Clinical evidence

Atopic eczema

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This review is one of over 60 chapters included in the first issue of *Clinical Evidence*, a new information resource for clinicians available from 28 June 1999. The compendium will be updated and expanded every six months. Future issues of *Clinical Evidence* will summarise the evidence on further interventions on eczema, including emolients, ichthammol and tar, PUVA, oral treatments, alternative treatments, and psychological approaches. For more information see the editorial by Fiona Godlee and advertisements facing p 1598 (clinical research), p 1621 (general practice) and p 1567 (other editions).

Background

Definition: Atopic eczema (atopic dermatitis) is an inflammatory skin disease, characterised by an itchy, erythematous, poorly demarcated skin eruption, which has a predilection for the skin creases.[1]

Incidence/prevalence: In the United Kingdom atopic eczema affects 15-20% of schoolchildren[2] and 2-3% of adults. Prevalence has increased substantially over the past 30 years,[3] possibly because of environmental and lifestyle changes.

Aetiology is believed to be multifactorial. Recent interest has focused on the role of airborne allergens (house dust mites, pollen, animal dander), outdoor pollution, climate, diet, and prenatal or early life factors such as infections.

Prognosis: Although there is currently no cure, various interventions exist to control symptoms. Atopic eczema can be expected to clear in 60-70% of children by their early teens, although relapses may occur.

Aims: To reduce the risk of atopic eczema in predisposed infants and children; to minimise the impact of the disease on quality of life.

Outcomes: Severity of symptoms (pruritus, sleep disturbance) and signs (erythema, oozing or crusting, lichenification, cracking, oedema or papulation, excoriation, and dryness); quality of life; area of skin involvement.

Methods

Systematic reviews and controlled clinical trials (RCTs) were located by searching the Cochrane Library (1998), Best Evidence (1998), Medline (1966 to 1998), and Embase (1988 to June 1998). We included all randomised controlled trials that met *Clinical Evidence* quality criteria. Because of the limited studies available for many questions, we included some with methodological shortcomings but have specifically mentioned any problems in the text. Trials used a range of scoring systems for atopic eczema, including SCORAD, the six area six sign atopic dermatitis severity score (SASSAD), Rajka and Langeland scoring system, and dermatology life quality index.

Interventions in atopic eczema

Beneficial:
- Topical steroids

Likely to be beneficial:
- Control of house dust mite

Unknown effectiveness:
- Dietary manipulation
- Prolonged breast feeding in predisposed infants
- Dietary restriction during lactation in mothers of predisposed infants

Unlikely to be beneficial:
- Combinations of topical antimicrobials and steroids

Treatment in adults and children

Option: Topical steroids

Small, short term, placebo controlled RCTs have found that topical corticosteroids applied for two to four weeks improve atopic eczema. We found little good information on the effects of long term use; their effect, if any, on the course of atopic eczema is unknown. No systemic effects have been reported in short term RCTs or in one longer term cohort study. Volunteer studies found that potent topical steroid preparations cause skin thinning after application twice daily for six weeks, but skin thickness returns to normal within four weeks of stopping treatment.

Benefits

We found no systematic review of treatment with topical steroids.

Topical steroids versus placebo: We found nine RCTs (double blind vehicle controlled studies) comparing

Topical steroids versus placebo in atopic eczema: results of randomised controlled trials[4-6]

Trial	Participants: No	Participants: Age (years)	Outcome
Prednicarbate ointment, 0.25% twice daily for 4 weeks[4]	51	18-60	Dermatitis reduced in 87% of treated patients, 8% of controls Pruritis significantly reduced by treatment (patient's assessment)
Hydrocortisone valerate cream, 0.2% thrice daily for 2 weeks[5]	20	2-75	Excellent results, or eczema better, in 75% of treated patients, 20% of controls
Clobetasol propionate cream, 0.05% twice daily for 4 weeks[6]	81	⩾12	Good or excellent results, or eczema clear, in 82% of treated patients, 29% of controls

Confidence intervals were not reported in these trials.

topical steroids versus placebo cream (vehicle) in patients with atopic eczema. Three trials included patients with non-atopic forms of eczema, and another three did not specify the type of eczema. The three remaining trials all found substantial improvement with steroid compared to placebo (table).[4–6]

Topical steroids versus each other: We found 11 further double blind RCTs comparing a variety of topical steroids against each other (no placebo) in children and adults with atopic eczema. These showed significant improvements in 41-97% of patients after two to six weeks of treatment.

Harms

No serious or systemic effects or cases of skin atrophy were reported in these short term trials, nor in a longer cohort study in 14 prepubertal children.[7] Minor adverse effects such as burning, stinging, irritation, folliculitis, hypertrichosis, contact dermatitis, and pigmentary disturbances occurred in less than 10% of patients.

