention was available. It was planned to take duration of treatment into account when these data were interpreted.

Tertiary outcome measures

- (a) Global changes in composite rating scales, using a published named scale.
- (b) Changes in the individual signs of atopic eczema as assessed by a physician, e.g. erythema (redness), papules (spots that protrude from the skin surface), vesicles (water blisters), scaling.
- (c) Duration of remission and/or prevention of subsequent flares.
- (d) Change in isolation rate of *S. aureus*, i.e. isolated or not isolated.
- (e) Change in bacterial counts of *S. aureus*, i.e. an assessment of quantity of *S. aureus*.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Skin Group's Specialised Register (March 2008) using the following strategy:

((atopic and dermatitis) or (atopic and eczema) or (neurodermatitis)) AND (staphylococc* or (S. and Aureus) or (Staphylococcus and aureus) or (staphyl* and aureus)) AND (antibiotic* or antiseptic* or anti-infective or dermol or oilatum or emulsiderm or fucidic or fucidic or fucibet or gregoderm or nystaform or quinocort or terra-cortril or timodine or vioform or locoid or betnovate or dermovate or trimovate or synalar or aureocort or triadcortyl or bactroban or flucloxacillin or erythromycin or clinadmycin)

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1,2008) using the strategy in [Appendix 1](#):

We searched MEDLINE (OVID) (from 2002 to March 2008) using the strategy in [Appendix 2](#)

We searched EMBASE (OVID) (from 2002 to March 2008) using the strategy in [Appendix 3](#)

The UK Cochrane Centre has an ongoing project to systematically search MEDLINE and EMBASE for reports of trials which are then included in the Cochrane Central Register of Controlled Trials. The searching of MEDLINE and EMBASE was done for this review by the Cochrane Skin Group to cover the years that had not been searched by the UKCC.

Ongoing Trials

We searched the following databases for ongoing trials in March 2008 using the terms atopic eczema, atopic dermatitis and *Staphylococcus aureus*, antimicrobial, antiseptics and anti infective agents.

- The metaRegister of Controlled Trials www.controlled-trials.com
- The U.S. National Institutes of Health ongoing trials register www.clinicaltrials.gov
- The Ongoing Skin Trials register on www.nottingham.ac.uk/ongoingskintrials

Searching other resources

References lists

We checked the references of all of the studies that were obtained for assessment for further trials.

Correspondence

Where possible we corresponded with trial authors about unpublished and ongoing trials, and by contacting pharmaceutical companies who produce relevant products.

The following drug companies were contacted:

- Dermal (Dermol products and Emulsiderm);
- Stiefel (Oilatum plus);
- Leo (FucidinH, Fucibet);
- Unigreg (Gregoderm);
- Typharm (Nystaform-HC);

- Quinoderm Ltd (Quinocort);
- Pfizer (Terra-cortril);
- R&C (Timodine);
- Novartis Consumer Health (Vioform-Hydrocortisone);
- Yamanouchi (Locoid C);
- GlaxoSmith Kline (Betnovate C, Betnovate N, Dermovate NN, Trimovate);
- Bioglan (Synalar C, Synalar N);
- Lederle (Aureocort);
- Squibb (Triadocortyl);
- Beecham (Bactroban).

Grey literature

Conference proceedings from these meetings were checked for RCTs and where appropriate the trial authors were contacted for further information:

British association of dermatologists annual meeting (from 1980 to 2006);

The American academy of dermatology annual meeting (2006);

The European academy of dermatology and venereology annual meeting (1995, 1998, 1999, 2002, 2003, 2005, 2006).

Language restrictions

There were no language restrictions when we searched for publications. We sought translations of papers in languages other than English by asking dermatological colleagues. Carsten Flohr interpreted papers in German and Yukihiro Ohya performed the data extraction on the paper in Japanese (Hizawa 1998).

Data collection and analysis

Selection of studies

Two authors checked the titles and abstracts identified from the searches (JR, JP up to December 2003 and then subsequently AB alone). If it was clear that the study did not refer to a randomised controlled trial on atopic eczema, it was excluded. If it was unclear, then the full text of study was obtained for independent assessment by two authors (AB, HCW). The authors decided which trials fit the inclusion criteria. Any disagreement was resolved by discussion between the authors. It was not necessary to refer to a third author. We recorded excluded studies and reasons for exclusion in the excluded studies table.

Data extraction and management

This was performed by two authors (AB, HCW), who independently entered data onto a data extraction form. The authors (AB, HCW) discussed discrepancies between themselves. Missing data were obtained from trial authors where possible. Data were checked and entered into RevMan by AB and FBH. The authors were not blinded to the names of trial authors, journal or institutions.

In the original published protocol outcomes were considered at the end of treatment and this was considered short-term where treatment had been given for two weeks or less and long-term for periods of one month or greater. After discussion (between AB & HCW) however, it was decided that studies of under a month's duration would be considered as reflecting short-term benefit and those of greater than a month as a reasonable minimal time to reflect some disease chronicity. Where the patient rated global assessment was not available, the medical practitioner global rating was used. Both measures were taken into account where both were available. No attempt was made to combine these measures, as they are often not well correlated. In the published protocol skin irritation was to be reported separately as well as within the minor patient adverse events. After discussion (between AB and HCW), it was decided that it was not necessary to report on skin irritation twice and thus it was included in the "minor patient reported adverse events" section only.

Assessment of risk of bias in included studies

The quality assessment included an evaluation of the following components for each included study, since there is some evidence that these are associated with biased estimates of treatment effect (Juni 2001):

- (a) the method of generation of the randomisation sequence;
 - (b) the method of allocation concealment - it was considered 'adequate' if the assignment cannot be foreseen;
 - (c) who was blinded/not blinded (participants, clinicians, outcome assessors);
 - (d) how many participants were lost to follow-up in each arm (split into post-randomisation exclusions and later losses if possible), and whether participants were analysed in the groups to which they were originally randomised (intention to treat).
- In addition, assessment was made of the following:
- (e) degree of certainty that participants have atopic eczema;
 - (f) baseline comparison for severity of disease;
 - (g) baseline comparison of presence of *S. aureus*;
 - (h) amount of topical steroid used during study period.

The information is recorded in Table 1 and a description of the quality of each study is given based on a summary of these components.

Table 1. Quality of studies

Study ID	Allocat'n genera- tion	Allocat'n conceal- men	Blinding	Loss to follow up	Included in analysis	Diag- nostic certainty	Baseline severity	Baseline S. aureus	Amount of steroid
Bogu- niewicz 2001	Unclear	Unclear	Participant blinded. Clinician and outcome assessor unclear	None	ITT	Unclear. Atopic dermatitis who had S. aureus cultured from their skin	Not stated	Similar	Not reported
Breneman 2000	Unclear	Unclear	Participant blinded. Clinician and outcome assessor unsure	Unsure	Not stated	Hanifin & Rajka	Not stated	Similar	No statistical difference between groups (p=0.86)
Ewing 1998	Unclear	Adequate - by phar- maceutical company	Participant blinded. Clinician and outcome assessor unclear	Four	Per protocol	Hanifin & Rajka	Similar	Similar	Flu- cloxacillin group used mean of 61.0g, placebo group used 29.2g.
Fattah 1976	Unclear, though stated "a code of randomi- sation"	Unclear	Partici- pants not blinded as creams different colours. Clinician and outcome assessor unclear	None	Not stated	Unclear	Not stated	Not stated	Not reported
Gong 2006	Unclear	Unclear	All blinded. Clinician nd outcome assessor	Unclear	Per protocol (though in text states was ITT)	Hanifin & Rajka criteria	Similar	Similar	Not reported

Table 1. Quality of studies

<i>(Continued)</i>									
			unclear						
Harper 1995	Computer generated random code	Unclear	Unclear	Four	Per protocol	Unclear	“Total clinical score” of control 6.4 +/- 3.8 and intervention 9.6 +/- 2.6	Not reported	Not reported
Hizawa 1998	By lots	Unclear	Participant and clinician unclear. Outcome assessor blinded	None	ITT	Unclear. “Atopic dermatitis”	Not stated	Not stated	No steroid permitted during trial
Hjorth 1985	Unclear	Unclear	Participant blinded. Clinician and outcome assessor unclear.	None	ITT	Unclear	Not stated	Not stated	Not reported
Holland 1995	Unclear	Unclear	Unclear	Five	Unclear	Unclear	Similar	Similar	Not reported
Juenger 2006	“Randomisation list” by independent biometrician using SPSS	Unclear; hidden in closed envelope, but not stated to be opaque	Participant blinded. Clinician and outcome assessor unclear	None	ITT	Unclear; “acute” atopic dermatitis	Unequal. SCORAD in silver group 74.6, SCORAD in non-silver group 51.9	Unequal. Silver group 31 +/- 0.7, Non-silver group 1.8 +/- 1.1	Very unequal. Silver group used 135g prednicarbate ointment per person, non-silver group used 13 g per person
Korting 1994	Unclear	Unclear	Participant blinded. Clinician and outcome	Unclear	Per protocol	Unclear	Similar	Similar	Not reported

Table 1. Quality of studies

<i>(Continued)</i>									
			assessor unclear						
Lever 1988	Unclear	Unclear	Unclear for participant and clinician. Outcome assessor blinded	Four	Per protocol	Unclear. “Typical clinical features”	“Pre- treatment severity scores” Mupirocin first: 59.5 +/- 6.4; Placebo first 69.9 +/- 6.9	Similar	Not reported
Leyden 1977	Unclear	Unclear	Unclear for all	Unclear	Not stated	Unclear. “Typical atopic der- matitis”	Not stated	S. aureus counts: Treatment group - 420000/cm ² ; Control group - 200000/cm ²	Not reported
Masako 2005	Unclear	Unclear	Participant and outcome assessor blinded. Clinician unclear.	Not stated	ITT	Unclear; atopic dermatitis	Similar	Similar	Not reported
Nilsson 1992	Unclear	Unclear	Unclear	Two	Per protocol	Hanifin & Rajka criteria	Similar	Similar	Not reported
Polano 1960	Unclear	Adequate - states card was chosen at random through the pharmacy	Participant - unclear, Clinician and outcome assessor blinded	Ten. Reasons not specified	Per protocol	Unclear	Not stated	Not stated	Not reported
Ramsay 1996	Unclear	Unclear	Unclear	At least 12 (unclear)	Per protocol	Unclear, atopic dermatitis	Not stated	Not stated	Not reported

Table 1. Quality of studies

(Continued)									
Schempp	Unclear	Unclear	Participant	None,	Per	Unclear.	Similar	Similar	None
Schutteleaar 2005	Computer generation in blocks of four	Adequate - by pharmacy using concealed packs	All blinded	None	ITT	Modified Hanifin & Rajka criteria	Similar	Similar	462g in 2 weeks (Intervention group), 349g in 2 weeks (Control)
Wachs 1976	Unclear	Unclear	Unclear, though states was double blind	Four participants - no reason specified	Per protocol	Unclear; "infected atopic dermatitis"	Similar	<i>S.aureus</i> not specifically reported	Not reported
Weinberg 1992	Unclear	Unclear	Unclear	Three	Per protocol	Hanifin & Rajka	Similar	Similar	Not reported

Measures of treatment effect

For studies with a similar type of intervention (e.g. steroid antibiotic combinations) a meta-analysis was performed to calculate a weighted treatment effect across trials using a random effects model. The results are expressed as risk ratio (RR) and 95% confidence intervals (CI) for dichotomous outcomes, rather than odds ratio as the event rates are common and we do not wish to over estimate the effect, and mean differences (MD and 95% CI) for continuous outcomes. Where it has not been possible to perform a meta-analysis the data have been described qualitatively. Where appropriate we expressed results as number needed to treat (NNT) with 95% confidence interval and the baseline risk to which it applies.

Unit of analysis issues

We did not perform techniques appropriate for paired designs for cross-over studies due to insufficient data, however where data from the first period were available from a cross over study then they were analysed as if it were a parallel study as suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). For within patient trials, we abstracted from the original paper the paired analysis results and reported these in the review.

Dealing with missing data

If results for intention-to-treat were given then we used them as such (see [Characteristics of included studies](#)). Where a per protocol analysis was performed by the study in question or it was clear

that the number of participants completing the study were not the same as those randomised then we performed an available case analysis.

Assessment of heterogeneity

Heterogeneity was assessed using I^2 . Where substantial heterogeneity ($I^2 > 50\%$) existed between studies for the primary outcome, we explored reasons for heterogeneity, such as differing inclusion criteria.

Assessment of reporting biases

We performed funnel plots if greater than ten poolable studies were available.

Data synthesis

A random effects model was used when conducting a meta-analysis as the studies were deemed to be clinically heterogeneous.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was performed where adequate information was given. The planned subgroups were 'clinically infected eczema', 'mixed infection/colonisation with *S. aureus* and beta haemolytic streptococcus', and 'non infected or unspecified.' Heterogeneity was assessed as above

Sensitivity analysis

We explored reasons for heterogeneity in studies and, if necessary, we performed sensitivity analyses examining the effects of exclud-

ing study subgroups, e.g. those studies with low methodological quality.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

We identified 45 possible studies, of which 38 were RCTs; 41 were fully published papers, 2 letters to the editor and 2 papers presented at meetings (1 of which was not published). One paper was in Japanese and the data extraction was kindly performed by YO. The full text or abstract of each trial was examined independently by two authors (AB & HCW).

