CHAPTER 4

INTERVENTIONS FOR HAND ECZEMA

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INTRODUCTION

Definition and epidemiology
The term ‘hand eczema’ implies an inflammation of the skin (dermatitis) that is confined to the hands. Hand eczema is considered a ‘common condition’, with a point prevalence of 1 to 5% among adults in the general population, and a one-year prevalence of up to 10%, depending whether the disease definition includes more pronounced or mild cases.\textsuperscript{1-3} The prevalence may be increasing in some countries.\textsuperscript{3} Recently, a decreased prevalence has been observed, and attributed to decreased occupational exposure to irritants.\textsuperscript{4} It is twice as common in women as in men, with the highest prevalence in young women.\textsuperscript{3 5} Reasons for this sex difference are unknown, although greater exposure of women to wet work is probably contributory.

Causes
Predisposing and external factors both play a role in hand eczema. Being atopic (having a tendency to develop asthma, hay fever or eczema) is the major predisposing factor responsible for hand eczema; one-third to half the patients with hand eczema can be considered atopics.\textsuperscript{6-8} The commonest external cause is contact irritants, or mild-toxic agents. Water is an example of a contact irritant. A distinction is made between irritant contact dermatitis and allergic contact dermatitis, which is caused by skin contact with allergens. Allergic contact dermatitis is less common than irritant contact dermatitis, and only occurs in persons who have developed a specific contact allergy to a specific substance such as rubber. Ingested allergens (e.g. nickel) may also provoke hand eczema.\textsuperscript{9} There are also several types of hand eczema where the cause is unknown. These forms of hand eczema may be referred to as pompholyx, dyshidrotic eczema or dyshidrosis, nummular eczema, tylotic eczema and hyperkeratotic eczema. In many patients with chronic hand eczema a combination of the above mentioned factors seems to play a role. Hand eczema may be accompanied by similar skin changes on the feet. The relevance of psychosomatic factors remains speculative.\textsuperscript{10}

Impact
Itch is common among patients with hand eczema. Itch itself can result in sleep loss to patients and to members of their family. A vicious cycle of symptoms and skin damage can develop, the so-called itch/scratch/itch cycle.

In addition to itch, the social stigmata associated with a visible skin disease can be a great burden. The hands are important organs of communication and expression. Therefore, any impairment in function and form may result in major psychosocial problems, e.g. anxiety, low self-esteem and social phobia.
Interventions for hand eczema

Painful cracks and blisters, besides their effect on daily life outside work, can prevent manual work leading to significant disability and huge economic loss to both individuals and society. Hand eczema accounts for an estimated 90% of occupational skin disease. High prevalence has been documented in specific occupational groups, such as nurses, hairdressers and bakers. These estimates exclude people affected through housework and many other occupational groups not included in routine surveillance systems.

Treatment
Theoretically, identifying and eliminating an allergic contact factor (e.g. rubber allergy) could cure the eczema. In clinical practice, such cases are rare. This has led to many diverse therapies being used to control the disease such as:
1. Skin protection measures, including gloves
2. Topical treatments (bland emollients, corticosteroid creams or ointments, coal tar and derivatives, irradiation with UV-light or X-rays)
3. Systemic treatments (oral corticosteroids, other immunosuppressants such as ciclosporin).

Prognosis
Previous studies have suggested that hand eczema tends to run a long lasting and chronic relapsing course.

Rationale for doing a review
The high prevalence of hand eczema, along with its poor prognosis and associated disability with economic loss, makes hand eczema an important disease to study from an individual and a societal perspective. This, coupled with the large list of diverse treatments of unknown effectiveness and several conflicting studies suggests that a systematic review is needed. Even if methodological constraints do not permit clarification of existing conflicts, then the review will be an important first step in identifying the research gaps.

OBJECTIVES
To assess the effects of interventions for hand eczema.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW
Types of studies
Only randomised controlled trials of interventions for hand eczema, regardless of hand eczema type and other affected localisations. No language restrictions will be imposed. The trial should not have been published elsewhere; where
there are duplicate publications, the paper with the most relevant data will be used. Studies dealing with side effects or biological outcomes only are excluded.

**Types of participants**
Anyone who has been diagnosed with hand eczema by a physician, regardless of the underlying assumed aetiology. The terms ‘eczema’ and ‘dermatitis’ are acceptable, wherever it refers to the hands. Other terms as ‘pompholyx’, ‘dyshidrosis’ and ‘pulpitis’ are deemed acceptable if diagnosed by a physician. There are no age limits.

**Types of interventions**
Only studies comparing the intervention with no treatment, placebo, vehicle or other active treatments were included. All types of interventions were considered, and can be described within the following subgroups:
1. Emollients and keratolytic agents (such as salicylic acid)
2. Antipruritic and antihyperproliferative agents (such as tar)
3. Anti-inflammatory agents (such as topical corticosteroids)
4. Systemic anti-inflammatory agents (such as oral corticosteroids)
5. Local immunomodulating agents (such as pimecrolimus)
6. Systemic immunomodulating agents (such as ciclosporin)
7. Photo and ionising radiation therapy (local or systemic)
8. Skin protection measures, including allergen avoidance
9. Skin care education
Interventions to prevent hand eczema will be dealt with in another review.\textsuperscript{16}

**Types of outcome measures**
Primary outcome measures:
- Percentage of patients with self-rated good/excellent control of symptoms with adequate length of follow-up
- Percentage of patients with investigator-rated good/excellent control of symptoms with adequate length of follow-up.
Secondary outcome measures:
- Reduction in severity (patient- and physician-rated scoring systems)
- Time until relapse.
Tertiary outcome measures:
- Dose reduction: reduction in treatment dose per time unit or cumulative prescribed treatment dose; for example: decrease in daily topical medication, or decrease in weekly photoradiation
- Side effects: adverse effects (long and short term) of the intervention.
Interventions for hand eczema

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Electronic databases
This review drew on the search strategy developed for the Cochrane Skin Group as a whole. Relevant trials will be identified from:
1. The Cochrane Skin Group Specialised Register and the Cochrane Central Register of Controlled Trials (Central)
2. Medline (1966 through present)
3. Old Medline (1957-1965)
4. Embase (1974 through present)
5. Pascal (1984 through present)
6. Jicst-Eplus (1985 through present)
7. AMED (1985 through present).

The following draft search strategy was adapted where necessary:

Ad 1: Search strategy for the Cochrane Central Register of Controlled Trials (Central), via the Cochrane Library:
1. eczema* or dermatitis or tyloct or pompholyx or cheiropompholyx or pulpitis or pulpite or dyshidro* or dyshydro* or dishidro* or dishydro*
2. hand or hands or finger* or acra* or palm* or dors* or apron
3. treat* or therap* or cream* or medicat*
4. #1 and #2 and #3

* = truncation symbol.

Ad 2: Search strategy for Medline, via Silver Platter:
1. explode “skin-diseases-eczematous”/ all subheadings
2. explode “eczema”/ all subheadings
3. explode “dermatitis”/ all subheadings
4. eczema* or dermatitis or tyloct or pompholyx or cheiropompholyx
5. pulpitis or pulpite or dyshidro* or dyshydro* or dishidro* or dishydro*
6. explode “hand”/ all subheadings
7. hand or hands or acra or acral or acras or finger or fingers or fingertip*
8. dors* or apron or palm or palms or palmal or palmar or palmoplant*
9. (#1 or #2 or #3 or #4 or #5) and (#6 or #7 or #8)
10. #9 and (treat* or therap*)
11. “hand-dermatoses”/ all subheadings
12. #11 and (treat* or therap*)
13. #10 or #12
14. #13 and (trial* or random* or placebo* or prospectiv* or volunteer*)
15. #13 and PT(“clinical-trial” or “controlled-clinical-trial” or “guideline” or “meta-analysis” or “multicenter-study” or “practice-guideline” or “randomized-controlled-trial” or “review”)
16. #13 and (blind* or mask* or crossover* or cross-over* or factorial*)
17. #13 and (controlled or singl* or doubl* or trebl*)
18. #14 or #15 or #16 or #17

* = truncation symbol.
PT = publication type.

Ad 3: Search strategy for Old Medline, via DIMDI, www.dimdi.de, applying Expert Mode:
1. explode “skin-diseases-eczematous”/ all subheadings
2. explode “eczema”/ all subheadings
3. explode “dermatitis”/ all subheadings
4. eczema* or dermatitis or tylotic or pompholyx or cheiropompholyx
5. pulpitis or pulpote or dyshidrotic or dyshyrdrotic or dishidrotic or dishydrotic
6. explode “hand”/ all subheadings
7. hand or hands or acra or acral or acras or finger or fingers or fingertip*
8. dors* or apron or palm or palms or palmar or palmoplant*
9. (#1 or #2 or #3 or #4 or #5) and (#6 or #7 or #8)
10. “hand-dermatoses”/ all subheadings
11. #9 or #10
12. #11 and (treat* or therap* or trial* or placebo* or control* or random* or blind* or mask* or prospectiv* or volunteer*)

* = truncation symbol.