Skin thinning: We found no RCTs looking at skin thinning in patients with atopic eczema. Four small RCTs in healthy volunteers (n = 12) used ultrasound to evaluate skin thickness.[8–11] Skin thinning occurred with three preparations (triamcinolone acetonide 0.1%, clobetasol 17-propionate 0.05%, and betamethasone 17-valerate 0.1%) after twice daily application for six weeks but reversed within four weeks of stopping treatment.

Comment

The RCTs used different clinical scoring systems, making it difficult to compare results.

Option: Combinations of topical antimicrobials and steroids

Two RCTs have found that these agents have no benefit over topical steroids alone in improving the clinical signs and symptoms of atopic eczema. Only one of the trials used patients with clinically infected eczema.

Benefits

We found no systematic review of the effects of combinations of topical antimicrobials and steroids.

Combinations versus topical steroid alone: We found two RCTs comparing topical antimicrobial-steroid combinations versus topical steroid alone in patients with atopic dermatitis.[12 13] These trials showed no significant difference in the improvement in clinical signs and symptoms with hydrocortisone acetate-fusidic acid compared with hydrocortisone (186 participants) or betamethasone-fusidic acid compared with betamethasone (60 participants) after two weeks' and one week's treatment.

Combinations versus each other: Four further RCTs (34-207 patients) compared different topical steroid-antimicrobial preparations with each other in clinically infected eczema (atopic eczema not specified).[14–17] These found no significant difference between the various preparations with respect to improvement in clinical signs and symptoms. However, patients treated with acetate-fusidic acid responded more quickly than those treated with miconazole-hydrocortisone, and bacteriological responses to betamethasone and acetate-fusidic acid were superior to those with betamethasone-clioquinol and miconazole-hydrocortisone.

Harms

Minor adverse effects—itching, stinging, burning, and irritation—were reported in < 2% of patients.

Comment

Only the second study specified a degree of infection in most participants at recruitment. This study also included patients with contact dermatitis in the overall analysis, and the use of left-right comparisons within individual participants may have reduced any observed beneficial effect of combination therapy due to systematic absorption of the antimicrobial agent.[13] In practice, topical antimicrobial-steroid combinations are usually reserved for clinically infected eczema.

Option: Control of house dust mite

Based on the results of a single small RCT, extreme reduction in dust levels (achieved by Gore-tex covered mattresses, acaricidal spraying, and high filtration vacuuming) may reduce eczema severity score. However, it is impossible to say from this evidence how many patients might benefit and for how long. The clinical relevance of the reduced severity score is uncertain. Bedding covers seem to be the most effective intervention for reducing levels in the home (box on next page).

Benefits

We found no systematic review. We found three controlled trials, one of which did not mention randomisation. A double blind RCT in 48 atopic patients (24 adults and 24 children > 7 years old; skin prick and radioallergosorbent test (RAST) status not specified) compared Gore-tex bedcovers, benzyltannate spray, and high filtration vacuuming against cotton bedcovers, placebo spray, and standard vacuum cleaners. After six months there was a significantly greater reduction in eczema severity scores in treated patients than with placebo (mean difference in severity score (maximum 108 units) = 4.3 units, 95% confidence interval 1.3 to 7.3). This was associated with a 98% reduction in mean mattress dust load compared

Reducing house dust mite levels: results of randomised controlled trials

Mattress, pillow and duvet covers (microporous or polyurethane coated): Very effective (3 RCTs).[18–20] Dust mite allergen levels 1-25% of control levels after 3-12 months; 44-98% reduction in dust load after 3 months

Washing bedding at 55°C: Effective (2 CCTs). Reduces levels of Der p1 by >95% and kills 100% mites

Removal of carpets and curtains: Unknown

Acaricides (benzyl benzoate, etc): Conflicting results from RCTs—better when used on carpets than on mattresses. Effect may be short lived

Intensive vacuuming: Small effect on mite levels in mattresses (1 RCT, 1 CCT) but not correlated with improvement in symptoms, possibly because conventional rather than high filtration cleaners may increase levels of airborne mite allergens, which may aggravate atopic disease (1 RCT in 16 rooms).

Air filters and dehumidifiers: Conflicting results from RCTs

Trials have tended to use a combination of control measures, making it difficult to see which measures were responsible for beneficial effects.

with 16% in the placebo group (P=0.002) and a 91% and 76% reduction in the concentration of bedroom and living room carpet mite allergen Der p1 compared with 89% and 38% in the placebo group (P=0.94 and P=0.27).[20] A double blind RCT using natamycin or placebo spray with or without vacuuming in 20 patients with atopic dermatitis (aged 12-47 years) with positive skin prick and RAST tests to house dust mite showed no correlation between improvement in clinical score and lowered numbers of mites. However, the study was small and the maximum reduction in mite numbers in mattresses was only 68%.[21] A controlled trial (randomisation not mentioned) in patients with atopic eczema showed induction of an itch free period and prolonged remission in 30 patients with positive mite RAST scores after three to four weeks in a "clean room" with reduced dust levels (levels of Der p1 were not measured). Neither an itch free period nor prolonged remission were seen in the 11 patients with negative RAST scores treated in a similar environment, or in the 10 controls with positive mite RAST scores treated in a common hospital room.[22]

Harms

No harmful effects were reported in the trials.