Included studies

Twenty one studies with 1018 participants were included in this review and are described in the [Characteristics of included studies](#) table. All studies were randomised controlled trials; 12 parallel group, 4 cross-over and 5 within-patient studies. The studies involved sample sizes between 4 and 186 participants and all that specified the setting (2 did not) were conducted in secondary care. Eleven of the studies were conducted in Western Europe, five in North America and five elsewhere in the world. Five of the studies were conducted using multiple centres, 14 were single centre and 2 did not specify. Three studies looked specifically at children and two specifically at adults, seven included both and in nine studies it was not clear. All the studies included both males and females. The included studies fell into seven very broad categories;

1. Oral antibiotics (three RCTs),
2. Antibacterial soaps (one RCT),
3. Topical steroid plus an antibiotic and an antifungal (one RCT),
4. Antibacterial bath additives (two RCTs),
5. Topical antiseptic/antibiotic (four RCTs),
6. Topical steroid plus antibiotic (nine RCTs),
7. Silver impregnated textiles (one RCT).

Control groups most commonly received vehicle alone (four RCTs) or a placebo tablet (three RCTs) with the exception of those studies involving steroid antibiotic combinations in which case the controls used a topical steroid without the antibiotic added (ten RCTs). The studies had multiple stated outcomes, a number of which were not reported in the results. Six studies intended to report on global improvement, seven on adverse events. A large number of studies looked at microbiological data including sensitivity of or resistant organisms (4 RCTs), isolation rates (10 RCTs) and colony counts (13 RCTs) of *S. aureus*. Some studies assessed outcome based on a published named scale including SCORAD

(SCORing Atopic Dermatitis) (three RCTs), EASI (Eczema Area & Severity Index) (one RCT) and SASSAD (Six Area, Six Sign Atopic Dermatitis) (one RCT) ([Schmitt 2007](#)). The majority used an arbitrary, unvalidated scale to assess efficacy (nine RCTs).

We did not consider that any of the first five categories, or the seventh category, had studies sufficiently similar to pool. In the sixth category four papers reported within-patient studies or parallel group studies of potent steroids plus antibiotic that were pooled in groups of two ([Wachs 1976](#); [Leyden 1977](#); [Hjorth 1985](#); [Korting 1994](#); [Schuttelaar 2005](#)). For the initial pooling we did not take into consideration whether it was infected or non-infected atopic eczema that was being treated.

Trial periods

Only 1 of the 21 included studies ([Breneman 2000](#)) was of greater than a month's duration and therefore considered a reasonable time to reflect disease chronicity. We considered the remainder to provide short-term data. [Ewing 1998](#) did report data from 56 days after the trial period had ended, though the intervention itself was for a short-term only.

Excluded studies

We excluded 24 studies and their details can be found in the [Characteristics of excluded studies](#) table. Seven were not RCTs, nine were excluded as they did not provide separate results for atopic eczema (only "steroid responsive dermatoses" in general), one was an in-vitro study, one a duplicate study and six were excluded as they only compared anti-staphylococcal agents against each other or against an inappropriate control. On this final point, it was agreed that a vehicle was not an appropriate comparator for a steroid/antibiotic combination as it is well recognised that topical steroids are an effective treatment for inflamed eczema and thus one could not establish whether it is the addition of the antibiotic, or the steroid itself that has efficacy. This is not a change from the original protocol, rather a clarification of the inclusion criteria.

Risk of bias in included studies

The overall methodological quality of the trials was poor. Please see [Table 1](#) for further information on the quality of the included studies. Since no meta-analyses were performed involving more than two studies, sensitivity analysis based on methodological quality was not performed.

Allocation

In 17 of the 21 trials in this review the method of randomisation was not described at all or was unclear. [Harper 1995](#) used a computer generated random code, [Hizawa 1998](#) drew lots, [Juenger 2006](#) used a randomisation list created by an independent biometrician using statistics software and [Schuttelaar 2005](#) used a computer generated list in blocks of four. In only three of the trials

have the trial authors clearly demonstrated that concealment of allocation was adequate; one study had the medication pre-prepared by the drug company (Ewing 1998), one had identical tubes pre-prepared by pharmacy (Polano 1960) and one had concealed packs in pharmacy (Schuttelaar 2005).

Blinding

Blinding of outcome assessment was attempted for most of the trials. However, the method as to how this was done was generally unclear and poorly described. In only one study were the authors (AB & HCW) convinced that everyone (the participants, clinicians and outcome assessors) was adequately blinded (Schuttelaar 2005) and in only three others that the outcome assessor was adequately blinded (Polano 1960; Lever 1988; Hizawa 1998). Of studies in which patient assessment of outcome was included only five had adequately described blinding of the participants (Ewing 1998; Schempp 2003; Masako 2005b; Schuttelaar 2005; Gong 2006).

Follow up and exclusions

In many of the trials analysis of outcome was carried out only on those participants who completed the trial. Only 6 of the 21 trials were analysed by intention to treat (Hjorth 1985; Hizawa 1998; Boguniewicz 2001; Masako 2005b; Schuttelaar 2005; Juenger 2006). Six trials definitely had no losses to follow up. Eight trials were either not clear as to how many patients were lost to follow up or did not specify any reasons why they were (Polano 1960; Wachs 1976; Leyden 1977; Korting 1994; Ramsay 1996; Breneman 2000; Masako 2005b; Gong 2006). One study (Korting 1994) was particularly unclear; it reported that 180 were enrolled, but only 143 were recruited. It appeared that the final number recruited depended on an assessment, but this was not clear. See also Table 1.

Selective reporting

The abstract of one study (Breneman 2000) concludes that daily bathing with an antibacterial soap provides clinical improvement, but the actual results in each group along with the significant values are not given; the results are plotted on a graph with very different baselines in each group with improvement looking parallel.

Harper 1995 reported that “the most significant result” of the study was a significant change in score from baseline at weeks two and four in the treatment group. However, the correct statistic was not reported i.e. the difference between the change in score for the two treatments.

In the summary, despite having results that are not statistically significant, Wachs 1976 states that “combination therapy reduced the mean scores for infection, inflammation and overall severity to a greater extent than the antibiotics or corticosteroid alone.”

There was no significant difference in the stated global outcome of Gong 2006, however they performed a post hoc subgroup analysis

in which they found that participants with specific clinical scores fared better in the treatment group compared to the control. They reported this in the abstract and used it to suggest, as one of their main conclusions, that early combined treatment is beneficial to that specific subgroup.

Juenger 2006 claimed that use of the silver textiles “led to an impressive improvement of atopic dermatitis,” but the evidence provided was not sufficient to back up this claim.

Other potential sources of bias

A concern with the Juenger 2006 study is that the treatment arm (with silver textiles) used 135 g of topical steroid whereas the control arm used only 13 g which suggests that unblinding may have taken place.

We were unable to assess for publication bias as there were not enough studies to perform a funnel plot. There were a couple of duplicate publications. Identical results were published by Korting 1994 and Zienicke 1993. Schempp 2003 also published an identical study in German (Schempp 2003a).

Certainty of diagnosis

Six of the 21 included studies used the Hanifin and Rajka definition or the UK modification for the diagnosis of atopic eczema (Nilsson 1992; Weinberg 1992; Ewing 1998; Breneman 2000; Schuttelaar 2005; Gong 2006) whereas the remaining 15 relied on the diagnosis being made by a physician. Only two studies specified infected atopic eczema in their inclusion criteria (Wachs 1976; Weinberg 1992). A number of studies had inclusion criteria such as “super infected” or “acute” atopic eczema, but these descriptions were not defined.

Baseline comparison for severity

Eight of the 21 did not provide data for baseline comparison (Polano 1960; Fattah 1976; Leyden 1977; Hjorth 1985; Ramsay 1996; Hizawa 1998; Breneman 2000; Boguniewicz 2001). In Lever 1988 the “pre-treatment severity scores” were not the same in the two treatment groups of the cross-over study (69.9 +/- 6.9, 59.5 +/- 6.4) and in Harper 1995 the “total clinical score” was not comparable; control being 6.4 +/- 3.8 and intervention 9.6 +/- 2.6. In the other studies, severity of the atopic eczema was comparable at baseline. In one of the studies (Juenger 2006) the baseline SCORAD was so different (74.6 in the treatment group and 51.9 in the control) that it affected the outcome of the study and thus the unadjusted results should be interpreted with caution. Disease duration was only reported in four of the studies (Polano 1960; Fattah 1976; Weinberg 1992; Juenger 2006) and previous responses to treatment were not generally reported.

Baseline comparison of presence of *S Aureus*

Six of the studies did not include a baseline comparison of the presence of *S. aureus* (Polano 1960; Fattah 1976; Hjorth 1985; Hizawa

1998; Harper 1995; Ramsay 1996). Wachs 1976 did record the presence or absence of staphylococcus, but did not specify whether it was *S. aureus*, or another strain such as *S. epidermidis*. The remainder of the studies did include baseline comparisons which were similar, with the exception of Leyden 1977 and Juenger 2006.

Amount of topical steroid used during study period

This was generally not reported. In Hizawa 1998 no topical corticosteroid was permitted during the trial period. Ewing 1998 did record a striking difference in the amount used both at the end of the trial period (day 28) in which the intervention (flucloxacillin) group used a mean of 61.0 g/2 weeks (95% CI 26.3, 95.7) and the placebo group only 29.2 g/2 weeks (95% CI 18.6, 39.7), and at 56 days post treatment the intervention group had used 50.2 g/2 weeks (95% CI 18.4, 82.1) and the placebo group 33.4 g/2 weeks (95% CI 10.3, 56.6). Breneman 2000 reported that there was no significant difference in the amount of topical steroid used between groups ($p = 0.86$). Another study in which the amount of topical steroid used was recorded was Schuttelaar 2005 in which an astonishing 462 g was used in the intervention group and 349 g in the control group in 2 weeks. This is substantially different from normal practice and would make the results from this study difficult to interpret for use in a clinical setting. There was no limitation on the amount of topical steroid used in one study (Juenger 2006) which resulted in an elevated positive result in the treatment group which used more than ten times the amount of steroid as in the control.

Effects of interventions

Please see table of [Characteristics of included studies](#).

Subgroup analysis was not performed as there were no appropriate studies to pool.

I. Oral Antibiotics- three RCTs

We included 3 RCTs; one cross over study of 20 participants (Boguniewicz 2001) and 2 parallel studies (Weinberg 1992; Ewing 1998).

Short-term:

1) Primary outcome measures

(a) Global degree of improvement in symptoms and/or signs as rated by patient or medical practitioner.

Two studies reported global degree of improvement in signs and symptoms as rated by the medical practitioner (Weinberg 1992; Ewing 1998). One study of 46 participants (Ewing 1998) found a significant improvement in the placebo group compared to flucloxacillin (RR 2.49; 95% CI 1.27, 4.89) [Analysis 1.1]. The other

study of 33 participants (Weinberg 1992) found a non significant improvement in the cefadroxil group for global outcome (RR 0.40; 95% CI 0.13, 1.24) [Analysis 1.1]. One study (Boguniewicz 2001) reported no change in clinical severity, but provided no data.

(b) Improvement in Quality of Life questionnaires.

There were no results given for this outcome

(2) Secondary outcome measures

(a) Severe adverse events, i.e. severe enough to require withdrawal of treatment, including severe skin irritation.

One study reported no adverse events (Boguniewicz 2001). Pooled analysis from two studies (Weinberg 1992; Ewing 1998) showed no significant differences for adverse events requiring withdrawal (RR 1.64; 95%CI 0.21,12.78) [Analysis 1.2].

(b) Minor patient reported adverse events.

This included mild skin irritation not sufficient to require cessation of treatment.

No study reported minor patient adverse events.

(c) Emergence of antibiotic resistant micro-organisms.

See long-term results.

(3) Tertiary outcome measures

(a) Global changes in composite rating scales, using a published named scale.

No data were provided for this outcome

(b) Changes in the individual signs of atopic eczema as assessed by a physician.

Two studies (Weinberg 1992; Ewing 1998) found no significant difference in erythema in the control groups compared to oral antibiotic (MD 0.40; 95% CI -0.03, 0.83) [Analysis 1.3], (RR 0.93; 95% CI 0.38, 2.28) [Analysis 1.5]. The two studies could not be pooled because one used a continuous and the other a dichotomous measure (score). One study (Weinberg 1992) found significantly fewer clinically apparent infection in the treatment group at the end of the study compared to control (RR 0.06; 95%CI 0.00, 0.94) [Analysis 1.6].

(c) Duration of remission and/or prevention of subsequent flares.

No results were given for this outcome of interest.

(d) Change in isolation rate of *S. aureus*, i.e. isolated or not isolated.

One study (Ewing 1998) found significantly fewer people had *S. aureus* isolated in the flucloxacillin group compared to the control (RR 0.68; 95% CI 0.49, 0.95) [Analysis 1.7], though the mean log of *S. aureus* counts was not significantly reduced in the treatment group compared to placebo (MD -1.4; 95% CI -3.09, 0.29) [Analysis 1.8]. The isolation rates of *S. aureus* from affected skin reduced from 24/24 patients to 15/22 in the flucloxacillin group and from 24/25 to 22/24 in the placebo group as reported in the text.