Ad 4: Search strategy for Embase, via STN
1. hand dermatoses+NT/CT
2. skin diseases, eczematous+NT/CT
3. eczema+NT/CT
4. dermatosis+NT/CT
5. eczema? or dermatitis or tylotic or pompholyx or cheiropompholyx or pulpitis or pulpote or dyshidrotic or dishidrotic or dyshyrdrotic or dishydrotic
6. hand+NT/CT
7. hand or hands or finger or fingers or fingertip? or dors? or apron or acra or acral or acras or palm or palms or palmar or palmoplant?
8. (#2 or #3 or #4 or #5) and (#6 or #7)
9. #1 or #8
Interventions for hand eczema

10. trial? or controlled clinical?/DT or randomized controlled?/DT or review/DT or meta analysis/DT or multicenter study/DT or practice guideline/DT or consensus?/DT
11. #9 and #10
12. #9 and general review/DT and (therap? or treat?)
13. #9 and (meta analysis/CT or practice guideline/CT or clinical trial+NT/CT)
14. #9 and (random? or placebo? or blind? or mask? Or volunteer? or prospectiv? or control?)
15. #11 or #12 or #13 or #14

? = truncation symbol.
CT = controlled term.
NT = narrower terms (= explode).
DT = document type.

Ad 5: Search strategy for Pascal, via STN:
1. eczema? or dermatos? or dermatitis or tylotic or pompholyx or cheiropompholyx or pulpitis or pulpite or dyshidrotic or dishydrotic or dyshidrotic or dishydro?
2. hand or hands or acra or acral or acras or finger or fingers or fingertip? or dors? or apron or palm or palms or palmal or palmar or palmoplant?
3. treat? or therap? or manag?
4. general review/DT or trial? or double blind? or random? or mask? Or control? or volunteer? or prospectiv? or placebo?
5. #1 and #2 and #3 and #4

? = truncation symbol.
DT = document type.

Ad 6: Search strategy for Jicst-Eplus, via STN:
1. hand dermatoses+NT/CT
2. skin diseases, eczematous+NT/CT
3. eczema+NT/CT
4. dermatosis+NT/CT
5. eczema? or dermatitis or tylotic or pompholyx or cheiropompholyx or pulpitis or pulpite or dyshidro? or dishidro? or dyshydro? or dishydro?
6. hand+NT/CT
7. hand or hands or finger or fingers or fingertip? or dors? or apron or acra or acral or acras or palm or palms or palmal or palmar or palmoplant?
8. (#2 or #3 or #4 or #5) and (#6 or #7)
9. #1 or #8
10. #9 and (therap? or treat?)
11. #10 and (general review/DT or meta analysis/CT or practice guideline/CT or clinical trial+NT/CT or trial? or random? or placebo? or control? or volunteer? or prospectiv? or blind? or mask?)

?= truncation symbol.
CT = controlled term.
DT = document type.
NT = narrower terms (= explode).

Ad 7: Search strategy for AMED, via SilverPlatter:
1. eczema* or dermatitis or tylotic or pompholyx or cheiropompholyx or pulpit* or dyshydro* or dishydro* or dyshidro* or dishidro*
2. hand or hands or acra* or palm* or dors* or apron or finger*
3. #1 and #2

*= truncation symbol.

References from published studies.
These were checked for further trials.

Unpublished literature
Unpublished, on-going trials, and grey literature were obtained via correspondence with authors and pharmaceutical companies.

Conference proceedings
Dermatology conference proceedings were handsearched for further RCTs.

Other
Hand-searching was performed on the terms ‘eczema’, ‘dermatitis’, ‘hand’ or ‘hands’, ‘palmoplantar’, ‘inflammatory’ for 15 English journals, one major German, one major Italian and one major Dutch dermatology journal (all journals 1977 through 2004). The following journals were searched:
1. Acta Dermatovenereologica
2. Archives of Dermatological Research
3. Archives of Dermatology
4. British Journal of Dermatology
5. British Medical Journal
6. Clinical and Experimental Dermatology
7. Contact Dermatitis
8. Cutis
Methods of the review

Study selection
Titles and abstracts identified from the searches will be checked by two reviewers. All those that may be trials will be retrieved as full text articles for further independent examination by two other reviewers. These two reviewers will decide which trials fit the inclusion criteria, and record their methodological quality. Discrepancies will be resolved by discussion between the two reviewers, or, if no agreement can be found, by a third reviewer. Missing data will be obtained from the authors where possible. Where there are duplicate publications of the same trial, the paper with the most relevant data will be used.

Assessment of the methodological quality
The following criteria on methodological quality are adopted from Chalmers, Colditz, Moher, Schulz and the Cochrane Skin Group Criteria.\textsuperscript{17-20} The quality assessment is an evaluation of six components. Each component is characterised as Adequate, Unclear or Inadequate.

1. Randomisation procedure:
   Adequate when the allocation sequence protects against biased allocation to the comparison groups.

2. Concealment of allocation:
   Adequate when clinicians and participants are unaware of future allocations.

3. Blinding:
   Adequate when the outcome assessor is unaware of the allocation.

4. Loss to follow-up and intention-to-treat analysis (ITT):
   Adequate when more than 80% of participants are followed-up and analysed in the groups to which they were originally randomised.

5. Baseline comparison for severity of the disease:
Chapter 4

Adequate when a comparison between the groups is made and does not show a significant difference.

6. Certainty that participants have hand eczema:
   Adequate when the diagnosis is made or confirmed by a physician.

Data extraction
Data extraction will be done independently by two reviewers using a data extraction form. Discrepancies will be resolved by a third reviewer if no agreement can be found. Data will be checked and entered into Review Manager by one reviewer.

Analysis
If studies are sufficiently similar, statistical pooling will be done using a weighted treatment effect. Random effect analysis will be used because of the anticipated differences across studies in, amongst other things, the patient base included. The results will be expressed as odds ratio (OR and 95% confidence intervals, CI) and risk difference (RD with 95% CI) for dichotomous outcomes and weighted mean difference (WMD and 95% CI) for continuous outcomes. The result will also be expressed as number needed to treat (NNT) where appropriate with different rates of baseline risk.

Reasons for heterogeneity in studies will be explored and, if necessary, sensitivity analyses will examine the effects of excluding study subgroups (e.g. children vs. adults, or atotics vs. allergic contact hand eczema), or those studies with lower reported methodological quality ('Inadequate').

Cross-over studies will be dealt with by analysing the first period only as a simple parallel group study.

Other
Where there is uncertainty, authors will be contacted for clarification.

A consumer will be consulted throughout, particularly for readability and comprehension of the final results.

RESULTS
Please note that these results are still under review by the Cochrane Skin Group. Therefore, the results are preliminary and cannot yet be cited or otherwise referred to as a Cochrane Systematic Review.

We identified 56 potential eligible papers. Of these, 22 had to be excluded. Some were excluded because they were not an RCT, others due to a wide range
of other reasons. For an overview of the excluded studies and the reasons for exclusion, see table 1.

In total 34 RCTs were included in this review. Tables 2 through 35 describe the methodological quality and other characteristics: participant characteristics, the interventions investigated, the outcomes and the allocation concealment are given. The latter is in the tables abbreviated to ‘All. conceal.’. In addition, some notes on the studies are provided.

Following the protocol, with a few additions, we divided the trials into the following categories:
1. Skin protection measures, including gloves.
2. Topical treatments
   a. Bland emollients
   b. Topical corticosteroids
   c. Coal tar and derivatives
   d. Irradiation with UV-light
   e. Irradiation with ionising radiation (X-rays and Grenz-rays)
   f. Topical calcineurin inhibitors
   g. Other topical interventions.
3. Systemic treatments
   a. Oral corticosteroids
   b. Oral immunosuppressants
   c. Oral retinoids
   d. Other oral interventions.

The 33 RCTs covered a large variety of treatments and many different ways of reporting outcomes. There was substantial heterogeneity in the studies in terms of interventions, outcome measures and timing of the outcome assessments. Most studies had as comparators no treatment, variants of the same medication, or vehicle or placebo. There were very few studies comparing two different classes of interventions: one study comparing phototherapy (PUVA) with X-rays,\textsuperscript{21} one study comparing a topical calcineurin inhibitor (tacrolimus) with a corticosteroid,\textsuperscript{22} one study comparing ciclosporin with a topical corticosteroid,\textsuperscript{23} and one study comparing cromoglycate with a diet.\textsuperscript{24}

Statistical pooling was considered for the studies of corticosteroids, UV-phototherapy, or ionising radiation (X-rays) (5 to 6 studies in each category). For the trials on corticosteroids, the types of corticosteroid and their dosage schedules were too heterogeneous for pooling.

For the phototherapy studies (UVA, UVB, PUVA) pooling was considered for three studies with data comparing UVB with no UVB or placebo,\textsuperscript{25-27} but we found these studies too heterogeneous in terms of design, outcome assessment and presentation of data.
Chapter 4

Among the trials evaluating the effect of ionising radiation (X-rays), pooling of the results of the 4 studies comparing X-rays with placebo-radiation was considered, but the dosages, presentation of results and follow-up time were considered too heterogeneous.

In the next section, a short description of every RCT will be given, in addition to a summary of the outcome measures, following the protocol, with the corresponding results.