Comment

Additional, small, uncontrolled studies have suggested a beneficial effect of mite reduction measures on symptoms, although mite or allergen levels were not quantified. The use of bedding covers seems to be the simplest and most effective measure to reduce house dust mite levels in the home.

Option: Dietary manipulation

We found insufficient evidence to recommend dietary manipulation such as exclusion of egg and cow's milk in children with atopic eczema; such intervention should be reserved for highly motivated patients with eczema that does not respond to conventional treatment. We found no good evidence that dietary manipulation alters the severity of eczema in adults.

Benefits

In infants: We found one systematic review that identified one small RCT in 17 breastfed infants with atopic eczema. This looked at the effect of excluding allergenic foods, such as cow's milk and eggs, from the mother's diet. It found no effect on the severity of eczema.[23] However, soya milk, which is potentially allergenic itself, was used as a cow's milk substitute in this trial.

In children: We found no systematic review. We found two RCTs (double blind crossover) evaluating the effects of an egg and milk exclusion diet in unselected children with eczema. Both used potentially allergenic soya based milk substitute during the trial period.[24 25] One RCT in 40 children aged 2-8 years found a significant improvement in eczema severity (14/20 treated children improved versus 1/20 controls).[24] The other RCT, involving 40 children and young adults, showed no effect.[25] Double blind placebo controlled food challenges have been used to identify patients with food allergy, but the clinical relevance of positive reactions (which may comprise gastrointestinal, respiratory, or cutaneous symptoms) to subsequent eczema control is unclear. In three studies, double blind placebo controlled food challenges caused immediate hypersensitivity reactions in 63% of children (n=320) with moderate to severe atopic eczema and in 33-39% of children (n=211) with mild to severe atopic eczema. Egg, milk, and peanut accounted for 67-78% of the reactions. The effect of subsequent dietary elimination was studied in only 27 of these children. This showed a greater improvement in patients on exclusion diets than in non-randomly selected controls, using a crude scoring system.[26] Only one RCT (in 85 children) has looked at a "few foods diet," in which all but a handful of foods are excluded. This found no difference in eczema severity compared with normal diet.

In adults: We found no systematic review. We found one RCT (double blind crossover) that had analysed adults separately. This found no significant improvement in eczema severity with an egg and cow's milk exclusion diet in 18 adults, although potentially allergenic soya milk was used as a cow's milk substitute.[25]

Harms

Calcium, protein, and calorie deficiency are risks of dairy-free diets in children.

Comment

The clinical relevance to patients of the changes in severity scores obtained in many studies is unknown. We have not included studies looking at the role of food additives, fatty acid supplementation, or trace elements in eczema.

Prevention in predisposed infants

Option: Prolonged breast feeding

We found limited observational studies suggesting that exclusive breast feeding for at least five months reduces the risk of eczema in infants with a family history of atopy.

Benefits

We found no systematic review or RCTs. One 17 year prospective study of 236 healthy infants found that those who were breast fed exclusively for more than six months had a significantly lower prevalence of eczema at one year (all infants) and three years (infants with a family history of atopy) than those breast fed for less than one month and weaned onto cow's milk formula.[27] Infants who were intermittently breast fed for two to six months showed no reduction in the prevalence of eczema. Two prospective studies[28 29] compared prevalence of eczema in exclusively breast fed infants and in non-breast fed infants. Non-breast fed infants were randomised to different formulae. In infants with a family history of atopy, those who were exclusively breast fed for an average of five months had a significantly lower prevalence of eczema at 18 months compared with non-breast fed infants randomised to soya or cow's milk, but not compared with those randomised to whey hydrolysate or casein hydrolysate. One further prospective study showed a significantly lower incidence of eczema at three years in infants breast fed for 6-13 months (with or without milk supplements) than in those fed conventional adapted formula, but a comparable incidence with those fed hydrolysed milk formulae. Some studies found no beneficial effect of breast feeding, but all had methodological problems.

Harms

We found no evidence of harms associated with prolonged breast feeding.

Comment

Much of the available evidence suffers from methodological difficulties such as selection and information bias, short duration of breast feeding, and inadequate control for confounding factors such as introduction of supplemental milk or solid foods. Choosing to breast feed exclusively for prolonged periods may be associated with other factors that protect against eczema, leading to bias.