(e) Change in bacterial counts of *S. aureus*, i.e. an assessment of quantity of *S. aureus*.

One study (Ewing 1998) found a non significant reduction in the log *S. aureus* counts/cm² in the flucloxacillin group compared to placebo, though this may well have been significant had the baselines been comparable. Another study (Boguniewicz 2001) suggested that addition of an antibiotic resulted in a reduction in colony counts, however when the antibiotic was discontinued the skin was quickly recolonised.

Long-term:

(1) Primary outcome measures

(a) Global degree of improvement in symptoms and/or signs as rated by patient or medical practitioner.

There were no results given for this outcome.

(b) Improvement in Quality of Life questionnaires.

There were no results given for this outcome.

(2) Secondary outcome measures

(a) Severe adverse events, i.e. severe enough to require withdrawal of treatment, including severe skin irritation.

There were no results given for this outcome.

(b) Minor patient reported adverse events. This included mild skin irritation not sufficient to require cessation of treatment.

There were no results given for this outcome.

(c) Emergence of antibiotic resistant micro-organisms.

Only one study (Ewing 1998) reported that the number of methicillin resistant strains (MRSA) increased in the treatment group up until 14 days after treatment, but did not give individual patient data. Any increase in the number of MRSA had returned to almost baseline at day 56.

(3) Tertiary outcome measures

(a) Global changes in composite rating scales, using a published named scale.

There were no results given for this outcome.

(b) Changes in the individual signs of atopic eczema as assessed by a physician.

One study reported no significant difference in erythema at 56 days post treatment with oral flucloxacillin compared to placebo (MD -0.10; 95% CI -0.59, 0.39) [Analysis 1.4].

(c) Duration of remission and/or prevention of subsequent flares.

There were no results given for this outcome.

(d) Change in isolation rate of *S. aureus*, i.e. isolated or not isolated.

There were no results given for this outcome.

(e) Change in bacterial counts of *S. aureus*, i.e. an assessment of quantity of *S. aureus*.

In one study (Ewing 1998) bacterial counts returned to almost pre-treatment levels by 14 days after completion of treatment.

2. Antibacterial soaps- one RCT

One very poor quality study compared 1.5% Triclocarban soap versus placebo in 49 adults with moderate severity atopic eczema (Breneman 2000) provided little or no data to substantiate claims of efficacy. Some data were provided in graphs, however this was impossible to interpret. No data in relation to our outcomes were given.

3. Topical steroid plus an antibiotic and antifungal- one RCT

Fattah 1976 compared 0.1% halcinonide with neomycin plus nystatin versus 1% hydrocortisone cream in a right-to-left study of eight people with steroid responsive dermatoses. Only results for those with atopic eczema were considered (n=4).

Short-term:

(1) Primary outcome measures

(a) Global degree of improvement in symptoms and/or signs as rated by patient or medical practitioner.

One study showed no significant difference in global outcome; out of a total of four participants three achieved a good or excellent

response with the combination treatment and two with hydrocortisone alone.

(b) Improvement in Quality of Life questionnaires.

There were no results given for this outcome.

No results were reported for any of the other outcomes of interest.

Long-term:

There were no long-term data presented relevant to our outcomes.

4. Antibacterial bath additives - two RCTs

Two studies compared a mineral oil based bath emollient (Oilatum) versus the same emollient incorporating triclosan and benzalkonium chloride (Oilatum Plus) bath emollient; one was a cross-over study of 26 children (Harper 1995) and the other a parallel group study of 15 children and adults (Holland 1995). Results for the first period of the cross-over study (Holland 1995) were not given which precluded the pooling of results, also no numbers were given in the text and extracting data from the figures was not possible.

Short-term:

(1) Primary outcome measures

(a) Global degree of improvement in symptoms and/or signs as rated by patient or medical practitioner.

One study (Harper 1995) suggested, in the text, no statistically significant difference between the treatment groups. The results given are difficult to interpret since baseline data were absent and no firm numbers were given for the individual patient groups.

(b) Improvement in Quality of Life questionnaires.

There were no results given for this outcome.

No results were reported for any of the other outcomes of interest.

Long-term:

There were no long-term data presented relevant to our outcomes.

5. Topical antiseptic/antibiotic- four RCTs

Four different studies compared very different interventions versus placebo. One cross-over study of 45 participants (Lever 1988) and three right-and-left comparisons (Hizawa 1998 [n=15], Masako 2005b [n=17], Schempp 2003 [n=18]). Pooling of data was not possible for these four studies.

Short-term:

(1) Primary outcome measures

(a) Global degree of improvement in symptoms and/or signs as rated by patient or medical practitioner.

No numbers were given, but Hizawa 1998 reported that there was a statistically significant improvement in the povidone iodine group for appearance of skin lesions, however no between group analysis was done.

(b) Improvement in Quality of Life questionnaires.

There were no results given for this outcome.

(2) Secondary outcome measures

(a) Severe adverse events, i.e. severe enough to require withdrawal of treatment, including severe skin irritation.

There were no results given for this outcome.

(b) Minor patient reported adverse events. This included mild skin irritation not sufficient to require cessation of treatment.

There were no results given for this outcome.

(c) Emergence of antibiotic resistant micro-organisms.

There were no results given for this outcome.

(3) Tertiary outcome measures

(a) Global changes in composite rating scales, using a published named scale.

Schempp 2003 suggested a significant reduction in modified SCORAD in the Hyperforin 1.5% group of 6.5 compared to 2.5 in the control. However, data were not available for the number of patients in each group and therefore interpretation of these data was limited.

(b) Changes in the individual signs of atopic eczema as assessed by a physician.

Masako 2005b compared 0.2% farnesol + 5% xylitol cream vs placebo and stated that scores of dryness and scaling were significantly improved in both groups, but no data were provided.

(c) Duration of remission and/or prevention of subsequent flares.

There were no results given for this outcome.

(d) Change in isolation rate of S. aureus, i.e. isolated or not isolated.

For the first period of the cross-over study (Lever 1988) there was a significant reduction in *S. aureus* colonisation in the mupirocin group compared with the control group (RR 0.06; 95% CI 0.01, 0.44) [Analysis 2.1].

(e) Change in bacterial counts of *S. aureus*, i.e. an assessment of quantity of *S. aureus*.

No numbers were given, but Hizawa 1998 reported that there was a statistically significant improvement in the povidone iodine group for *S. aureus* colony counts, however no between group analysis was done. Masako 2005b reported that at end of treatment there was a significant difference in the number of *S. aureus* in favour of 0.2% farnesol + 5% xylitol cream compared with placebo.

Long-term:

There were no long-term data presented relevant to our outcomes.

6. Topical corticosteroids plus antibiotic- nine RCTs

There were 9 RCTs, with a total of 677 participants, comparing corticosteroid plus antibiotic versus corticosteroid; all were of poor methodological quality with the exception of 1 with 44 participants (Schuttelaar 2005). There were a number of different corticosteroid potencies and the majority added an antibiotic to a corticosteroid and compared it to the same corticosteroid. Two studies (Polano 1960 [n=14]; Hjorth 1985 [n=60]) gave no data for the outcomes of interest.

Short-term:

(1) Primary outcome measures

(a) Global degree of improvement in symptoms and/or signs as rated by patient or medical practitioner.

One study (Korting 1994) compared prednicarbate 0.25% cream plus didecylidimethyl - ammonium chloride 0.25% to prednicarbate 0.25% cream, in 143 participants, and found no significant difference in global outcome at the end of treatment (RR 0.64; 95% CI 0.25, 1.68) [Analysis 3.1]. One study comparing betamethasone valerate plus gentamicin cream vs betamethasone valerate cream vs gentamicin cream in 79 participants (Wachs 1976) showed no significant difference in global outcome (RR 0.31; 95% CI 0.07, 1.35) [Analysis 3.1]. When these latter two studies were pooled the combination treatment did not show a significant improvement compared to steroid alone in infected/heavily colonised eczema (RR 0.52; 95% CI 0.23, 1.16) [Analysis 3.1]. Nilsson 1992 compared the super-potent clobetasol versus the potent betamethasone plus neomycin cream, in 28 individuals, and found a significant improvement in global outcome in favour of clobetasol using a subjective interval scale self-evaluation (MD 1.2; 95% CI 0.25, 2.15) [Analysis 3.2].

(b) Improvement in Quality of Life questionnaires.

There were no results given for this outcome.

(2) Secondary outcome measures

(a) Severe adverse events, i.e. severe enough to require withdrawal of treatment, including severe skin irritation.

Pooled results from 2 studies of 198 participants (Ramsay 1996; Schuttelaar 2005) showed no significant difference in adverse events requiring withdrawal from treatment (RR 0.49; 95% CI 0.09, 2.78) [Analysis 3.3].

(b) Minor patient reported adverse events. This included mild skin irritation not sufficient to require cessation of treatment.

Pooled results from two studies (Ramsay 1996; Schuttelaar 2005) showed significantly fewer minor adverse events not requiring withdrawal from treatment in the combination treatment group compared to the control, (RR 0.34; 95% CI 0.15, 0.77) [Analysis 3.4].

(c) Emergence of antibiotic resistant micro-organisms.

There were no results given for this outcome.

(3) Tertiary outcome measures

(a) Global changes in composite rating scales, using a published named scale.

One study (Schuttelaar 2005) showed no significant difference in SCORAD at the end of treatment between 3% tetracycline plus 0.1% triamcinolone and 0.1% triamcinolone (MD -0.40; 95% CI -10.39, 9.59) [Analysis 3.5]. Gong 2006 reported that both hydrocortisone and mupirocin and hydrocortisone alone showed significant within group improvement in EASI (Eczema Area and Severity Index) scores, however at the end of treatment there was no significant difference in EASI scores (MD -1.08; 95% CI -2.51, 0.35) [Analysis 3.6].

(b) Changes in the individual signs of atopic eczema as assessed by a physician.

There were no results given for this outcome.

(c) Duration of remission and/or prevention of subsequent flares.

There were no results given for this outcome.

(d) Change in isolation rate of *S. aureus*, i.e. isolated or not isolated.

In one study (Korting 1994) isolation of *S. aureus* in the prednicarbate 0.25% cream plus didecylidimethyl - ammonium chloride 0.25% group reduced from 47/69 to 5/69 and from 54/74 to 7/74 in the steroid only group as reported in the text. One study of 36 participants (Leyden 1977) showed a significant reduction (85%) in the isolation of *S. aureus* when using the combination cream (Fluocinolone acetonide plus 0.5% neomycin sulphate) compared with fluocinolone acetonide cream alone (RR 0.32; 95% CI 0.11, 0.94) [Analysis 3.7]. Pooled analysis from two studies (Leyden 1977; Schuttelaar 2005) showed an 83% reduction in the isolation rate of *S. aureus* in the combination group compared to steroid alone at the end of treatment (RR 0.37; 95% CI 0.20, 0.69) [Analysis 3.7]. Gong 2006 reported that 89/119 people with eczema had *S. aureus* present in lesional skin at baseline and 41/119 in non-lesional skin, but no data for the end of the study, comparing hydrocortisone and mupirocin and hydrocortisone alone, other than a statement that there was no significant difference between experimental groups and control groups.

(e) Change in bacterial counts of *S. aureus*, i.e. an assessment of quantity of *S. aureus*.

In one study of 30 participants (Nilsson 1992) both steroid plus antibiotic and steroid alone completely cleared *S. aureus* (presented as log counts).

Long-term:

There were no long-term data presented relevant to our outcomes.

7. Silver impregnated textiles- one study

One study of 30 participants compared silver impregnated underclothes with polyester underclothes (Juenger 2006).

Short-term:

(1) Primary outcome measures

(a) Global degree of improvement in symptoms and/or signs as rated by patient or medical practitioner.

One study (Juenger 2006) reported no significant difference in the overall disease control of atopic dermatitis in the silver textile group compared with the non-silver textile as assessed by the patient or their carer (RR 2.67; 95% CI 0.98, 7.22) [Analysis 4.1].

(b) Improvement in Quality of Life questionnaires.

There were no results given for this outcome.

(2) Secondary outcome measures

(a) Severe adverse events, i.e. severe enough to require withdrawal of treatment, including severe skin irritation.

There were no results given for this outcome.

(b) Minor patient reported adverse events. This included mild skin irritation not sufficient to require cessation of treatment.

There were no results given for this outcome.

(c) Emergence of antibiotic resistant micro-organisms.

There were no results given for this outcome.

(3) Tertiary outcome measures

(a) Global changes in composite rating scales, using a published named scale.

One study (Juenger 2006) reported a reduction in the median SCORAD from 74.6 to 29.95 in the silver group and from 51.9 to 48.2 in the control group.

(b) Changes in the individual signs of atopic eczema as assessed by a physician.

There were no results given for this outcome.

(c) Duration of remission and/or prevention of subsequent flares.

There were no results given for this outcome.

*(d) Change in isolation rate of *S. aureus*, i.e. isolated or not isolated.*

There were no results given for this outcome.

*(e) Change in bacterial counts of *S. aureus*, i.e. an assessment of quantity of *S. aureus*.*

In one study (Juenger 2006) both groups showed a similar degree of reduction in *S. aureus* counts (MD 0.0; 95% CI -0.93, 0.93) [Analysis 4.2].