1. SKIN PROTECTION MEASURES, INCLUDING GLOVES
We identified no trials

2. TOPICAL TREATMENTS
2a. Bland emollients: ceramide containing emollients
A comparison was made between an emollient with ceramides in 17 patients versus a regular petrolatum-based emollient in 15 patients. Primary outcomes:
   a. Percentage of patients with self-rated good/excellent control: Approximately two-third (there is only a graphic presentation) improved or cleared in the ceramide group, versus 69.2% in the comparison group. There was no statistically significant difference between the groups.
   b. Percentage of patients with investigator-rated good/excellent control: Graphic presentation, no exact figures given. There was improvement in both groups, but the difference between the groups was not significant.
Secondary outcomes:
   a. Reduction in severity, patient-rated scoring: Itching improved or disappeared in 75% of the ceramide group and 69% of the comparison group (graphic presentation). The difference was not statistically significant (details not given, graphic presentation).
   b. Reduction in severity, physician-rated scoring: There was a graphic presentation of HEASI (hand eczema area and severity index), but exact figures were not given. There was a significant decrease in both groups, but the difference between the groups was not statistically significant (no details given).
   c. Time until relapse: Not stated.
Tertiary outcomes:
   a. Dose reduction: In the ceramide group, 62.2% used less corticosteroids, in the comparison group 38.4%. In the comparison group, 46.1% stated that they had to use more corticosteroids. The difference was not statistically significant, but details were not given.
b. Side effects: Exacerbation of hand eczema in 2 patients of the ceramide group and in 1 patient in the comparison group.

2b. *Topical corticosteroids: flupredniden cream vs. betamethasone valerate cream*

Two topical corticosteroids were compared to study whether the less potent flupredniden was equally effective as the more potent betamethasone-17-valerate.\(^\text{32}\) Either product was applied once daily, in the evenings, for a study period of 3 weeks in 76 patients. In both study groups a specific emollient was used if required. The patients were examined before treatment, after 1 weeks and after 3 weeks treatment.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.
b. Percentage of patients with investigator-rated good/excellent control: In the betamethasone group 14 patients healed and in the flupredniden group 8 healed.

Secondary outcomes:

a. Reduction in severity, patient-rated scoring: Patient-rated general assessment did not show significant differences between the two treatments.
b. Reduction in severity, physician-rated scoring: General assessment did not show significant differences between the two treatments. After three weeks treatment 23 of 38 patients treated with betamethasone and 27 out of 37 patients treated with flupredniden showed an improvement of over 50%.
c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.
b. Side effects: Eight patients in the betamethasone group and seven in the flupredniden group reported side effects such as redness, smarting, swelling, irritation or dryness.

2b. *Topical corticosteroids: betamethasone dipropionate in a polyacrylic film-forming lotion vs. a thickened lotion*

In this study, 58 patients were randomised to two study groups.\(^\text{33}\) One group received betamethasone dipropionate polyacrylic film-forming lotion. The other group received a traditional betamethasone dipropionate lotion, slightly thickened to resemble the consistency of the other product.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.
b. Percentage of patients with investigator-rated good/excellent control: Global evaluation at day 7 demonstrated a significant difference in favour
Chapter 4

of the polyacrylic film-forming lotion group: clearing was noted in five patients and improvement in 23 patients. The corresponding figures for the thickened lotion group was 0 and 18 patients.

Secondary outcomes:


b. Reduction in severity, physician-rated scoring: 23 patients (82%) in the polyacrylic film-forming lotion group showed reduction in severity compared to 10 (38%) in the thickened lotion group. However, it is unclear how the change in overall severity was calculated and how differences were tested.

c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.

b. Side effects: In the polyacrylic film-forming lotion group two participants had stinging on the application site, one stinging in the eyes and one a ‘melting’ feeling. In the thickened lotion group one experienced headache and two had an exacerbation of the hand eczema.

2b. Topical corticosteroids: intermittent maintenance therapy with clobetasol propionate and flupredniden acetate

A multicentre study was designed to study whether twice weekly application of a corticosteroid was effective in keeping hand eczema, which had been brought into remission, under control.34 To induce remission, 61 patients with symmetrical hand eczema of at least 6 months duration were treated with clobetasol propionate cream twice weekly. Then, the 55 (out of the 61) patients who were healed were included in a maintenance study and were followed for a mean period of 138 days (range 55-193 days); this was in the form of an RCT which compared one hand (receiving clobetasol) with the contralateral hand (receiving flupredniden). When relapse occurred during the maintenance phase, the cream allocated to that hand could be applied more frequently; if this failed, the cream of the other (best) hand could be used temporarily. The patients were allowed to use an emollient (Essex cream) as needed. Calculations were made of the number of hands that relapsed and time of relapse.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.

b. Percentage of patients with investigator-rated good/excellent control: No relapses were observed in 32 (70%) hands treated with clobetasol and in 14 (30%) treated with flupredniden.

Secondary outcomes:

b. Reduction in severity, physician-rated scoring: Efficacy judgement (not specified) at an unknown point in time, considered the two preparations equal in 15 patients, superior in 29 treated with clobetasol and superior in two treated with flupredniden.

c. Time until relapse: In patients with relapses, this occurred after an average period of 66 days on the clobetasol treated side and of 36 days on the side treated with flupredniden.

Tertiary outcomes:

a. Dose reduction: Not stated.

b. Side effects: In four patients side effects occurred with clobetasol and in three patients with flupredniden. One patient had side effects from both glucocorticoids.

2b. Topical corticosteroids: desonide cream 0.1% vs. 0.05%

Two strengths of the same topical corticosteroid were compared in a within-patient (left-right) design. 35 Patients were treated twice daily with desonide cream 0.1% on one hand and desonide cream 0.05% on the other. The patients had not been treated for eczema for at least one week prior to the study. The duration of the study was only 14 days.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.

b. Percentage of patients with investigator-rated good/excellent control: Not stated.

Secondary outcomes:

a. Reduction in severity, patient-rated scoring: There was no significant difference in the overall effect. At the second follow-up visit 19 patients evaluated the 0.1% preparation and 11 the 0.05% preparation as best while 14 patients evaluated the two preparations as equally effective.

b. Reduction in severity, physician-rated scoring: There was no significant difference between the two creams in any of the parameters studied.

c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.

b. Side effects: Not stated.

2b. Topical corticosteroids: long-term, intermittent treatment with topical mometasone furoate

The aim of a relatively large study (100 women and 20 men) was to compare mometasone 3 times per week with 2 times per week. 36 Initially all patients were treated for 3 weeks with daily application of mometasone furoate in order to bring their eczema under control. The RCT dealt with the 106 patients whose
eczema was brought under control. They were randomised to three parallel study groups for up to 36 weeks: A) treatment with mometasone furoate fatty cream once daily 3 times a week; B) treatment with mometasone furoate fatty cream once daily 2 times a week; C) treatment with only emollients. In case of recurrence, all groups were permitted to use mometasone daily for a maximum of two separate periods of 3 weeks. In case of obvious bacterial infection a course of oral antibiotics and/or potassium permanganate soaks was permitted. All patients were given an emollient to be used freely.

Clinical evaluations were carried out after 3, 6, 12, 18, 24 and 30 weeks of maintenance treatment. Recurrence was defined as eczema score equal to or higher than initial score. If recurrences occurred during the maintenance phase, daily treatment with mometasone furoate was permitted for a maximum of two separate periods of three weeks followed by the same maintenance treatment schedule as before the recurrence. If there were more than two recurrences during the maintenance period, the patient dropped out.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.
b. Percentage of patients with investigator-rated good/excellent control:
   Patients treated with mometasone 3 times a week had less recurrences (17%) compared to those treated with mometasone twice a week (32%) and those only treated with emollients (74%).

Secondary outcomes:

c. Time until relapse: Patch-test positive patients had the same number of recurrences as patch-test negative patients. For the groups given active treatment, there was no difference between the results for wet or dry occupations. A diagnosis of atopic dermatitis did not increase the risk of recurrence.

Tertiary outcomes:

a. Dose reduction: Not stated.
b. Side effects: For 10 patients, mild skin atrophy was noted at some point during the study. In five patients the atrophy disappeared during the study.

2c. Coal tar and derivatives
We found no trials.

2d. Irradiation with UV-light: UVB vs. no phototherapy
Treatment with a portable UVB-phototherapy unit, to be used at home, was compared with treatment by non-specific topical treatment in a study among 48 patients with occupational hand eczema. It seems that the UVB treated group...
also applied this non-specific topical treatment. The patients were randomised to either treatment group, but details about the procedure were not given. There were no details about the number of patients allocated to each group; probably it was 24 versus 24. The UVB treated group irradiated their hands at home 5 days per week for 8 weeks according to a predetermined dosage scheme.

Primary outcomes:
- Percentage of patients with self-rated good/excellent control: Not stated.
- Percentage of patients with investigator-rated good/excellent control: Not stated.

Secondary outcomes:
- Reduction in severity, patient-rated scoring: Not stated.
- Reduction in severity, physician-rated scoring: According to the text (i.e. data not given) both treatment groups showed improvement in clinical parameters and TEWL, but there was no significant difference between the two groups. A part of the results was presented graphically: for the outcome parameter lichenification the UVB treatment was significantly better. It is not clear if this is based on all patients or only those who completed the treatment. In the subgroups with mild eczema (not specified), UVB was significantly better for the parameters vesiculation and excoriation. There was no difference in healing rates between allergic, atopic or irritant hand eczema.
- Time until relapse: Not stated.

Tertiary outcomes:
- Dose reduction: Not stated.
- Side effects: In both groups two patients showed an exacerbation. Side effects were limited to stinging and burning in some patients.

2d. Irradiation with UV-light: UVB vs. placebo phototherapy vs. whole body UVB

Three groups were compared in a trial of 18 patients with chronic hand eczema. They were randomised, six patients in each group, to receive the following treatments: one group UVB-phototherapy of the hands, one group exposure of the hands to filtered light without UVB (placebo-UVB), and one group whole body (except the hands) UVB-exposure with additional UVB-phototherapy of the hands. This phototherapy was given 4 times weekly for 8 weeks.