Option: Restricting mother's diet during lactation

Restricting the mother's diet during lactation may protect against the development of eczema in infants with a family history of atopy, but we found insufficient evidence to recommend such restrictions routinely.

Benefits

We found one systematic review that identified three RCTs.[30] These found a lower prevalence of eczema in breast fed infants whose mothers took antigen avoidance diets compared with those on normal diets during lactation.

Harms

No harms of restricting mother's diet during lactation were reported.

Comment

Methodological shortcomings in all three trials argue for caution in applying these results.[30]

Competing interests: None declared.

Key messages

- Small RCTs have found that topical corticosteroids relieve symptoms of atopic eczema and are safe in the short term. We found little good information on their long term side effects or on their effects, if any, on the natural history of atopic eczema.
- We found limited evidence suggesting that the routine addition of antimicrobial agents to topical steroid preparations provides no additional benefit.
- We found limited evidence that control of house dust mite reduces severity of symptoms, especially in patients with positive mite RAST scores and in children, but only if very low levels are achieved. Bedding covers were found to be the most effective control method.
- We found insufficient evidence that dietary manipulation in adults or children reduces the severity of symptoms.
- We found insufficient evidence that either prolonged breast feeding or manipulation of mother's diet during lactation protects against the development of eczema in infants with a family history of atopy.

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Lesson of the week

Cavernous haemangioma mimicking multiple sclerosis

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Patients diagnosed with multiple sclerosis before the advent of magnetic resonance imaging and whose symptoms could be attributable cavernous haemangioma should be reviewed with magnetic resonance imaging

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Cavernous haemangiomas are vascular malformations that rarely affect the brain, but their clinical presentation can simulate multiple sclerosis. The likelihood of mistaking cavernous haemangioma for multiple sclerosis is increased further by the fact that cavernous haemangiomas are poorly identified by angiography, and even computed tomography has a relatively low sensitivity and specificity for these lesions.[1] However, high field magnetic resonance imaging is able to distinguish cavernous haemangiomas, and since its introduction increasing numbers have been reported.[1]

We describe two patients who had been diagnosed as having multiple sclerosis many years before the widespread use of computed tomography or the advent of magnetic resonance imaging. Magnetic resonance imaging subsequently showed that they had cavernous haemangioma.

Case reports

Case 1

A 17 year old boy presented in 1975 with diplopia, left sided facial weakness, and dizziness. He was right handed. Physical examination showed that he had left VI nerve palsy and mild weakness of the lower left side of his face. The patient was admitted to hospital for further investigation. A lumbar puncture showed clear cerebrospinal fluid under normal pressure but a slightly high γ globulin fraction (0.04 g/l; 12.1% of total protein), a red cell count of 4×10^9/l, and a white cell count of 1×10^9/l.

The patient's facial weakness resolved over several months, but the left VI nerve palsy persisted. About eight months after his initial presentation, he had a further episode of neurological dysfunction with numbness of the right hand. He had reduced sensations of light touch and pain, and a lumbar puncture again showed an increased γ globulin fraction. One month later, the numbness in the right hand had resolved, but the palsy in the left VI nerve remained unchanged. A diagnosis of probable multiple sclerosis was made.

The patient had no further problems until he was 34 years old, when he presented with numbness of the right hand and left side of the face and impaired balance. Physical examination showed a subjective sensory disturbance in the right hand, continuing palsy of the left VI nerve, and considerably reduced visual acuity in the left eye.

Electrophysiological studies, computed tomography, and magnetic resonance imaging were arranged. Visual stimuli either failed to evoke recordable cortical responses or produced abnormal waveforms on both sides. Stimulation of the left median nerve produced well formed responses at the cervical cord, but a poor cortical response. Stimulation of the right median nerve produced poor responses at the cervical cord and the cerebral cortex. Computed tomography showed hyperdense, ill defined lesions with irregular calcification in the posterior aspect of the pons, the right frontal lobe, and the periventricular region of the right parietal lobe. There was no enhancement after contrast. With magnetic resonance imaging (figure), the lesions returned mixed signals, there was no surrounding cerebral oedema and no mass effect. It was concluded that this patient had multiple cavernous haemangioma.

Case 2

A 36 year old man presented to a neurologist in 1964. He was right handed. He had a five year history of laughing without reason (which had led to considerable embarrassment) and increasing weakness of the right arm and leg. Physical examination showed that he had a right spastic hemiparesis and a pseudobulbar palsy. No abnormalities were detected by a radioisotope scan or angiography of the brain, and multiple sclerosis was considered the most likely diagnosis.

Despite the neurological impairment, his disability over the next 15 years was slight, and he continued to work as a manager for an advertising company. However, at the age of 51, the right sided weakness and spasticity began to progress. His inappropriate laughter was also becoming more troublesome. He presented again, aged 56, when he developed a squint in his left eye. At this time physical examination showed palsy of