Long-term:

There were no long-term data presented relevant to our outcomes.

Number needed to treat:

It was deemed inappropriate to calculate the number needed to treat (NNT) for any of the interventions due to lack of significance of data.

DISCUSSION

Summary of main results

None of the trials showed any clear benefit in terms of short-term eczema control for any of the interventions tested, although several interventions were associated with decreased numbers of *S. aureus* on the skin.

One poorly reported study (Schempp 2003) suggested a significant reduction in eczema severity using a modified SCORAD (SCORing Atopic Dermatitis) rating scale when Hyperforin 1.5% cream was compared with placebo. Although this result is statistically significant, a median difference of four points on the modified SCORAD may not be clinically beneficial.

There was no clear evidence that the widely used topical steroid/antibiotic combinations were any better than the topical steroids used alone. A range of different potencies of topical steroid combined with an antibiotic have been appropriately compared to the same steroid. However, Nilsson 1992 compared the super-potent clobetasol versus the potent betamethasone plus neomycin, which is not a fair test. Not surprisingly, that study found a significant improvement in global outcome in the super-potent steroid group. Interestingly, *S. aureus* was completely cleared in both groups in that same study (Nilsson 1992), demonstrating that the use of topical steroids alone on eczematous skin will result in the reduction of *S. aureus*. This raises the question as to whether the addition of antibiotics to a topical preparation is justified in any clinical scenario.

Pooled analysis of two studies (Wachs 1976; Korting 1994) found no significant difference in global outcome in steroid/antibiotic combinations compared to steroid alone in people with infected/heavily colonised eczema (RR 0.52; 95% CI 0.23, 1.16) [Analysis 3.1]. There were significant differences between these studies, in particular one study used a medium potency steroid, prednicarbate (Korting 1994), and the other a potent steroid, betamethasone valerate (Wachs 1976) and they both used different antibiotics, but as they were both in infected/heavily colonised eczema they were thought to be similar enough to pool.

There was no significant difference in adverse events requiring withdrawal from treatment when comparing topical steroid/antibiotic combinations (pooled results from two studies Ramsay 1996 and Schuttelaar 2005). However, in one study (Schuttelaar 2005) there were fewer minor adverse events not requiring withdrawal from treatment in the combination treatment group compared to steroid alone. In that study participants in both treatment arms were instructed to apply substantially more topical treatment than would be expected in normal practice. Large quantities of topical steroids can induce a folliculitis and the antibiotic seemed to have a protective effect against this, thus explaining the fewer adverse events in those using the combination treatment.

In general, the reporting of adverse effects from the use of topical treatments was poor. Although those studies that did record them did not find many, supporting the notion that such topical treatments are generally well tolerated in people with eczema. One study (Polano 1960) concluded by not recommending the com-

bination of neomycin with a topical steroid due to the risk of the development of sensitivity to the antibiotic.

Only one study reported on the emergence of resistant bacterial strains in the group treated with oral antibiotics. It is disappointing that so few studies looked at the development of resistant strains as one of the concerns of the potential over-use of antibiotic containing preparations is the development of bacterial resistance (El-Zimaity 2004, Ravenscroft 2000).

Overall completeness and applicability of evidence

Failure to demonstrate evidence that anti-staphylococcal interventions control eczema flares does not necessarily mean that they could not prevent further flares and contribute to long-term management in general. It is disappointing that no studies provided quality of life data and that so few made any attempt to examine the long-term effects of interventions.

It is also worth pointing out that in practice, most people with eczema will be using accessory care such as emollients or specific cleansing products and it would have been useful if studies had documented this.

Those studies that recorded whether the eczema was “clinically infected” did not make it clear what was meant by infection. Indeed, many of the “clinically” infected participants in one study (Wachs 1976) were not infected according to microbiological criteria. It is already widely recognised that eczematous areas of the body are more colonised with *S. aureus* than non-eczematous and the results of a number of the studies were in agreement with this (Lever 1988; Gong 2006).

The results of this review corroborate with both the NICE (NICE 2007) and the British Association of Dermatologists and the Primary Care Dermatology Society guidelines (PCDS 2003) on the management of atopic eczema which state that the role of *S. aureus* as an important exacerbating factor in atopic eczema is a matter of debate, that oral antibiotics are often necessary in moderate to severe infection and that steroid-antibiotic combinations are effective in clinical practice although evidence for superiority in efficacy is lacking.

Quality of the evidence

We included 21 randomised controlled trials involving 1018 participants. Quality of reporting was generally poor. Both studies of antibacterial bath additives were poorly reported (Harper 1995; Holland 1995). In Harper 1995, baseline data were absent and no clear data were given for the individual patient groups. The study by Holland et al (Holland 1995) was also poorly reported: no actual data were provided in the text and extracting data from the figures was not possible. Instead, only “P values” were given for individual groups, with no comparison across the two groups i.e. the key hypothesis under test in a comparative trial. Five other studies also failed to conduct appropriate between group compar-

isons in their analyses (Leyden 1977; Lever 1988; Harper 1995; Holland 1995; Hizawa 1998).

It is also worth highlighting a major limitation of the study of silver impregnated textiles (Juenger 2006). Although they reported a significant improvement in the treatment arm and not in the placebo (though not between groups), those using silver textiles used 135 g of topical steroid whereas those in the control arm used only 13 g, suggesting that all of the benefit could have been due to confounding from additional use of topical steroids.

Potential biases in the review process

It is a possibility that not all relevant studies have been included in this review, and that we failed to find some unpublished trials. Every effort has been made to locate such studies, but some authors of older studies had deceased and many failed to respond to requests for additional information. Some studies containing potentially useful data on people with atopic eczema had to be excluded because their results were lumped together with other people with a range of other skin problems. Our pre-specified choice of clinically important outcomes also meant that some studies that failed to use a published rating scale were excluded. Some studies simply made up their own unvalidated composite scoring systems by pooling the individual signs of atopic eczema. Although many composite scales were used, very few studies reported improvement in individual clinical signs like redness or scaling, making it difficult to comment on which aspects of the condition improved.

Agreements and disagreements with other studies or reviews

There have been no previous systematic reviews on this subject.

AUTHORS' CONCLUSIONS

Implications for practice

We found insufficient evidence to recommend the addition of oral antibiotics to the management of non-infected atopic eczema in children or adults and indeed one study (Ewing 1998) suggested that the addition of long-term flucloxacillin may hinder improvement in eczema and lead to an increase in resistant strains. Whilst we have found insufficient evidence to make any firm recommendations on the use of oral antibiotics in the management of infected atopic eczema, the use of oral antibiotics under such circumstances is standard clinical practice and is recommended by bodies such as the National Institute for Health and Clinical Excellence (NICE 2007). Whilst it would be helpful to see future studies quantifying the benefit of additional oral antibiotics in those with clinically infected atopic eczema with clear definitions of what constitutes clinically infected atopic eczema, we recommend that the use of

appropriate oral antibiotics for overtly infected eczema should be continued, unless future evidence suggests otherwise.

There is evidence that topical antibiotics/antiseptics, whether used alone (four studies) or in combination with a topical steroid (nine studies), reduce colonisation of *S. aureus* in atopic eczema. However none of the 13 studies showed statistically significant effects to suggest that a reduction in *S. aureus* adds to the global improvement of atopic eczema. Their continued use has to be challenged, especially in view of the possibility that widespread use of topical antibiotics might contribute to antibiotic resistance in the community (El-Zimaity 2004).

We found insufficient evidence to support the use of any of the other interventions that aim to reduce *S. aureus* in atopic eczema including antibacterial soaps (one study), antibacterial and antifungal agents both added to a topical steroid (one study), antiseptic bath additives (two studies), and silver textiles (one study). There is little evidence to justify their continued use. Whether they have a role to play in long-term control of eczema remains to be seen.

Implications for research

Very few randomised controlled trials have been conducted on the management of atopic eczema that include interventions that aim to reduce *S. aureus*. Those that have been done have been of poor methodological quality and have mostly been of short duration. Existing studies have tended to focus on microbiological outcomes rather than whether the intervention helps overall eczema severity or quality of life.

It is important that any future studies clearly define what they mean by "infected eczema." Although studies have failed to show any benefit of topical steroid/antibiotic combinations for clinically uninfected eczema, there is still a need for a large, good quality study comparing steroid plus topical antibiotic versus steroid alone in patients with clinically infected eczema, and this ideally ought to be combined with long-term follow-up. There is also a need for a good quality study comparing oral antibiotic plus topical steroid versus topical steroid alone in clinically infected eczema.

There is also a need to more clearly define study participants, including those who fail to respond to conventional treatments, or who are prone to recurrent infected eczema flares, as such a subgroup may benefit from anti-staphylococcal treatments. Studies thus far have failed to address whether the reduction of *S. aureus* has any impact on the long-term reduction of flares. We would recommend that future studies evaluating anti-staphylococcal measures in people with atopic eczema include long-term outcomes such as number of flares or duration of remission in addition to short-term control. Future studies may also choose to standardise accessory care, such as emollients or cleansing agents, or if wishing to have a more pragmatic approach at least to document patients' use of such accessory care.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Boguniewicz 2001

Methods	D: cross over AC: not stated RS: not stated B: participant Y, clinician & outcome assessor U ITT +
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Boguniewicz 2001

<i>(Continued)</i>	
Participants	Two care, two centres, USA
Interventions	cefuroxime axetil orally (dose not stated) b.d. vs placebo orally b.d. given for two weeks each with one week washout inbetween
Outcomes	Colony counts from two involved areas and inguinal area
Notes	Outcomes not clear

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Breneman 2000

Methods	D: parallel group AC: not stated RS: not stated B: participant Y, clinician U, outcome assessor U ITT not stated
Participants	Setting not specified but conducted in conjunction with dept of dermatology in Cincinnati and Portland. Incl: atopic dermatitis (Hanifin and Rajka criteria) Excl: not stated Age: mean 35 (male), 34.6 (female) Duration: not stated Randomised: 50 m/f: 15/35 Evaluable: not stated
Interventions	Soap containing triclocarban 1.5% vs placebo soap Whole body to be washed at least daily for 42 days
Outcomes	Change from day 0 to day 14, 28, 42 as assessed by investigator (-5 = severe worsening, 5 = total clearing) mean log colony forming units of S aureus at 0, 2, 4, 6, 9 weeks
Notes	participants also used standard moisturiser and 0.025% triamcinolone acetonide cream as required Patient rating on itching, % with S aureus isolated and % of body surface area affected stated as outcomes, but not reported in results

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ewing 1998

Methods	D: parallel group AC: by drug company RS: not stated B: Participant Y, clinician U, Outcome assessor U ITT -
Participants	Two-care, single centre, UK Incl: Hanifin & Rajka criteria atopic dermatitis with no sign of bacterial infection, treated with topical steroids, age 1 to 16 years, regular outpatient attendance Excl: systemic steroids (past four weeks), systemic or topical antibiotics (past three weeks) Age: FLX 7.5, P 5.2 Duration: not stated Randomised: 50 m/f: not stated Evaluable: 46
Interventions	Flucloxacillin (FLX) 250mg vs placebo qds for 4 weeks (dose halved for < 10 yrs old)
Outcomes	1. Patient and assessor global degree of improvement 2. Emergence of resistant organisms 3. Physician rated severity of erythema (1 to 5) 4. Isolation of <i>S aureus</i> from affected and non-affected skin 5. mean log <i>S aureus</i> counts

Notes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Fattah 1976

Methods	D: with-in patient study (left/right comparison) AC: not stated RS: not clear B: participant N, clinician U, outcome assessor U ITT not stated
Participants	Two-care, Egypt Incl: atopic dermatitis Excl: secondary infection Age: not stated Duration: mean 14.5 weeks Randomised: four m/f: not stated Evaluable: four
Interventions	0.1% halcinonide cream with 0.25% neomycin and 100000u/g nystatin vs 1% hydrocortisone both applied three times daily for not more than 3 weeks

Outcomes	Physician assessed response to treatment made weekly		
Notes	The creams were different colours		
<i>Risk of bias</i>			
Item	Authors' judgement		Description
Allocation concealment?	Unclear		B - Unclear

Gong 2006

Methods	D: parallel group AC: Not stated RS: Not stated B: participant Y, clinician Y, outcome assessor Y ITT -
Participants	Two-care, multicentre, China Incl: Hanifin & Rajka criteria atopic dermatitis Excl: severe fungal infection, other skin diseases which might disturb the diagnosis and treatment, other severe systemic infrcction, pregnancy, lactation, diseases affecting immune function eg DM, AIDS, autoimmune disease, tumours, and severe heart, liver, kidney, mental diseases, treatment with systemic corticosteroids, immuno-suppressive agents last four weeks, allergy to drugs in the study, or in another study in the last four weeks. Age: range 2 to 65 Duration: not stated Randomised: 337 Evaluable: 119 (10 dropouts and 208 with unspecified eczema)
Interventions	Hydrocortisone butyrate ointment and mupirocin ointment both applied o.d. versus hydrocortisone butyrate and vehicle ointment applied o.d. (with 2 to 3h between each application) for 28 days.
Outcomes	1. EASI (Eczema Area and Severity Index) score at start and at 28 days. 2. Swabs from most severe lesion and non lesional skin.
Notes	Performed subgroup analysis at end of study which were not part of the pre-determined outcomes.
<i>Risk of bias</i>	
Item	Authors' judgement Description
Allocation concealment?	Unclear B - Unclear