Primary outcomes:
- Percentage of patients with self-rated good/excellent control: Not stated.
- Percentage of patients with investigator-rated good/excellent control: Of the patients receiving local UVB two cleared, while in the group receiving
filtered light (placebo UVB) one patient cleared; in the group receiving whole body UVB with UVB on the hands all cleared.

Secondary outcomes:
- b. Reduction in severity, physician-rated scoring: Combining the outcome cleared/improved, this occurred in all patients receiving UVB, but in two of the patients receiving filtered light (placebo UVB).
- c. Time until relapse: There was a postal questionnaire follow-up three months after completion of the treatment, asking the patients about the course of their hand eczema: the number of weeks in remission were presented in a descriptive way.

Tertiary outcomes:
- b. Side effects: Not stated.

2d. Irradiation with UV-light: oral PUVA vs. no phototherapy vs. UVB
In one trial among 35 patients there were three within-patient (left-right) studies, combined with a parallel study. Different comparisons were studied: oral PUVA was compared with no phototherapy on the contralateral hand in one group; UVB was compared with no phototherapy on the contralateral hand in another group; the PUVA treated hands of the first group were compared with the UVB treated hands of the second group. Randomisation between the PUVA group (18 patients) versus the UVB group (17 patients) was based on year of birth. The results of the three components of this trial will be presented separately in the next paragraphs.

Oral PUVA on one hand versus no phototherapy on the contralateral hand was studied in 18 patients. Patients were allocated to this group (and not to the group described below) if they were born in even years. The treatment was given up to 12 weeks, or until the treated hand had cleared. Patients were encouraged to use emollients with 2% salicylic acid or 10% urea. The patients also rubbed white petrolatum on their hands before each treatment, but it was not stated whether this was also rubbed on the non-treated hands.

Primary outcomes:
- a. Percentage of patients with self-rated good/excellent control: Not stated.
- b. Percentage of patients with investigator-rated good/excellent control: In the 14 patients who fulfilled the study, the PUVA treated hands all cleared according to the global evaluation. In the untreated (contralateral) hands, one hand was cleared.

Secondary outcomes:
Interventions for hand eczema

b. Reduction in severity, physician-rated scoring: Using a scoring system (not validated) of severity and a global evaluation. A table showed the results of the assessments of outcome in the remaining 14 patients at the end of their treatment, i.e. probably at varying points in time. According to the above-mentioned table, the PUVA treated hands showed a 92% reduction in severity score. In the untreated (contralateral) hands there were also improvements: the severity score decreased 49%. A graphic presentation showed a better response in the PUVA treated hands over a period of 12 weeks, but it was not clear on how many patients at each point in time it was based.

c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.

b. Side effects: Two patients withdrew because of nausea due to the methoxypsoralen and four of the remaining 14 patients experienced severe nausea from the 8-methoxypsoralen tablets. Side effects developed in 7 out of the 14 patients (50%). Three patients of the 14 who continued the study developed severe oedema, pain and itching in the treated hand, resulting in temporary interruption of the treatment for 1-3 weeks. Another patient developed hyperpigmented spots on the backs of the fingers. Two patients reported soreness and stiffness in the fingertips of the treated hand. In three patients with allergic contact eczema, the eczema spread to the arms and face, which had not occurred earlier. However, the treated hand did not deteriorate.

UVB on one hand versus no phototherapy on the contralateral hand was studied in 17 patients. The design was the same as the PUVA study described in the paragraph above: patients were allocated to this group (and not to the group described above) if they were born in uneven years. The treatment was given up to 12 weeks, or until the treated hand had cleared. Patients were encouraged to use emollients with 2% salicylic acid or 10% urea. The patients also rubbed white petrolatum on their hands before each treatment, but it was not stated whether this was also rubbed on the non-treated hands.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.

b. Percentage of patients with investigator-rated good/excellent control: No hand was cleared.

Secondary outcomes:


b. Reduction in severity, physician-rated scoring: Using a scoring system (not validated) of severity and a global evaluation. A table showed the results of
the assessments of outcome in the remaining 16 patients at the end of their
treatment, i.e. probably at varying points in time. According to the above-
mentioned table, the UVB treated hands showed a 51% reduction in
severity score and seven showed much improvement according to the
global evaluation. In the untreated (contralateral) hands there were also
improvements: the severity score decreased 37% and four hands showed
much improvement. The difference in score was considered statistically
significant in favour of the UVB treatment, but was statistically not
significant for the proportion of much improved hands. A graphic
presentation showed a better response in the UVB treated hands over a
period of 12 weeks, but it was not clear on how many patients at each point
in time it was based.

c. Time until relapse: Not stated.

Tertiary outcomes:
a. Dose reduction: Not stated.
b. Side effects: One patient withdrew because of an infection. Adverse
reactions were reported in two out of the 16 patients (13%) who continued
the study. Two patients developed bullae in the treated palm, probably due
to the irradiation. Another patient was treated twice with flucloxacillin for
to Staphylococcus aureus infection of the eczema.

Oral PUVA versus UVB. The above-mentioned 14 patients who had one hand
treated with PUVA were compared with the above-mentioned 16 who had one
hand treated with UVB.26

Primary outcomes:
a. Percentage of patients with self-rated good/excellent control: Not stated.
b. Percentage of patients with investigator-rated good/excellent control:
According to the global evaluation of outcome, all 14 PUVA treated hands
had cleared, versus none in the UVB treated hands.

Secondary outcomes:
b. Reduction in severity, physician-rated scoring: The results were presented
graphically as the mean combined severity score at 3, 6, 9 and 12 weeks.
The mean of the total severity score (no exact figure given) at the end of the
12 week study was said to be significantly lower (better) in the PUVA
treated group. As mentioned in the paragraphs above, there was also
improvement in the untreated hands.
c. Time until relapse: Not stated.

Tertiary outcomes:
a. Dose reduction: Not stated.
b. Side effects: the number of patients with side effects was greater in the PUVA than in the UVB group (p<0.001).

2d. Irradiation with UV-light: oral PUVA vs. topical bath PUVA
In a randomised controlled parallel study oral PUVA-phototherapy, whereby the hands were irradiated by the patients themselves at home, was compared with bath-PUVA, whereby the hands were soaked in a psoralen (trioxsalen) solution followed by UVA in the clinic. The aim was to demonstrate equal clinical efficacy, assuming the costs for home treatment would be substantially lower. Treatment was given for 10 weeks, and there was a follow-up after treatment for another 8 weeks. Emollients were allowed in both groups. A total of 158 were randomised into either oral/home-PUVA (78 patients) or hospital-based bath-PUVA (80 patients).

Primary outcomes:
   a. Percentage of patients with self-rated good/excellent control: Not stated.
   b. Percentage of patients with investigator-rated good/excellent control: Not stated.

Secondary outcomes:
   b. Reduction in severity, physician-rated scoring: At the end of the treatment phase (10 weeks) in the home-PUVA group 56/78 patients (72%) showed improvement, versus 49/80 patients (61%) in the hospital/bath-PUVA group.
   c. There was a significant improvement in the mean of the hand eczema scores in both groups, while there was no statistically significant difference between the groups: the mean reduction in score was 41% versus 31%. At 8 weeks after the treatment phase the reduction in mean score from baseline was 3.1 versus 2.7; the difference between the two groups was not statistically significant.
   d. Time until relapse: Not stated.

Tertiary outcomes:
   a. Dose reduction: Not stated.
   b. Side effects: Only side effects that were a reason to discontinue were analysed. In the oral/home-PUVA group three patients dropped out because of side effects (nausea). In the hospital/bath PUVA group 1 dropped out because of side effects (burn).

2d. Irradiation with UV-light: topical PUVA vs. UVA
In a 16 weeks within-patient (left-right) study, topical PUVA was compared with UVA. The study was double-blind, with UVA as a surrogate placebo. Randomisation appeared to be adequate. Patients were patients with recurrent
bilateral vesicular hand eczema. It was a relatively small study: 15 patients were enrolled.

The PUVA treatment was performed by applying a liquid (‘paint’) containing methoxypsoralen on one hand. The comparator was the application of an inactive paint on the contralateral hand, whereupon both hands were irradiated with UVA. The treatment had a duration of 8 weeks. After that, there was a follow-up of 8 weeks. Emollients were allowed for both hands.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.
b. Percentage of patients with investigator-rated good/excellent control: Not stated.

Secondary outcomes:

a. Reduction in severity, patient-rated scoring: The VAS for improvement increased over 12 weeks, and remained unchanged until week 16. There was no statistical significant difference between the treated and untreated hands at any stage.
b. Reduction in severity, physician-rated scoring: According to a graphic presentation of the outcome, the mean global severity rating improved for both hands until the end of the treatment phase (8 weeks), to remain stable until week 16. The scoring system showed the same pattern. The improvement in the means of both outcomes was statistically significant for both hands, i.e. also the UVA irradiated hands improved. The differences between the PUVA and the UVA treated hands were not statistically significant.
c. Time until relapse: Four of nine patients answering a questionnaire were free from hand eczema after 11.6 months (±2.1, range 1.5-18).

Tertiary outcomes:

a. Dose reduction: Not stated.
b. Side effects: Probably two patients had to be withdrawn due to exacerbation of eczema. Only one patient who completed the study experienced a burning episode on the back of his PUVA treated hand.

2d. Irradiation with UV-light: UVA1 vs. placebo

UVA1 irradiation for 3 weeks in 15 patients with dyshidrotic hand eczema was compared with placebo (simulated blue light) in 13 patients.\textsuperscript{39} Emollients seem to have been allowed in both groups.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.
b. Percentage of patients with investigator-rated good/excellent control: Not stated.
Secondary outcomes:

a. Reduction in severity, patient-rated scoring: There was a clear reduction in the mean VAS for itch in the UVA1 group when compared to placebo after three weeks of treatment (2.31 versus -1.37; \( p=0.005 \)).

b. Reduction in severity, physician-rated scoring: The severity score (DASI) decreased in the UVA1 group, and was at week 3 significantly better compared with the (slightly increased) score in the placebo group (8.67 versus -0.38; \( p=0.005 \)). At six weeks after the phototherapy, only summary results are given for the UVA1 group, which “still showed a mean improvement of 10.85 points”. Desquamation and itch. Components of the severity score showed at week 3 a significant reduction in the UVA treated group, however, there was no difference between the UVA1 treated group and placebo regarding subscore of vesicles.

c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.

b. Side effects: Apart from some minor erythemal reactions, no side effects occurred.

2e. Irradiation with ionising radiation (X-rays and Grenz-rays): X-rays vs. placebo

In four double-blinded studies different radiation-therapies were compared with placebo-radiation. Two studies had superficial X-rays 300 Rad as active treatment,\(^{29, 40}\) one study Grenz-ray 1800 Rad 10 kV,\(^{30}\) and one study Grenz-ray 900 Rad 10 kV.\(^{28}\) All studies were self-controlled: after randomisation one hand was irradiated and the contralateral hand treated with sham irradiation. Long term side effects were not investigated in these studies.

The double-blind study by King et al. included 20 patients and hand eczema treated one hand with three fractionated doses of 100 Rad at 45 kV given at 1 week intervals.\(^{40}\) 15 patients completed the trial.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.

b. Percentage of patients with investigator-rated good/excellent control: After 1 month in 7 out of 15 patients the hand treated with X-rays was categorised as good response (defined as ‘clear’ or ‘nearly clear’), whereas all 15 placebo treated hands were categorised as poor response (defined as ‘partly clear’, ‘no change’ or ‘relapse’). After 3 months 10 radiated hands and six placebo treated hands were categorised as good response, and after 6 months there was a good response in 11 radiated and eight placebo treated hands.
Secondary outcomes:

b. Reduction in severity, physician-rated scoring: One month after completion of radiotherapy seven patients (46%) showed a good response on the treated side but none of the untreated palms had improved. This difference was statistically significant (p<0.01). After 3 and 6 months there was no significant difference between response in treated and untreated palms.

Tertiary outcomes:

a. Dose reduction: Not stated.
b. Side effects: Not stated.

In another double-blind study 24 patients were treated with a combination of topical therapy and superficial X-ray therapy were assessed at 6, 9, and 18 weeks after starting X-ray therapy. One hand was treated with 100 Rad at 50 kV on three occasions at intervals of 21 days, the other hand with placebo. Patients continued treatment with tar paste or corticosteroid ointments on both hands throughout the trial.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.
b. Percentage of patients with investigator-rated good/excellent control: Not stated.

Secondary outcomes:

a. Reduction in severity, patient-rated scoring: The score (scale range 0 to 10) of the eczema was significantly lower on the radiated hand compared to the hand receiving placebo after 6, 12, and 18 weeks. This was a graphic presentation, exact data were not given. The patients were also asked at each visit which hand had improved more since treatment commenced. A statistically significant greater improvement on the irradiated hand was found at week 6 and 9, but not at week 18.
b. Reduction in severity, physician-rated scoring: The mean grade of eczema was significantly lower on the radiated hand compared to the hand receiving placebo after 6, 12, and 18 weeks. This was a graphic presentation, exact data were not given.
c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.
b. Side effects: No systemic or local adverse reactions were noted.

The effect of Grenz-ray therapy was investigated by Lindelöf et al. Twenty-four patients had irradiation on one hand while the contralateral hand received placebo irradiation. Topical treatment was continued unchanged during the trial.
Grenz-ray therapy was administrated using 10 kV, 10 mA. Six fractionated doses of 3 Gy were given at 1 week intervals. Placebo-therapy was achieved by allowing the apparatus to hum without emitting radiation.

Primary outcomes:
- Percentage of patients with self-rated good/excellent control: Not stated.
- Percentage of patients with investigator-rated good/excellent control: Not stated.

Secondary outcomes:
- Reduction in severity, patient-rated scoring: Not stated.
- Reduction in severity, physician-rated scoring: This seemed to be statistically significant, but exact data were not given in the graphic presentation of this outcome. The mean total symptom scores were lower on the hands receiving Grenz-rays than those receiving placebo at 5 and 10 weeks.
- Time until relapse: Not stated.

Tertiary outcomes:
- Dose reduction: Not stated.
- Side effects: Five patients showed slight pigmentation of the Grenz-ray treated hand.

In 30 patients one hand was irradiated with 3 Gy (300 Rad) of Grenz-rays and the contralateral hand treated in an exactly similar manner with sham radiation. Treatments were repeated at 21-day intervals for a total of three visits. Evaluation was performed by the physician and the patient at 3, 6, 9, 12, 15, and 18 weeks after the initial treatment.

Primary outcomes:
- Percentage of patients with self-rated good/excellent control: Not stated.
- Percentage of patients with investigator-rated good/excellent control: Not stated.

Secondary outcomes:
- Reduction in severity, patient-rated scoring: There was no difference in the mean grade of the eczema between the Grenz-ray treated and the placebo treated hands at any of the posttreatment visits. This was shown by a graphic presentation; exact data were not given.
- Reduction in severity, physician-rated scoring: There was no difference in the mean grade of the eczema between the Grenz-ray treated and the placebo treated hands at any of the post-treatment visits. This was shown by a graphic presentation; exact data were not given.
- Time until relapse: Not stated.

Tertiary outcomes:
- Dose reduction: Not stated.
b. Side effects: One patient developed pigmentation of the hand, which had been treated with Grenz-rays.

2e. Irradiation with ionising radiation: X-rays vs. Grenz-rays
A self-controlled study on 25 patients compared superficial X-ray and Grenz-ray. Both radiation therapies were given in three divided doses at 21 day intervals. One hand received 1 Gy of conventional superficial X-ray 50 kV, the other 3 Gy of Grenz-ray 10 kV. Each patient was seen 3, 6, 12 and 18 weeks after the first exposure to X-ray therapy.
Primary outcomes:
   a. Percentage of patients with self-rated good/excellent control: Not stated.
   b. Percentage of patients with investigator-rated good/excellent control: Not stated.
Secondary outcomes:
   a. Reduction in severity, patient-rated scoring: The score of the eczema was significantly lower on the X-ray treated hand compared to the hand receiving Grenz-ray therapy at 3, 6, 12 and 18 weeks after starting treatment. Only graphic presentation, exact data not given.
   b. Patients’ indication which hand improved the most: 6/20 on X-rays versus 1/10 on Grenz-rays (difference not statistically significant).
   c. Reduction in severity, physician-rated scoring: The mean grade of eczema (score range 0 to 4) was significantly lower on the X-ray treated hand compared to the hand receiving Grenz-ray therapy at 3, 6, 12 and 18 weeks after starting treatment. Only graphic presentation, exact data not given.
   d. Time until relapse: Not stated.
Tertiary outcomes:
   a. Dose reduction: Not stated.
   b. Side effects: There were no side effects from either therapy.

2e. Irradiation with ionising radiation: X-rays vs. PUVA
Superficial X-ray therapy (0.9 Gy at 50 kV administered on three occasions at 21 day intervals) was compared with topical PUVA therapy (three times a week for 6 weeks) in 25 patients. Assessments were performed before and 6, 9, and 18 weeks after starting treatment.
Primary outcomes:
   a. Percentage of patients with self-rated good/excellent control: Not stated.
   b. Percentage of patients with investigator-rated good/excellent control: Not stated.
Secondary outcomes:
   a. Reduction in severity, patient-rated scoring: For both treatment modalities a significant improvement compared to the pre-treatment scores were seen at
Interventions for hand eczema

6, 9, and 18 weeks. The score for the superficial radiotherapy was significantly better than topical PUVA therapy at 9 (p=0.046) and 18 weeks (p=0.013). This was by a graphic presentation and exact data not given.

b. Reduction in severity, physician-rated scoring: For both treatment modalities there was a significant improvement of mean clinical severity scores compared to the pre-treatment scores at 6, 9, and 18 weeks. The superficial radiotherapy was significantly better than topical PUVA therapy only at 6 weeks but not at 9 and 18 weeks. This was by a graphic presentation and exact data not given.

c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.

b. Side effects: The application of the psoralens in an organic solvent base was painful in some patients with fissures of the skin though only transiently.

2f. Topical calcineurin inhibitors: tacrolimus ointment vs. mometasone furoate

A relatively small study (12 hand eczema patients completed the study) compared topical tacrolimus with a corticosteroid in a within-patient left-right design.22 A selection on disease severity may have occurred, because originally more patients (20) were enrolled, of which a fifth were excluded in the pre-treatment washout period due to poor disease control.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.

b. Percentage of patients with investigator-rated good/excellent control: Not stated.

Secondary outcomes:

a. Reduction in severity, patient-rated scoring: not stated, although itch was a component of the scoring system that was used (DASI).

b. Reduction in severity, physician-rated scoring: Reduction in mean DASI showed improvement in scores for both treatments, but did not demonstrate a statistically significant superiority of tacrolimus. Exact figures for score reductions are only given for 2 weeks of active treatment, while for the outcome at 4 weeks only a bar-graph is given. It seems that the p-value for the difference at week 4 was 0.559.

c. Time until relapse: There was a follow-up after completion of the 4 weeks treatment period. No data are presented, but it was stated that there was no difference in time until exacerbation.