Harper 1995

Methods	D: cross over
Interventions to reduce <i>Staphylococcus aureus</i> in the management of atopic eczema (Review)	
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Harper 1995

(Continued)		
	AC: Not stated RS: Computer generated random code B: Unclear ITT -	
Participants	Two-care, Single centre, UK Incl: atopic eczema, > six months old Excl: Systemic or topical antibiotics or systemic steroids within two weeks of study Age: mean 4.5 (range 1 to 9) Duration: Not stated Randomised: 30 m/f: 9/17 Evaluable: 21	
Interventions	Oilatum Plus vs Oilatum 15 ml in an 8 inch bath of water, soak for 10 to 15 min daily for 4 weeks	
Outcomes	1. Global impression/change 2. Patients rating of skin 3. Adverse events 4. Total score in scale (Costa et al)	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hizawa 1998

Methods	D: with-in patient study (L/R comparison) AC: Not stated RS: Drawing lots B: Participant N, Clinician U, Outcome assessor Y ITT+	
Participants	Two-care, single centre, Japan Incl: mild to moderate atopic dermatitis with similar eczema in bilateral elbow fossae Excl: Skin infection showing pus on exudate Age: 12 to 29 Duration: Not stated Randomised: 15 m/f: 3/12 Evaluable: 15	
Interventions	Povidone iodine 10% vs unspecified placebo Applied bd for one week	

Outcomes	1. Visual analogue scale (VAS) of symptoms rated by dermatologists & patients 2. Itch rated on VAS 3. Colony counts of <i>S aureus</i> from elbow lesions
Notes	Paper kindly reviewed by Dr Yukihiro Ohya

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hjorth 1985

Methods	D: with-in patient study (L/R comparison) AC: Not stated RS: Not stated B: participant Y, clinician & outcome assessor U ITT +
Participants	Two-care, three centres, Denmark Incl: atopic dermatitis Excl: < two yrs old, pregnancy No separate data on age/sex/duration for atopic dermatitis Randomised: 60 Evaluable: 60
Interventions	0.1% betamethasone 17-valerate plus 2% microcrystalline fusidic acid (Fucibet) vs 0.1% betamethasone 17-valerate (Betnovate) Applied b.d. for seven days
Outcomes	1. Global degree of improvement 2. Adverse events 3. Sensitivity to fusidic acid 4. Isolation rate of <i>S Aureus</i>
Notes	Results taken from a larger study of "symmetrical steroid responsive dermatoses"

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Holland 1995

Methods	D: parallel group AC: not stated RS: not stated
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Holland 1995*(Continued)*

	B: Unclear ITT -
Participants	Two-care, single centre, UK. Incl: moderate or severe atopic eczema with <i>S Aureus</i> present on skin Excl: Use of bath emollients, antiseptic bath additives or medicated soaps in past 2 weeks. Systemic or topical antibacterials or oral steroids in last month. Age: mean 17.3 (range 4 to 34) Duration: not stated Randomised: 15 m/f: 6/9 Evaluable: not clear
Interventions	Oilatam Plus (containing triclosan & benzalkonium chloride) vs Oilatam. 15ml in 8 inches of water from 10 to 15 min soak daily for 4 weeks
Outcomes	1. composite scale of Staughton et al. 2. William & Kligman scrub method for non-lesional and lesional skin

Notes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Juenger 2006

Methods	D: parallel group AC: Closed envelopes, but not stated to be sequentially numbered or opaque. RS: Randomisation list by independent biometrician using statistics software. B: participant Y, clinician N, outcome assessor N. ITT: Y
Participants	Single centre, Germany. Incl: "acute" atopic dermatitis, participants > two yrs old. Excl: Acute viral infection, acute "staphyloiderma," other skin disease that could influence evaluation, u.v. treatment, topical or systemic immunosuppressive or immunomodulating treatment, topical or systemic antibiotics, severe generalised disease, pregnancy, female not on contraception, allergy to silver. Age (median): Silver textile group 21, silver free textile group 25.5, steroid ointment 20. Duration (yrs): silver textile 20.5, silver free textile 25.5, steroid oint 16. Randomised: 30 m/f: silver textile 6/4, silver free textile 3/7, steroid oint 5/5. Evaluable: 30
Interventions	Long-sleeved undershirt & long underpants with silver thread versus identical garment with polyester thread versus prednicarbate 0.25% ointment all for 14 days.

Juenger 2006*(Continued)*

Outcomes	1. Global rating of patient/carer "overall disease control" on scale from 0 (controlled) to 3 (not controlled). 2. Asked patients with regards adverse events. 3. SCORAD at day 14. 4. Skin lesional swabs - colony counts
Notes	Participants were allowed to use as much prednicarbate ointment as they wished; those in the silver textile group used almost as much as those in the prednicarbate group whereas those in the non-silver group barely used any. Do not provide adequate data for primary outcomes for this review.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Korting 1994

Methods	D: parallel group AC: not stated RS: not stated B: participant Y, clinician U, outcome assessor U ITT -
Participants	Two-care, six centres, Germany Incl: atopic eczema suggestive of heavy <i>S aureus</i> colonisation with > 10 to power 6 CFU/cm ² Excl: age < 12 (though varied later), infection requiring antibiotics, other severe disease, pregnant, antibiotics last 48h Age: not stated (> 18 yrs) Duration: not stated Randomised: unclear 143 "recruited" m/f: 54/89 Evaluable: unclear
Interventions	Prednicarbate 0.25% cream plus didecyltrimethyl - ammonium chloride 0.25% vs prednicarbate 0.25% cream applied b.d. for 5 days
Outcomes	1. Doctor's opinion of efficacy 2. Presence of <i>S aureus</i> at initially lesional site (William & Kligman method)
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Lever 1988

Methods	D: cross over AC: not stated RS: not stated B: participant U, clinician U, outcome assessor Y ITT -	
Participants	Two-care, single centre, UK. Incl: atopic dermatitis, participants > two yrs old. Excl: potent topical steroids, topical or systemic antibiotics during past 4 weeks. Age: (mean) M/P 22.4 (2 - 52), P/M 20.4 (2 -56). Duration: not stated Randomised: 49 m/f: M/P 12/12, P/M 12/9 Evaluable: 45	
Interventions	2% mupirocin ointment followed by placebo (polyethylene glycol ointment) or vice-versa Daily for two weeks	
Outcomes	1. Emergence of resistant organisms 2. Adverse events 3. Isolation rates of <i>S Aureus</i>	
Notes	Provides lots of data, but not corresponding to our outcomes	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Leyden 1977

Methods	D: parallel group AC: not stated RS: not stated B: Unclear ITT not stated
Participants	Two-care, single centre, USA. Incl: unclear. Not used antibacterial soaps or antibiotic therapy for previous month. Excl: None stated Age: not stated Duration: not stated Randomised: 36 m/f: not stated Evaluable: 36
Interventions	fluocinolone acetonide plus 0.5% neomycin sulphate (Neo-synelar) cream vs fluocinolone acetonide

Leyden 1977

(Continued)	
(Synelar) cream applied bd for one week.	
Outcomes	1. Pruritus score (0 to 3) 2. Improvement in erythema, lichenification, oozing and crusting, scaling (scored 0-3, then graded % reduction - unclear to what this refers) 3. Change in isolation rate of <i>S aureus</i> 4. Change in bacterial counts of <i>S aureus</i> .
Notes	Two studies were reported in this paper. Only study I was included as study II did not have proper controls.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Masako 2005b

Methods	D: with-in patient study (R/L comparison) AC: unclear RS: Unclear B: participant Y, clinician U, outcome assessor Y ITT: Y
Participants	Single centre, Japan. Incl: mild - moderate atopic dermatitis, (n=17) mean age 29.8 yrs. Exclusion criteria: None stated
Interventions	FX cream: 0.2% Farnesol + 5% xylitol cream versus placebo cream (identical in appearance) for 7 days to L or R arms.
Outcomes	1. Scores of dryness and scaling. 2. Change in CFU of SA using stamp bottle method
Notes	There were no loss to follow-up or adverse events.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Nilsson 1992

Methods	D: parallel group AC: not stated
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Nilsson 1992*(Continued)*

	RS: not stated B: Unclear ITT -
Participants	Two-care, single centre, Sweden. Incl: moderate - severe atopic dermatitis (Hanifin & Rajka criteria) Excl: skin infection requiring oral antibiotics. Age: unclear Duration: not stated Randomised: 30 m/f: not stated Evaluable: 28
Interventions	Betamethasone plus neomycin cream vs clobetasol cream applied to all affected areas except face bd for one week, then od for one1 week
Outcomes	1. Patient global scale (up to eight) 2. Changes in individual signs of one area (graded 0 to 3) 3. Isolation of <i>S aureus</i> from most severe lesion 4. Density of <i>S aureus</i> from most severe lesion

Notes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Polano 1960

Methods	D: crossover with four periods AC: identical tubes pre-prepared by pharmacy RS: unclear (selection of a card) B: participant U, clinician Y, outcome assessor Y ITT-
Participants	Two-care, single centre, The Netherlands. Incl: neurodermatitis without apparent secondary infection, having failed to react to standard treatment of outpatient department. Excl: none stated Age: not stated Duration: 'longstanding' Randomised: 24 m/f: not stated Evaluable: 14
Interventions	Metiderm (0.5% prednisolone plus 0.5% neomycin) vs 0.5% prednisolone vs 1% hydrocortisone vs petrolatum base (used in all other ointments). Applied for one week. Frequency not stated.
Outcomes	1. Score (0 to 5) for lichenification, redness, weeping, crusting, apparent secondary infection

Notes Outcomes were pooled without giving primary data, thus not fulfilling outcome measures

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ramsay 1996

Methods	D: parallel group AC: not stated RS: not stated B: unclear ITT-
Participants	Two-care, number of centres unclear, Canada Incl: mild - moderate atopic dermatitis, amenable to treatment with topical steroid, age > three years Excl: Systemic steroids or antibiotics, topical antibiotics or "other effective topical therapy" (past seven days) Age: not stated Duration: not stated Randomised: 186 m/f: not stated Evaluable: 154
Interventions	Fucidic acid 2% plus 1% hydrocortisone cream (FH) vs 1% hydrocortisone cream (H) for 2 weeks. Frequency not stated.
Outcomes	1. Patient severity score (0 to 3) 2. Investigator global response 3. Adverse events 4. Absent (0), mild (1), moderate (2), severe (3) for each of erythema, scaling, oedema, discharge, crusting 5. Lesional swabs
Notes	Reported two studies. Study II (comparing topical 2% fusidic acid) excluded as pooled data from study I. Unclear if pathogens were <i>S aureus</i>

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Schempp 2003

Methods	D: with-in patient study (left/right comparison) AC: not stated
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Schempp 2003

(Continued)

	RS: not stated B: participant Y, clinician Unclear (U), outcome assessor U ITT -
Participants	Two-care, single centre, Germany Incl: subacute atopic dermatitis with SCORAD <80 Excl: Infectious disease, severe underlying clinical disease, cancer, poor health, dependence on alcohol/drugs, pregnancy, breast feeding, other study < four weeks ago, use of oral steroids < two 2 weeks ago or topically < one week ago, current treatment with psychotropic, anti-inflammatory, antibiotic, immunomodulatory drugs. Age: 30.4 +/- 12.9 Duration: not stated Randomised: 21 m/f: 10/8 Evaluable: 18
Interventions	Hyperforin 1.5% vs placebo cream Applied b.d. for four weeks
Outcomes	1. modified SCORAD 2. effect on bacterial colonisation with <i>S aureus</i> (no. of colony forming units)
Notes	Cream was manufactured to GMP standards

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Schuttelaar 2005

Methods	D: parallel group AC: Concealed packs in pharmacy RS: Computer generated in blocks of four B: participant Y, clinician Y, outcome assessor Y ITT +
Participants	Two-care, single centre, The Netherlands. Incl: Atopic eczema (modified Hanifin & Rajka criteria, SCORAD >35), >18 years old Excl: investigational drugs, NSAIDs, light therapy, systemic steroids or topical/systemic antibiotics past four weeks, topical steroids >class I or tar past seven days, known hypersensitivity to drug, pregnant, breast feeding. Age: TT 36.8, T 31.1, overall mean 33.9 Duration: not stated Randomised: 44 m/f: TT 8/14, T 5/17 Evaluable: 44

Schuttelaar 2005*(Continued)*

Interventions	TT: 3% tetracycline + 0.1% triamcinolone acetonide in oculentum simplex FNA T: 0.1% triamcinolone in oculentum simplex FNA Applied all over body b.d. for two weeks
Outcomes	1. Severe and minor adverse effects 2. Global change in SCORAD and SASSAD 3. Isolation rates of <i>S aureus</i>

Notes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Wachs 1976

Methods	D: parallel group AC: not stated RS: not stated B: participant U, clinician U, outcome assessor U ITT -
Participants	Two-care, single centre, USA. Incl: clinically infected, moderate to severe atopic dermatitis Excl: Pregnant, age < one year, renal disease, symptoms requiring oral antibiotics or steroids Age: not stated Duration: not stated Randomised: 83 m/f: not stated Evaluable: 79
Interventions	Betamethasone valerate (Betnovate) plus gentamicin cream (BV/G) vs betmethasone valerate cream (BV) vs gentamicin cream (G) Applied three times daily for 22 days
Outcomes	1. Physician graded global assessment 2. Erythema, pustules, crusting, exudate, vesiculation, lichenification 3. Swabs

Notes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Weinberg 1992

Methods	D: parallel group AC: not stated RS: not stated B: participant U, clinician U, outcome assessor U ITT -
Participants	Two-care, South Africa. Incl: <i>S aureus</i> super-infected atopic dermatitis (Hanifin & Rajka criteria) Excl: Cefadroxil resistant organisms, 'concomitant medications that could have affected the variables being measured.' Age: Cef: 4.1, P 4.4 Duration (yrs): Cef: 3.2, P 2.6 Randomised: 33 (Cef: 16, P: 17) m/f: Cef: 7/6, P: 7/10 Evaluable: Cef: 13, P: 17
Interventions	Cefadroxil 50mg/kg/day in 2 equal doses vs placebo for 2 weeks
Outcomes	1. Patient and physician rated global evaluations 2. Adverse events 3. Pruritus 4. Skin swab sensitivity from three sites 5. Changes in erythema and peeling 6. Isolation of <i>S aureus</i>

Notes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

D: design
AC: method of allocation concealment
RS: method of generating randomisation sequence
B: blinding (participant, clinician, outcome assessor)
ITT: per protocol
PP: per protocol
two-care: secondary healthcare setting
Incl: inclusion criteria
Excl: exclusion criteria
m/f: male to female ratio
od: once daily
b.d.: twice daily
qds: four times a day

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bjornberg 1975	Study not randomised or controlled.
Breneman 1990	No separate results for atopic eczema.
Carpenter 1973	Studies "common dermatoses." No separate results for atopic eczema.
Clark 1974	Not specifically atopic dermatitis and not randomised.
Davis 1968	Did not specifically study atopic dermatitis, rather 'inflammatory and infective dermatoses.'
Eaglstain 1977	Studied secondarily infected "dermatitis" with no description of atopic dermatitis.
Gauger 2003	Open label, controlled R/L comparison. Not randomised.
GP medical research	Compared anti-staphylococcal - steroid combination with addition of antifungal.
Kimata 1998	Not randomised.
Lloyd 1969	Did not specify results for atopic dermatitis from amongst other dermatoses.
Masako 2005a	Was an in vitro study.
Meenan 1988	Compared two anti-staphylococcal - steroid combinations. i.e. comparator was not without an antibacterial agent.
Remitz 2001	No control, and not randomised
Rist 2001	Compared two anti-staphylococcal agents. i.e. comparator was not without an antibacterial agent.
Salo 1988	Compared two preparations of the same anti-staphylococcal agent. i.e. no appropriate control.
Sasai-Takedatsu 1997	Placebo controlled clinical trial. Treatment arbitrarily divided by a referee physician. i.e. not appropriately randomised.
Schempp 2003a	Same study as Schempp 2003 which is published in German in this case.
Stalder 1992	Compared two anti-staphylococcal agents. i.e. comparator was not without an antibacterial agent.
Thaci 1999	Compared two formulations of topical steroid and antibiotic plus vehicle control. Excluded as it cannot be determined whether the antibiotic has any effect - it is well known that a topical steroid will be better than placebo at controlling disease and reducing bacterial counts and thus it cannot be determined if the addition of antibiotic has any additional benefit.
Theodoridis 1979	Studied "eczematous dermatitis" without any further description of atopic dermatitis.
Weitgasser 1983	Compared two different anti-staphylococcal - steroid combinations in a variety of dermatoses with no separate atopic eczema results.
Whitefield 1998	Not randomised or controlled in vitro study and case series using antimicrobial lotion.
Wilkinson JD 1985	Compared two different steroid - antibiotic combinations in a mixture of eczemas with no separate results for atopic eczema.

(Continued)

Study	Reason for exclusion
Wilkinson RD 1980	Compared three steroid - antibiotic combinations. i.e. comparator was not without an antibacterial agent. No
Zienicke 1993	Duplicate of Korting 1994.

DATA AND ANALYSES

Comparison 1. Oral Antibiotics vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global outcome (not good or excellent)			Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse events requiring withdrawal from treatment	2	83	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.21, 12.78]
3 Mean erythema scores as assessed by a physician at end of treatment	1	46	Mean Difference (IV, Random, 95% CI)	0.40 [-0.03, 0.83]
4 Mean erythema scores as assessed by physician 56 days post treatment			Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Number of people with erythema at end of treatment			Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6 Presence of clinically apparent infection at the end of study			Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7 Number of patients in whom <i>S aureus</i> was isolated at end of study			Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8 Mean log of <i>S aureus</i> counts from lesional skin			Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 2. Topical antibiotic vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients in whom <i>S aureus</i> was isolated at end of study			Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 3. Topical steroid plus antibiotic vs topical steroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global outcome (Not good or excellent)	2	195	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.23, 1.16]
2 Global outcome (Not good or excellent)			Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Adverse events requiring withdrawal of treatment	2	218	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.09, 2.78]
4 Minor adverse events not requiring withdrawal from treatment	2	218	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.15, 0.77]
5 SCORAD at end of treatment			Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Mean EASI score at end of treatment			Mean Difference (IV, Random, 95% CI)	Totals not selected
7 No of patients in whom <i>S aureus</i> was isolated at end of study	2	80	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.20, 0.69]

Comparison 4. Silver textile garment vs non-silver textile garment

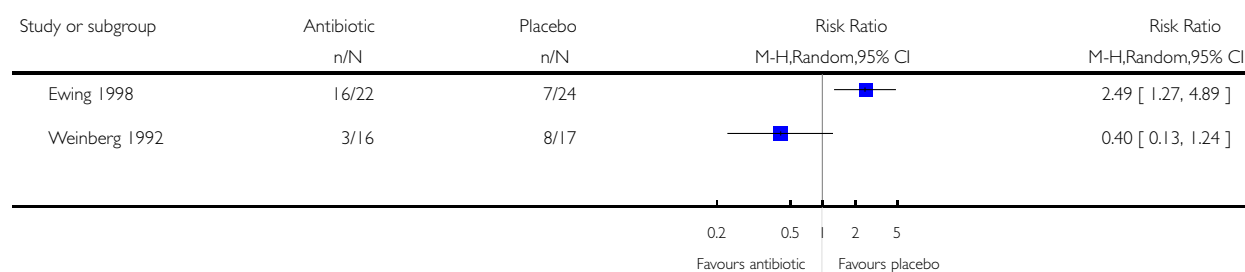
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients in complete remission or well under control at end of study			Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Mean log of <i>S aureus</i> counts from lesional skin			Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Oral Antibiotics vs placebo, Outcome 1 Global outcome (not good or excellent).

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 1 Oral Antibiotics vs placebo

Outcome: 1 Global outcome (not good or excellent)

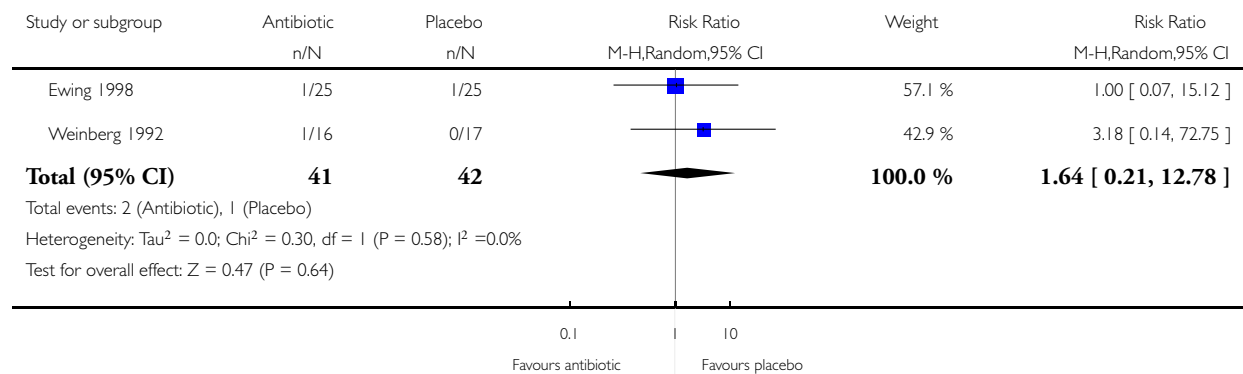


Analysis 1.2. Comparison 1 Oral Antibiotics vs placebo, Outcome 2 Adverse events requiring withdrawal from treatment.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 1 Oral Antibiotics vs placebo

Outcome: 2 Adverse events requiring withdrawal from treatment

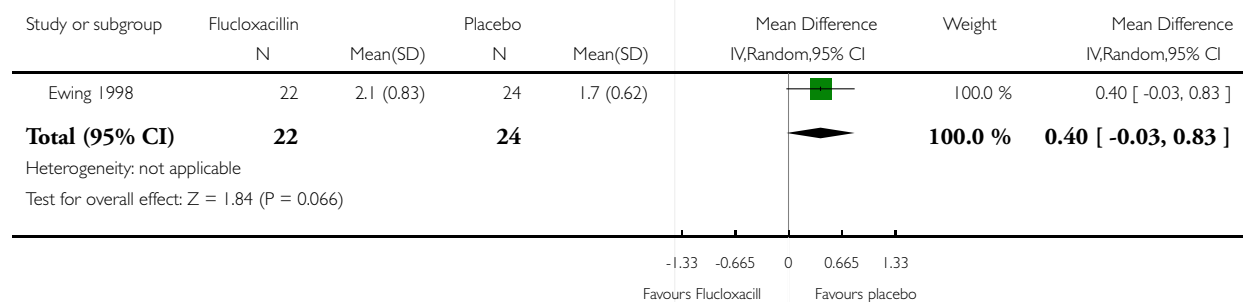


Analysis 1.3. Comparison 1 Oral Antibiotics vs placebo, Outcome 3 Mean erythema scores as assessed by a physician at end of treatment.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 1 Oral Antibiotics vs placebo

Outcome: 3 Mean erythema scores as assessed by a physician at end of treatment

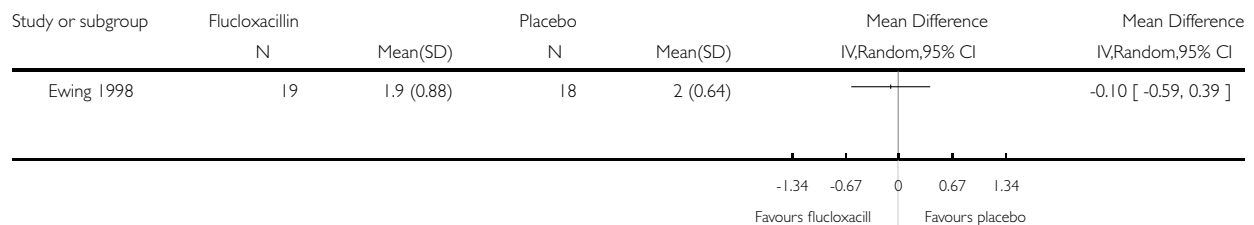


Analysis 1.4. Comparison 1 Oral Antibiotics vs placebo, Outcome 4 Mean erythema scores as assessed by physician 56 days post treatment.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 1 Oral Antibiotics vs placebo

Outcome: 4 Mean erythema scores as assessed by physician 56 days post treatment

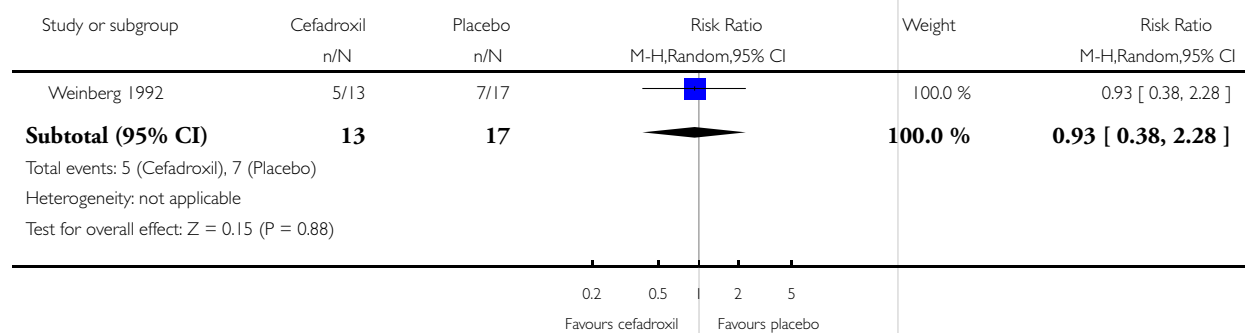


Analysis 1.5. Comparison 1 Oral Antibiotics vs placebo, Outcome 5 Number of people with erythema at end of treatment.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 1 Oral Antibiotics vs placebo