Tertiary outcomes:

a. Dose reduction: Not stated.

b. Side effects: Not stated.
2f. Topical calcineurin inhibitors: pimecrolimus cream vs. vehicle

A large multicentre study in 294 patients compared pimecrolimus cream in 151 patients with vehicle in 143 patients in a 3 week study. In both groups the evening application was followed by 6-hour occlusion.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.

b. Percentage of patients with investigator-rated good/excellent control: Clear or almost clear in the pimecrolimus group approximately 27%, and in the vehicle group approximately 17% (only graphic presentation, no exact figures); difference not significant (p-value seems to be 0.068). The difference was significant when there was stratification according to palmar involvement.

Secondary outcomes:


c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.

b. Side effects: Application site burning in the pimecrolimus group in 0.7% and in the vehicle group in 2.1%.

Only limited data can be extracted from one study comparing pimecrolimus (with or without occlusion) with vehicle, because it was published as a conference abstract. Only at day 29 (of the 42-days treatment period) there was statistically significant superiority of non-occluded pimecrolimus over vehicle, although at the end of treatment the results of occluded pimecrolimus pointed towards superiority.

2g. Other topical interventions: topical antibacterial agents, in combination with topical corticosteroids

Betamethasone valerate/clioquinol cream versus betamethasone valerate/fusidic acid cream.

Two antibacterial agents, each combined with a corticosteroid (betamethasone valerate) were compared in a multicentre study on 120 hand eczema patients with a confirmed or suspected secondary infection of their eczema. The study had a duration of 4 weeks. It was unblinded because of the different appearances of the two creams. Efficacy data were obtained for 57 patients given betamethasone/clioquinol and 53 patients given betamethasone/fusidic acid.
Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: There was no significant difference between the two groups, but exact data were not given.

b. Percentage of patients with investigator-rated good/excellent control: In the ITT analysis this was 54.8% in the betamethasone/clioquinol group, and 53.4% in the betamethasone/fusidic acid group, without comments on the statistical difference.

Secondary outcomes:

a. Reduction in severity, patient-rated scoring: There was no difference between the two groups in reduction of itching, but no data were given.

b. Reduction in severity, physician-rated scoring: This was by a graphic presentation, showing in both groups a significant reduction, but no difference between the two groups (details not given).

c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.

b. Side effects: In betamethasone/clioquinol group 11 patients with events: irritation five, deterioration four. In betamethasone/fusidic acid group nine patients with events: irritation five, deterioration four.

2g. Other topical interventions: topical retinoids

Bexarotene, a novel type of retinoid was evaluated in 55 patients by a 3-arm unblinded (phase I-II open label) study lasting 22 weeks. The intervention was application of bexarotene 1% gel in a stepwise accumulation every 2 weeks from once every other day to 3x daily. Comparators were bexarotene application in combination with mometasone furoate and in combination with hydrocortisone. All three groups used emollients. Differences between groups in the stepwise application could not be reconstructed.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.

b. Percentage of patients with investigator-rated good/excellent control: Treatment success (>90% clearance) in the bexarotene only group 39%, in the bexarotene/mometasone group 46%, in the bexarotene/hydrocortisone group 21%. Clinically significant response in the bexarotene only group 79%; in the bexarotene/mometasone group 77%; in the bexarotene-hydrocortisone group 50%. The differences between the groups were not statistically significant.

Secondary outcomes:

a. Reduction in severity, patient-rated scoring: Graphic presentation of pruritus without exact numbers; apparently no difference between groups.
Chapter 4

b. Reduction in severity, physician-rated scoring: The percentage with 90% reduction in HEASI score was in the bexarotene only group 36%; in the bexarotene/mometasone group 38%; in the bexarotene/hydrocortisone group 14%. The difference between the groups were not statistically significant.
c. Time until relapse: Not stated.

Tertiary outcomes:
a. Dose reduction: Not stated.
b. Side effects: In the bexarotene group: irritation/rash eight; stinging/burning two, eczema flare five. In the bexarotene/mometasone group: irritation/rash four, stinging/burning four. In the bexarotene/hydrocortisone group irritation/rash four, stinging/burning two, eczema flare four.

g. Other topical interventions: iontophoresis

In a left-right study pulsed direct iontophoresis on one hand was compared with no iontophoresis on the contralateral hand. It seems that this contralateral hand did not receive mock-iontophoresis. Explicit inclusion criteria were not listed, although the authors stated that they included only patients who were poorly responsive to conventional corticosteroid-free topical therapy in the stable phase, with mild to moderate dyshidrotic hand eczema. Both hands (in “basically all” patients) received topical therapy with alcoholic tar solution and zinc paste. The treatment lasted 3 weeks, but it was not clear at which point in time the outcome was assessed (probably at the end of the 3 weeks treatment).

Primary outcomes:
a. Percentage of patients with self-rated good/excellent control: Not stated.
b. Percentage of patients with investigator-rated good/excellent control: Not stated.

Secondary outcomes:
a. Reduction in severity, patient-rated scoring: There was a decrease in median pruritus score from 2 to 1 in the iontophoresis treated hands, versus no decrease in the untreated hands. The difference between the two was statistically significant (p=0.043).
b. Reduction in severity, physician-rated scoring: There was a decrease of median total score from 16 to 8 in the iontophoresis treated hands, versus from 16 to 15 in the untreated hands. The difference between the two was statistically significant (p=0.001).
c. There was a decrease in median vesicle formation from 3 to 1 in the iontophoresis treated hands, versus no change (from 2 to 2) in the untreated hands. The difference between the two was statistically significant (p=0.038).
d. Time until relapse: Not stated.
Tertiary outcomes:
  a.  Dose reduction: Not stated.
  b.  Side effects: Not stated.

3. SYSTEMIC TREATMENTS

3.1 Oral corticosteroids

We identified no trials.

3.2 Oral immunosuppressants: ciclosporin vs. topical betamethasone

There were two papers dealing with different aspects of the same trial: one paper reported on the effect of the intervention on the disease activity,²³ while the other reported on an analysis of the burden of disease in the same patients.⁴⁷

The study had enrolled 41 patients and had a partially overlapping three-phase design, which caused difficulties in interpreting the overall results. In the first phase, 20 patients were treated for 6 weeks with either oral ciclosporin or topical placebo cream, and 21 patients with topical betamethasone dipropionate cream with capsules containing vehicle as comparator. In both treatment arms patients were allowed to use their own emollients. There was a second phase, where patients who failed to respond to their intervention, were crossed over to the alternative intervention. All patients who were responding successfully in the first phase, entered a follow-up phase, while patients of the second phase entered this follow-up phase, apparently irrespective of the success of the intervention.

For the effect of the intervention on the eczema itself, our review can only focus on phase one, although relapse rates during the follow-up phase (phase three) were presented for those whose eczema was successfully treated in phase 1.²³

Primary outcomes:
  a.  Percentage of patients with self-rated good/excellent control: Overall assessment of efficacy good/very good in the ciclosporin group 60%, and 48% in the betamethasone group; the difference was not statistically significant.
  b.  Percentage of patients with investigator-rated good/excellent control: Overall assessment of efficacy good/very good in the ciclosporin group 60%, and 31% in the betamethasone group; the difference was not statistically significant.

Secondary outcomes:
  a.  Reduction in severity, patient-rated scoring: No difference in occurrence of itch between the two groups (graphic presentation).
b. Reduction in severity, physician-rated scoring: Treatment success (defined as >50% decrease in disease activity score) in the ciclosporin group 50% of the patients, and in the betamethasone group 32%; the difference was not significant (p=0.23). No statistically significant differences between the groups in mean disease activity scores (0.6; CI -3.2 to 1.9). No difference in extent of disease (graphic presentation).

c. Time until relapse: not stated in this first phase. The cumulative relapse rates in the patients who had successfully responded in the first phase were comparable according to a graphic presentation.

Tertiary outcomes:

a. Dose reduction: No difference between the groups in emollient use (graphic presentation).

b. Side effects: In the ciclosporin group dizziness, vomiting, facial oedema in one. “Some kind of adverse event in 19 of 28 on ciclosporin”. In the betamethasone group insomnia in one. “Some kind of adverse event in 15 of 27 on betamethasone”.

In a separate paper, burden of disease was assessed with the eczema disability index (EDI) at baseline, at the end of phase one, i.e. at week 6, and at the end of phase 2. At the end of phase two this assessment was restricted to those whose eczema had responded successfully in the preceding first phase. The total EDI score decreased significantly to the same degree in both groups, i.e. from the mean value of 30.5 to 20.9 in the ciclosporin group and from 27.2 to 18.9 in the betamethasone group. Irrespective of the dimension of the EDI (daily activity, school/work, personal relationship, leisure, treatment), the difference between the treatment groups at the end of the first treatment period was not significant.