Outcome: 5 Number of people with erythema at end of treatment

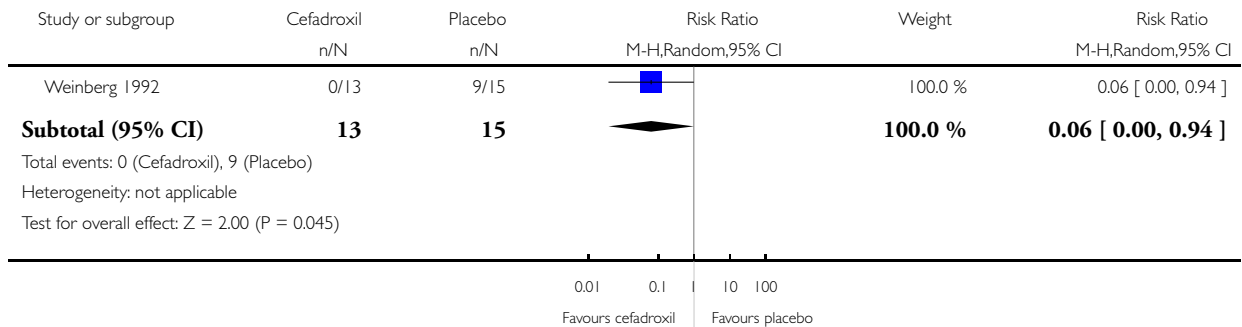


Analysis 1.6. Comparison 1 Oral Antibiotics vs placebo, Outcome 6 Presence of clinically apparent infection at the end of study.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 1 Oral Antibiotics vs placebo

Outcome: 6 Presence of clinically apparent infection at the end of study

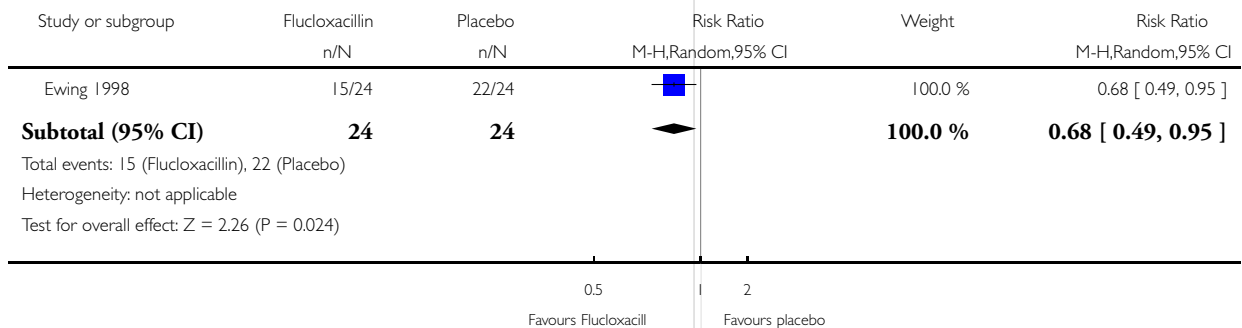


Analysis 1.7. Comparison 1 Oral Antibiotics vs placebo, Outcome 7 Number of patients in whom *S aureus* was isolated at end of study.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 1 Oral Antibiotics vs placebo

Outcome: 7 Number of patients in whom *S aureus* was isolated at end of study

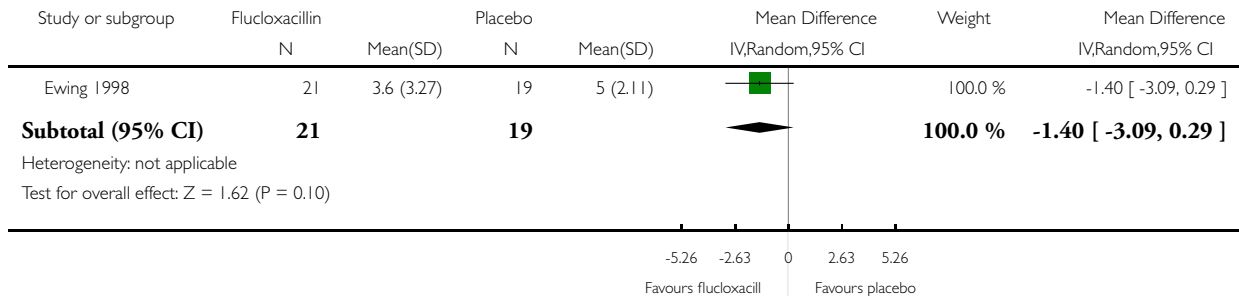


Analysis 1.8. Comparison 1 Oral Antibiotics vs placebo, Outcome 8 Mean log of *S aureus* counts from lesional skin.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 1 Oral Antibiotics vs placebo

Outcome: 8 Mean log of *S aureus* counts from lesional skin

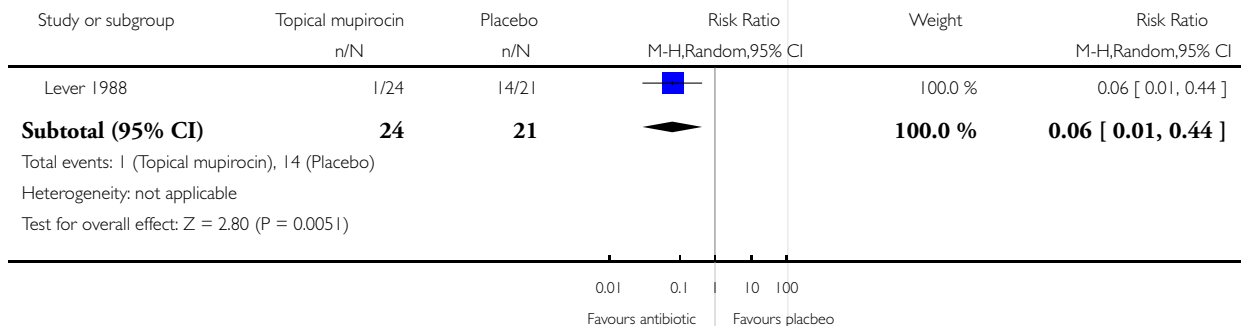


Analysis 2.1. Comparison 2 Topical antibiotic vs placebo, Outcome 1 Number of patients in whom *S aureus* was isolated at end of study.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 2 Topical antibiotic vs placebo

Outcome: 1 Number of patients in whom *S aureus* was isolated at end of study

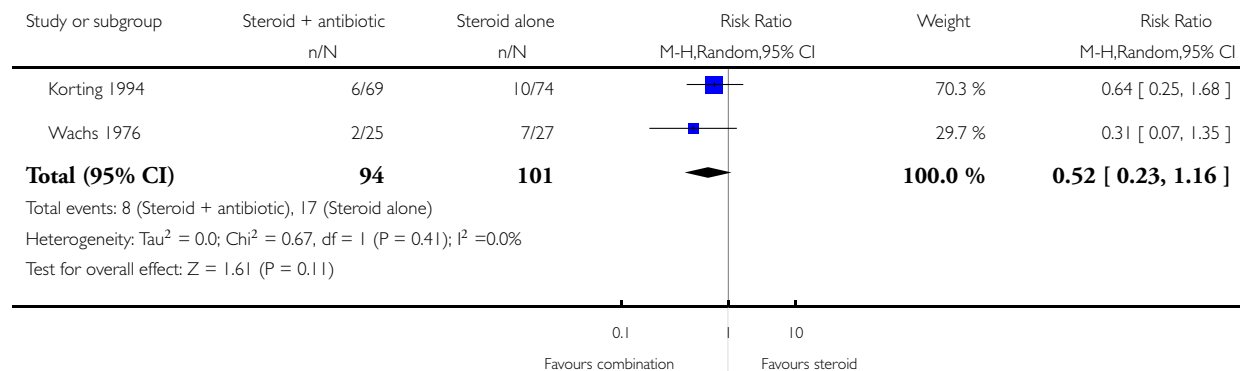


Analysis 3.1. Comparison 3 Topical steroid plus antibiotic vs topical steroid, Outcome 1 Global outcome (Not good or excellent).

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 3 Topical steroid plus antibiotic vs topical steroid

Outcome: 1 Global outcome (Not good or excellent)

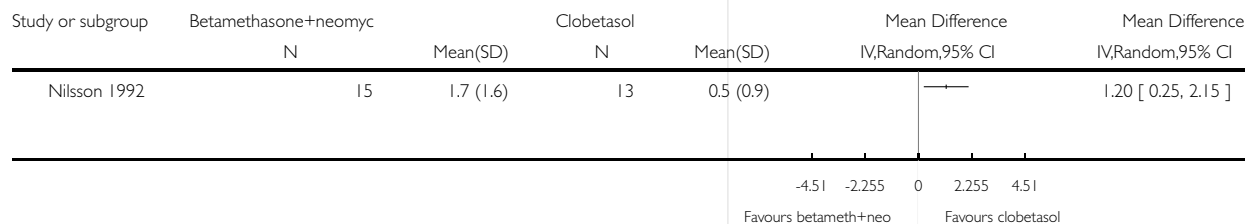


Analysis 3.2. Comparison 3 Topical steroid plus antibiotic vs topical steroid, Outcome 2 Global outcome (Not good or excellent).

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 3 Topical steroid plus antibiotic vs topical steroid

Outcome: 2 Global outcome (Not good or excellent)

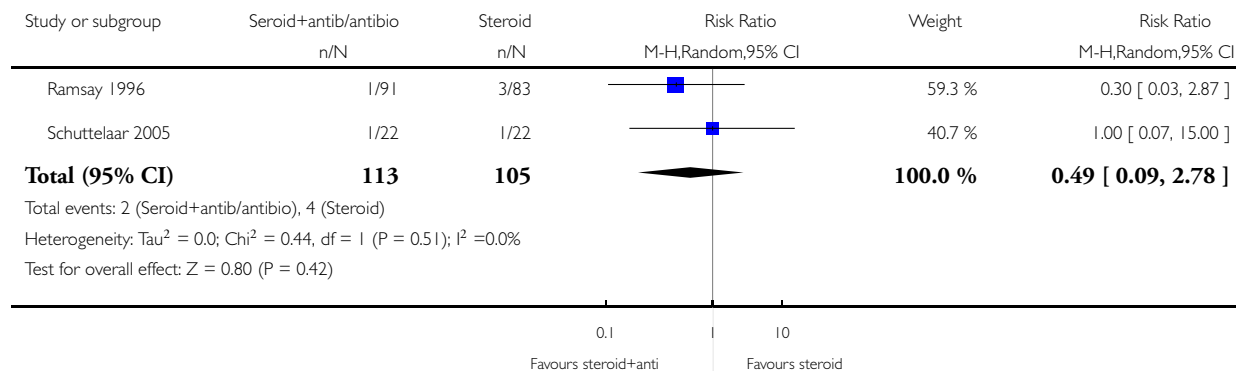


Analysis 3.3. Comparison 3 Topical steroid plus antibiotic vs topical steroid, Outcome 3 Adverse events requiring withdrawal of treatment.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 3 Topical steroid plus antibiotic vs topical steroid

Outcome: 3 Adverse events requiring withdrawal of treatment

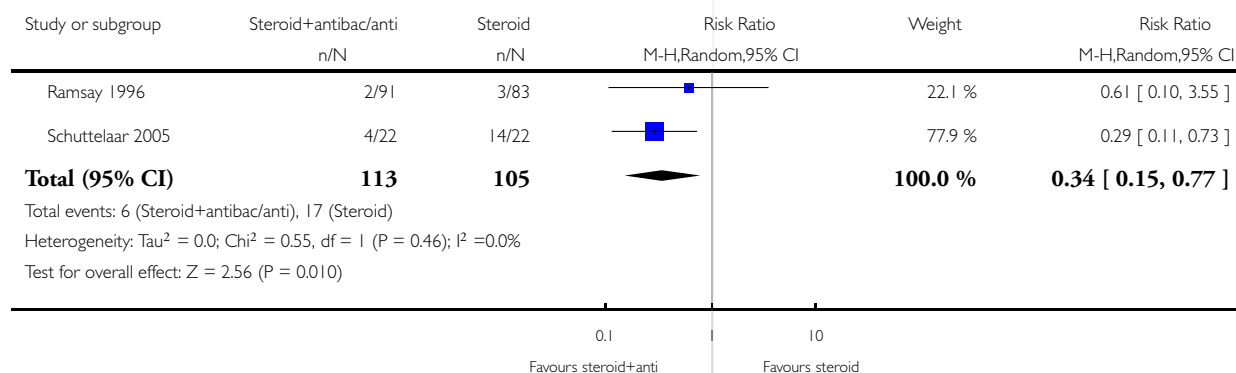


Analysis 3.4. Comparison 3 Topical steroid plus antibiotic vs topical steroid, Outcome 4 Minor adverse events not requiring withdrawal from treatment.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 3 Topical steroid plus antibiotic vs topical steroid

Outcome: 4 Minor adverse events not requiring withdrawal from treatment



Analysis 3.5. Comparison 3 Topical steroid plus antibiotic vs topical steroid, Outcome 5 SCORAD at end of treatment.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 3 Topical steroid plus antibiotic vs topical steroid