3c. Oral retinoids: acitretin vs. placebo

Oral acitretin was compared with placebo capsules in a study which enrolled 29 patients (21 men and 8 women, age range 30-76 years), with hyperkeratotic eczema of the palms. The authors called it a single-blind study, because patients were aware of the active medication due to the mild side effects (dry lips). Fourteen patients were allocated to 30 mg acitretin once daily for 8 weeks, and 15 patients took identically looking placebo capsules. No additional treatment was given other than topical emollients.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.

b. Percentage of patients with investigator-rated good/excellent control: Not stated.
Secondary outcomes:

a. Reduction in severity, patient-rated scoring: Percent reduction in the mean itch-score in the acitretin group 41%, and in the placebo group 19%. It is not stated whether the difference was statistically significant.

b. Reduction in severity, physician-rated scoring: In the acitretin group a 51% reduction in overall score, and in the placebo group 9%. In the acitretin group there were significant reductions in scores for hyperkeratosis (50%), fissures (67%) and scaling (48%); it was not stated whether this was significantly different from the score reductions in the placebo group (hyperkeratosis 14%, fissures 10%, scaling 0%).

c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.

b. Side effects: No side effects, biochemical parameters within normal limits.

3c. Oral retinoids: alitretinoin (different doses) vs. placebo

A large multicentre study compared three different oral dosages of a novel retinoid (alitretinoin) with placebo capsules: three groups, each receiving, respectively, 10 mg, 20 mg or 40 mg per day were compared with a placebo group. All groups used a standard emollient. The trial lasted 12 weeks. Of the 317 enrolled, 75 (23%) withdrew, of whom 24 because of side effects. Outcome was assessed by the different investigators at the 43 participating centres.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Cleared or almost cleared in the 10 mg group 29%; in the 20 mg group 34%; in the 40 mg group 43%; in the placebo group 12%. This was statistically significant for all doses compared with placebo.

b. Percentage of patients with investigator-rated good/excellent control: Cleared or almost cleared in the 10 mg group 39%; in the 20 mg group 41%; in the 40 mg group 53%; in the placebo group 27%. This was statistically significant for all doses compared with placebo.

Secondary outcomes:

a. Reduction in severity, patient-rated scoring: Improvement in DLQI in all groups, no details given.

b. Reduction in severity, physician-rated scoring: Median percentage reduction in total lesion symptom score in the 10 mg group 59%; in the 20 mg group 52%; in the 40 mg group 70%; in the placebo group 25%. This was statistically significant for all doses compared with placebo. Decrease of extent of disease in all groups, but no details given; 40 mg group significantly different from placebo group.
c. Time until relapse: At the end of the study period, i.e. at the end of treatment, the majority of the patients who had cleared or almost cleared were followed up. This was up to 12 weeks, probably until relapse. Details on this follow-up were not given, except that 26% required treatment at some time during this period because of relapse.

Tertiary outcomes:

a. Dose reduction: Not stated.
b. Side effects: The study listed in detail the side effects that were observed; headache was the most frequent event (22 in 40 mg group, eight in 20 mg group, four in 10 mg group), leading to 6 withdrawals. In the placebo group headache was reported by seven patients.

3d. Other oral interventions: metal chelating agents
Two studies aimed specifically at intervening on the imputed role of nickel allergy in hand eczema, and included only nickel-sensitive patients.

Oral triethylenetetramine versus placebo. The trial was designed as a cross-over study, but was terminated prematurely (23 patients had been included), because of literature reports on teratogenicity in rats. The study included a monitoring of urinary excretion of copper and nickel. It was unclear at which point in time outcome was assessed, and whether the cross-over had been taken into account.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.
b. Percentage of patients with investigator-rated good/excellent control: The table is unclear; probably improvement of in three out of 20 in the treatment group, and improvement in seven out of 20 when they received the placebo. Outcome was based on a global assessment (improved/no change/deterioration) by patient and physician, probably by consensus. According to the authors, there was no significant improvement in the hand eczema.

Secondary outcomes:

c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.
b. Side effects: Not stated.

Oral tetraethylthiuramdisulphide (TETDS) versus placebo. The trial was performed in 30 nickel-sensitive (patch-test positive) women with pompholyx-type hand eczema, of which six dropped out. Half of them (15) received
TETDS with gradually increasing dosage (up to 20 mg/day) for “at least six weeks”; probably this maximum dose was given for 6 weeks. Both groups were allowed to use a topical corticosteroid (desoxymethasone) and emollients. The timing of the outcome assessment was not clear.

Primary outcomes:
   a. Percentage of patients with self-rated good/excellent control: Not stated.
   b. Percentage of patients with investigator-rated good/excellent control: In the patients receiving the active compound, five out of 11 “healed”, versus two out of 13 in the placebo group; healing was, however, not described as an outcome parameter in the methods section. Data on statistical significance were not given.

Secondary outcomes:
   b. Reduction in severity, physician-rated scoring: There was a statistically significant difference between the groups on scaling and frequency of flares (no details given, comparison was based on the slopes of the linear regression of the scores). There was no statistically significant difference between the groups on the sum of parameters (probably these parameters were: area involved, erythema, number of vesicles and scaling).
   c. Time until relapse: Not stated.

Tertiary outcomes:
   a. Dose reduction: The amount of corticosteroid cream use per week was 1.6 gram for the treatment group, and 5.6 gram for the comparison group.
   b. Side effects: In the group receiving TETDS hepatic toxicity in two and headache in one. Mild acne in two, but not clear in which group.

3d. Other oral interventions: gamma linolenic acid
Oral gamma linolenic acid (GLA) was given to 20 patients for 16 weeks, and a comparison was made with 19 patients receiving a gelatin capsule with sunflower oil. Both treatment groups were allowed to use emollients and class III topical corticosteroid cream. Evaluation of outcome was at the end of treatment (16 weeks) and 8 weeks after cessation of the intervention (i.e. at week 24).

Primary outcomes:
   a. Percentage of patients with self-rated good/excellent control: Not stated.
   b. Percentage of patients with investigator-rated good/excellent control: Not stated.

Secondary outcomes:
   b. Reduction in severity, physician-rated scoring: In the GLA group there was a reduction in overall score from 45.684 to 24.263 at week 16 and to 12.369
at week 24. In the placebo group the reductions in overall score were from 51.667 to 26.333 at week 16, and to 23.357 at week 24. Details were not given, but the authors state that the differences between the two groups were not statistically significant. For the GLA group improvement was significant for all components of the overall score; in the placebo group this improvement was not significant for vesiculation, oedema and itch.

c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: At none of the assessment points was a statistically significant decrease in corticosteroid use documented in either group (details not given; p=0.07-0.94).

b. Side effects: Not stated.

3d. Other oral interventions: ranitidine

Patients (11 men, 26 women) whose hand eczema had atopic dermatitis as a major contributing factor were enrolled in an RCT on ranitidine. All patients had been patch-tested and none reacted to any of the substances. Of the 45 patients, five men and 18 women received ranitidine 300 mg twice daily, and six men and 18 women received placebo. Application of betamethasone cream and ointment and moisturisers were allowed in both groups.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: not stated.

b. Percentage of patients with investigator-rated good/excellent control: Although it was not clear whether this was patient- or physician-rated, 17 out of 23 with ranitidine cleared or markedly alleviated, versus eight out of 24 receiving placebo. This difference was statistically significant (p=0.02).

Secondary outcomes:


b. Reduction in severity, physician-rated scoring: Reduction of total score from 10.17 to 4.91 in the ranitidine group, and a reduction from 10.58 to 7.46 in the placebo group. This difference was not statistically significant (p=0.07).

c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.

b. Side effects: There were no side effects.

3d. Other oral interventions: disodium cromoglycate

Patients with dyshidrotic hand eczema (pompholyx) and positive patch-test to nickel, confirmed by reaction on oral challenge with nickel, were randomised into three study groups. Nine patients were treated with oral disodium
Interventions for hand eczema

cromoglycate (DSCG) for 3 months, without dietary restriction; eight patients were treated with a low nickel diet for 3 months; and seven patients, “who did not give consent to the study”, were observed without undergoing any treatment. Presumably the oral disodium cromoglycate was the intervention and diet the comparator, with the untreated group as controls, but this is not entirely clear.

Primary outcomes:

a. Percentage of patients with self-rated good/excellent control: Not stated.
b. Percentage of patients with investigator-rated good/excellent control: Not stated.

Secondary outcomes:

a. Reduction in severity, patient-rated scoring: There was improvement in itching in five out of eight in the DSCG group, one out of eight in the nickel diet group, and none out of eight in the control group. The difference between the DSCG group and the control group was significant.
b. Reduction in severity, physician-rated scoring: The number of vesicles on a 2x2 area at 12 weeks reduced from 112 to 22 in the DSCG group, from 128 to 64 in the nickel diet group and from 141 to 85 in the control group. The difference between DSCG and nickel diet was significant (p<0.05), and the difference between DSCG and controls was significant (p<0.01).
c. Time until relapse: Not stated.

Tertiary outcomes:

a. Dose reduction: Not stated.
b. Side effects: Not stated.

**DISCUSSION**

This review studied a wide range of treatments that have been evaluated by RCTs since 1977. Within the same period, many uncontrolled and non-randomised controlled studies have been published; an overview on study quality, covering almost the same period, is presented in chapter 2.

Although many systematic reviews focus on a single treatment modality or its closely related variants, we have tried to include all interventions in this review in an attempt to determine which therapy would reflect current standard treatment and to which extent there is evidence for its effectiveness. The wide range of treatments reflects the fact that there does not seem to be a single candidate for a standard-therapy. Major textbooks mention topical corticosteroids and UV-phototherapy, and, given the number of RCTs in these therapy-categories, calling topical corticosteroids and UV-phototherapy the first-choice options may be supported by this review. Nevertheless, most trials do not have one of these treatments as comparator. In fact, most trials have
either placebo, vehicle or a variant of its intervention as comparator, making it difficult to draw conclusions on the comparative advantage of the different treatments.