Outcome: 5 SCORAD at end of treatment

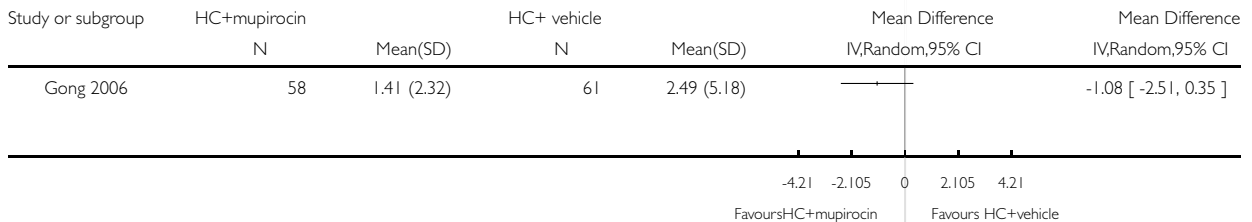


Analysis 3.6. Comparison 3 Topical steroid plus antibiotic vs topical steroid, Outcome 6 Mean EASI score at end of treatment.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 3 Topical steroid plus antibiotic vs topical steroid

Outcome: 6 Mean EASI score at end of treatment

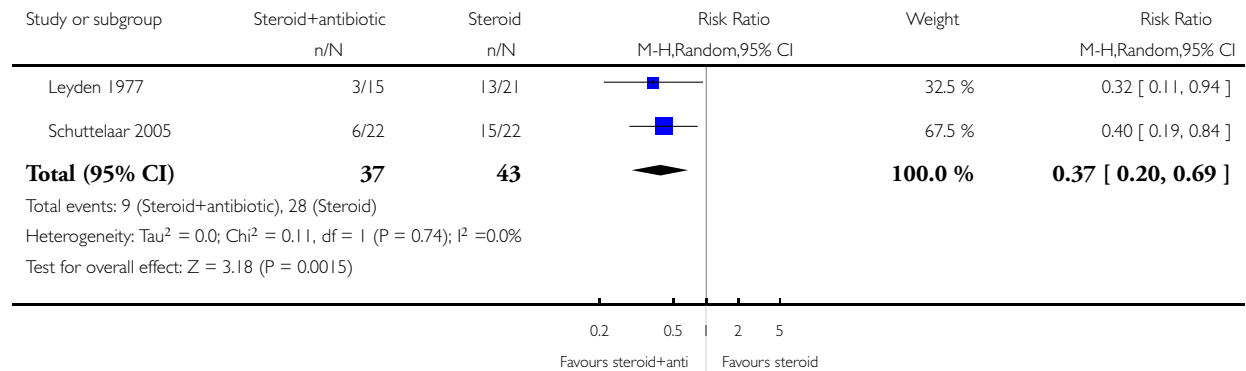


Analysis 3.7. Comparison 3 Topical steroid plus antibiotic vs topical steroid, Outcome 7 No of patients in whom *S aureus* was isolated at end of study.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 3 Topical steroid plus antibiotic vs topical steroid

Outcome: 7 No of patients in whom *S aureus* was isolated at end of study

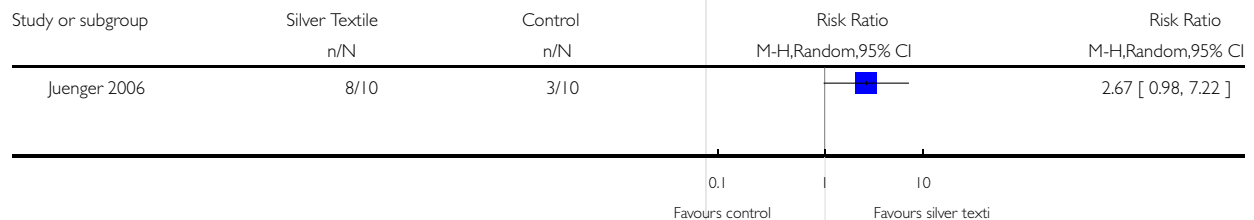


Analysis 4.1. Comparison 4 Silver textile garment vs non-silver textile garment, Outcome 1 Number of patients in complete remission or well under control at end of study.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 4 Silver textile garment vs non-silver textile garment

Outcome: 1 Number of patients in complete remission or well under control at end of study



Analysis 4.2. Comparison 4 Silver textile garment vs non-silver textile garment, Outcome 2 Mean log of *S aureus* counts from lesional skin.

Review: Interventions to reduce Staphylococcus aureus in the management of atopic eczema

Comparison: 4 Silver textile garment vs non-silver textile garment

Outcome: 2 Mean log of *S aureus* counts from lesional skin

Study or subgroup	Silver textiles		Non silver textiles		Mean Difference		Mean Difference	
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI	
Juenger 2006	10	2.1 (0.9)	10	2.1 (1.2)			0.0 [-0.93, 0.93]	

-1.42 -0.71 0 0.71 1.42
Favours silver text Favours non silver t

APPENDICES

Appendix I. Cochrane Central Register of Controlled Trials Search Strategy

#1(atopic eczema):ti,ab,kw or (atopic dermatitis):ti,ab,kw or (neurodermatitis):ti,ab,kw or (besniers prurigo):ti,ab,kw or (infant* or child*) and eczema:ti,ab,kw

#2MeSH descriptor Dermatitis, Atopic explode all trees

#3MeSH descriptor Eczema explode all trees

#4MeSH descriptor Neurodermatitis explode all trees

#5(#1 OR #2 OR #3 OR #4)

#6(staphylococcus aureus):ti,ab,kw or (staphylococc*):ti,ab,kw or (S. and Aureus):ti,ab,kw

#7MeSH descriptor Staphylococcus aureus explode all trees

#8(#6 OR #7)

#9(antibiotic* or antiseptic* or anti-infective*):ti,ab,kw or (dermol or oilatum or emulsiderm or fusidic or fucidic or fucibet):ti,ab,kw or (gregoderm or nystaform or quinacort or terra-cortril):ti,ab,kw or (timodine or viofrom or locoid or betnovate or dermovate or trimovate):ti,ab,kw or (synalar or aureocort or triadcortyl or bactroban or flucloxacillin or erythromycin or clindamycin):ti,ab,kw

#10MeSH descriptor Anti-Infective Agents, Local explode all trees

#11MeSH descriptor Fusidic Acid explode all trees

#12MeSH descriptor Clioquinol explode all trees

#13MeSH descriptor Betamethasone 17-Valerate explode all trees

#14MeSH descriptor Fluocinolone Acetonide explode all trees

#15MeSH descriptor Mupirocin explode all trees

#16MeSH descriptor Floxacillin explode all trees

#17MeSH descriptor Erythromycin explode all trees

#18MeSH descriptor Clindamycin explode all trees

#19(clioquinol):ti,ab,kw

#20(betamethasone):ti,ab,kw

#21(flucinolone):ti,ab,kw

#22(mupirocin):ti,ab,kw

#23(floxacillin):ti,ab,kw

#24(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)

#25(#5 AND #8 AND #24)

Appendix 2. MEDLINE Search Strategy

1. RANDOMIZED CONTROLLED TRIAL.pt.
2. CONTROLLED CLINICAL TRIAL.pt.
3. RANDOMIZED CONTROLLED TRIALS.mp.
4. RANDOM ALLOCATION.sh.
5. DOUBLE BLIND METHOD.sh.
6. SINGLE-BLIND METHOD.sh.
7. or/1-6
8. animal/ not human/
9. 7 not 8
10. CLINICAL TRIAL.pt.
11. CLINICAL TRIALS.mp.
12. (clin\$ adj25 trial\$).ti,ab.
13. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
14. PLACEBOS.sh.
15. placebo\$.ti,ab.
16. random\$.ti,ab.
17. RESEARCH DESIGN.sh.
18. or/10-17
19. 18 not 8
20. 19 not 9
21. COMPARATIVE STUDY.sh.
22. EVALUATION STUDIES.mp.
23. FOLLOW UP STUDIES.sh.
24. PROSPECTIVE STUDIES.sh.
25. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
26. or/21-25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28
30. exp Dermatitis, Atopic/
31. atopic dermatitis.mp.
32. atopic eczema.mp.
33. exp NEURODERMATITIS/
34. neurodermatitis.mp.
35. infantile eczema.mp.
36. childhood eczema.mp.
37. Besniers' Prurigo.mp.
38. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. staphylococcus.mp. or exp STAPHYLOCOCCUS AUREUS/ or exp STAPHYLOCOCCUS/
40. staphylococcus.mp. or *STAPHYLOCOCCUS AUREUS/ or *STAPHYLOCOCCUS/
41. antibiotics.mp. or exp Anti-Bacterial Agents/
42. antiseptic\$.mp. or exp Anti-Infective Agents, Local/
43. 39 or 40
44. (dermol\$ or oilatum or emulsiderm or fusid\$ or fucid\$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
45. (fucib\$ or gregoderma or nystaform or quinocort).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
46. (terra-cortril or timodine or vioform or locoid or betnovate).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
47. (dermovate or trimovate or synalar or aureocort or triadacortyl).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]

48. (bactroban or flucloxacillin or erythromycin or clindamycin).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
49. 41 or 42 or 44 or 45 or 46 or 47 or 48
50. 29 and 38 and 43 and 49

Appendix 3. EMBASE Search Strategy

1. RANDOMIZED CONTROLLED TRIAL.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
2. CONTROLLED CLINICAL TRIAL.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
3. RANDOMIZED CONTROLLED TRIALS.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
4. RANDOM ALLOCATION.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
5. DOUBLE BLIND METHOD.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
6. SINGLE-BLIND METHOD.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
7. or/1-6
8. animal/ not human/
9. 7 not 8
10. CLINICAL TRIAL.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
11. exp CLINICAL TRIALS/
12. (clin\$ adj25 trial\$).ti,ab.
13. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
14. PLACEBOS.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
15. placebo\$.ti,ab.
16. random\$.ti,ab.
17. RESEARCH DESIGN.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
18. or/10-17
19. 18 not 8
20. 19 not 9
21. COMPARATIVE STUDY.sh.
22. exp EVALUATION STUDIES/
23. FOLLOW UP STUDIES.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
24. PROSPECTIVE STUDIES.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
25. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
26. or/21-25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28
30. exp Dermatitis, Atopic/
31. atopic dermatitis.mp.
32. atopic eczema.mp.
33. exp NEURODERMATITIS/
34. neurodermatitis.mp.
35. infantile eczema.mp.

36. childhood eczema.mp.
37. Besniers' Prurigo.mp.
38. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. staphylococcus.mp. or exp STAPHYLOCOCCUS AUREUS/ or exp STAPHYLOCOCCUS/
40. staphylococcus.mp. or *STAPHYLOCOCCUS AUREUS/ or *STAPHYLOCOCCUS/
41. antibiotics.mp. or exp Anti-Bacterial Agents/
42. antiseptic\$.mp. or exp Anti-Infective Agents, Local/
43. 39 or 40
44. (dermol\$ or oilatum or emulsiderm or fusid\$ or fucid\$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
45. (fucib\$ or gregoderm or nystaform or quinocort).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
46. (terra-cortril or timodine or vioform or locoid or betnovate).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
47. (dermovate or trimovate or synalar or aureocort or triadcortyl).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
48. (bactroban or flucloxacillin or erythromycin or clindamycin).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
49. 41 or 42 or 44 or 45 or 46 or 47 or 48
50. 29 and 38 and 43 and 49

WHAT'S NEW

Last assessed as up-to-date: 12 March 2008

Date	Event	Description
14 March 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 3, 2008

CONTRIBUTIONS OF AUTHORS

Draft protocol: JR with contributions from all

Run search: JR, FD, AB

Identify relevant titles and abstracts from searches i.e. broad screen: JR, AB, HCW

Obtain copies of trials: JR, AB

Select which trials to include: AB, JR, HCW, FBH

Extract data from trials: AB, HCW, FBH

Enter data into RevMan: AB, FBH

Carry out analysis: AB, FBH

Interpret analysis: AB, FBH, HCW

Draft final review: AB, FBH

Advice on final review: HCW

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Queens Medical Centre NHS Trust, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have changed the title of this review to 'Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema'. In the protocol it was 'Interventions to reduce *Staphylococcus aureus* for atopic eczema'. We made this change in response to a comment from an external referee.

In the Background section under 'Description of the intervention' we have added a few sentences to the beginning of this section and a slight change of wording in the section 'How the intervention might work'.

Under 'Objectives' we have changed the text from 'To assess the efficacy and possible adverse effects of interventions to reduce *S. aureus* for treating atopic eczema' to 'To assess the effects of interventions to reduce *S. aureus* for treating atopic eczema'.

Under 'Types of interventions' in the review text we have added the following:

Antibacterial soaps, topical steroid plus antibiotic and antifungal agent, antibacterial bath additives and silver impregnated textiles.

Under 'Types of outcome measures' we have omitted the secondary outcome listed in the protocol 'we will report on skin irritation separately as it is a common occurrence' from the review. We have explained this in the Methods section under 'Data extraction and management' as have the definitions of short-term benefit and long-term benefit.

Also under 'Measures of treatment effects' we have analysed the results have been analysed as risk ratios rather than odds ratios as was planned in the protocol, this is in line with Cochrane Skin Group policy and has been explained in the text.

NOTES

The lead reviewer changed from JR to AB in 2004 and this has been reflected in the methods section. In March 2006 FB-H joined the review team.