In many trials there were also improvements in the comparison group that received placebo or vehicle or the same emollient as the intervention group; apparently the emollient or vehicle or other factors related to being a patient has a beneficial therapeutic effect.

There was too much heterogeneity in the three ‘major’ treatment categories (topical corticosteroids, UV-phototherapy, X-rays) to attempt any pooling and meta-analysis. The studies on ionising radiation might be eligible for pooling, but for a critical evaluation of this therapeutic modality, we felt that a long follow-up period (longer than in these studies) should be taken into consideration in view of the discussions around the long-term consequences of exposure to ionising radiation. Modern insights into potential short-term benefit versus long-term risk have made such therapies obsolete.

The five trials on topical corticosteroids dealt each with a different type of corticosteroid. Three trials had short a duration of, respectively, 1, 2 and 3 weeks. Two of the trials compared two different corticosteroids; the other trials each had a different application (respectively intermittent application, different dosage, different vehicle) of the same corticosteroid as comparator. Therefore, no generalisation or recommendation for practice can be made.

The six trials on UV-phototherapy were too heterogeneous for pooling. Two obvious questions from clinicians would be whether PUVA would be more effective than UVB treatment and whether PUVA or UVB-phototherapy would be more effective than corticosteroids. No trial compared phototherapy with topical corticosteroids. There was, however, one trial addressing the PUVA versus UVB comparison in an indirect way. The study had methodological problems, but suggested a comparative advantage of PUVA. Three studies had UVB as the main intervention, but in all three the comparator was placebo-UV or no treatment. All three trials stated that UVB was better. One study was designed to demonstrate equal efficacy of oral PUVA versus topical PUVA at home, under the assumption that home PUVA would be cheaper.

The time-frame of the studies covered in this review inevitably shows that there is a time trend in the treatments that are evaluated: earlier studies tend to focus on corticosteroids, UV-phototherapy, or X-rays, while more recent trials evaluate the effect of novel medicaments such as retinoids and calcineurin inhibitors.

Considering the high prevalence of hand eczema, it is remarkable that the results of all RCTs are based on approximately 1700 participants (1943...
Interventions for hand eczema

enrolled), whereby about a third were enrolled in two recent RCTs: one on an oral retinoid and one on the topical calcineurin inhibitor tacrolimus.

Serious limitations in the quality of reporting have been found. Frequent shortcomings were missing information on randomisation and blinding, no justification of the number of participants, and no analysis of dropouts. A range of outcome parameters were presented, most of which were not validated. About a third were internally controlled (left-right) studies. Although these studies show strength in terms of power to obtain a significant result with small participants numbers, this is at the expense of problems in interpreting studies that find no difference in effect because of cross-contamination of topical interventions and the possible systemic effects of topical preparations. Only a few papers addressed the issue of blinding and the problems with patient blinding when the therapy has side effects that can be perceived by the patients. Although hand eczema usually has a chronically relapsing course, less than half of the studies had a duration of more than 4 months required to document important data such as duration and frequency of disease relapse.

We could not find any evidence that any of the various scoring methods that were used in the trials are relevant to patients, and the interpretation of the changes in scores derived by adding several physical parameters together is obscure even to clinicians.

CONCLUSIONS

Implications for practice
This review is unable to inform clinical practice with regard to the best way of managing hand eczema, especially in the long term. Until such data are forthcoming, physicians will be tempted to use an array of treatments. Topical corticosteroids and UV-phototherapy appear to be the major standard treatment categories, but there is little evidence of a comparative advantage within these categories and little evidence of a comparative advantage with other types of treatment. New therapies, such as oral retinoids and topical calcineurin inhibitors, have recently been introduced, but their comparative advantage to other established treatments has not yet been assessed.

Implications for research
The most important implication from this review is the need to conduct high-quality RCTs of people with hand eczema comparing commonly used interventions using simple outcome measures that can be understood by patients and clinicians. Subgroup analysis on patients with different variants of hand eczema is desirable, although the multifactorial origin of hand eczema and the lack of consensus regarding definitions are potential limitations.
Studies should be of an adequate duration (greater than 6 months) in order to capture the effect of interventions on long-term disease control as well as short-term relief of symptoms.

There is currently no consensus on a standard severity scale for hand eczema. A validation of commonly used scoring systems, or of simple global ratings using photographic anchors is needed.\textsuperscript{35} Duration of remission, the way the disease is brought under control, side effects and simple outcome measures applicable to all patients are preferable.

If an RCT has placebo (or vehicle or inactive treatment) as only comparator instead of an established treatment modality, this should be clearly and convincingly justified.

Many deficiencies in trial reporting thusfar can be avoided if all specialist dermatology journals adopt CONSORT standards.\textsuperscript{56}

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### TABLES

Table 1. Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aertgeerts 1985</td>
<td>Study on patients with different diseases. Number of patients with hand eczema and the outcome in these patients are unknown.</td>
</tr>
<tr>
<td>Beitner 1996</td>
<td>Study on psoriasis and hand eczema, not randomised for each type of disease. Of the hand eczema patients, the numbers allocated to the interventions not stated. Not randomised.</td>
</tr>
<tr>
<td>Berndt 2001</td>
<td>Patients did not have hand eczema. The study was on slightly irritated hands in nurses. The study may be included in another Cochrane Skin Group Review.</td>
</tr>
<tr>
<td>Bock 2001</td>
<td>Not randomised.</td>
</tr>
<tr>
<td>Bollag 1999</td>
<td>Not randomised. Trial with historical control group, within an uncontrolled trial.</td>
</tr>
<tr>
<td>Draelos 2000</td>
<td>RCT on different diseases, mostly hand eczema. But number of patients with hand eczema, and the results in patients with this condition, impossible to reconstruct.</td>
</tr>
<tr>
<td>English 1989</td>
<td>Part of a larger study on eczema and psoriasis. Analysis and outcome among the 19 hand eczema patients not given.</td>
</tr>
<tr>
<td>Goh 1999</td>
<td>Study on different types of eczema on different body regions. Specific data on outcome among the eight hand eczema patients not given.</td>
</tr>
<tr>
<td>Grundmann-Kollmann</td>
<td>Study on different diseases and eczema on various anatomical locations. Not specified how many of the patients with eczematous diseases had hand eczema.</td>
</tr>
<tr>
<td>Hebeda 1992</td>
<td>Retrospective study based on patient files. Not randomised. Study on different diseases; unclear how many had hand eczema.</td>
</tr>
<tr>
<td>Hogen Esch 1998</td>
<td>Pilot study, in which it was unclear how many were allocated to each intervention. Not clear if the study was randomised.</td>
</tr>
<tr>
<td>Lassus 1981</td>
<td>Study on different diseases. Not clear how many had hand eczema, and how many were allocated to each intervention.</td>
</tr>
<tr>
<td>Levy 1981</td>
<td>Not randomised.</td>
</tr>
<tr>
<td>Petering 2004</td>
<td>Self-controlled (left-right) study, not randomised. It could be argued whether this randomisation is important in this left-right study with bilateral hand eczema of similar severity.</td>
</tr>
<tr>
<td>Schmied 1993</td>
<td>Not randomised.</td>
</tr>
<tr>
<td>Shephard 1998</td>
<td>Not randomised.</td>
</tr>
<tr>
<td>Simons 1997</td>
<td>Not randomised.</td>
</tr>
<tr>
<td>Singh 1993</td>
<td>Not randomised.</td>
</tr>
<tr>
<td>Sjövall 1994</td>
<td>Not randomised.</td>
</tr>
</tbody>
</table>
Table 1. Characteristics of excluded studies (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swartling 2002</td>
<td>Not randomised. Two patients possibly did not have eczema, but psoriasis.</td>
</tr>
<tr>
<td>Wollina 2002</td>
<td>Not randomised. Left-right study, with intervention applied to the most severely affected hand.</td>
</tr>
</tbody>
</table>

Table 2. Sheehan-Dare 1989

<table>
<thead>
<tr>
<th>Methods</th>
<th>Within-patient (self-controlled, left-right) randomised study. Hands were unit of randomisation and analysis. Randomisation procedure according to predetermined code. Patients and outcome observer blinded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>25 Patients with chronic constitutional hand eczema. Patients with irritant or allergic contact dermatitis were excluded. Dropouts: 4.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Topical PUVA 3x weekly for 6 weeks in 21/24 hands vs. radiotherapy 90 Rad 50 kV 3 times with 21 days interval in 21/24 contralateral hands.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No primary outcome variable defined.</td>
</tr>
<tr>
<td></td>
<td>1. Patient-rated severity on linear analogue scale.</td>
</tr>
<tr>
<td></td>
<td>2. Observer-rated score 1-4 (0=no eczema, 1=erythema, mild scaling, 2=erythema, scaling, shallow fissures, 3=erythema, severe scaling, deep bleeding fissures, 4=active pompholyx) at weeks 6, 9 and 18.</td>
</tr>
<tr>
<td>Notes</td>
<td>Means of outcome scores not given as exact figures, but as graphical presentation.</td>
</tr>
<tr>
<td>All. conceal.</td>
<td>Adequate.</td>
</tr>
</tbody>
</table>

Table 3. Schnopp 2002

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>12 Patients with moderate to severe chronic relapsing dyshidrotic hand eczema. No dropouts.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Tacrolimus 0.1% ointment 2x daily during 4 weeks on 12/12 hands vs. mometasone furoate 0.1% ointment on 12/12 contralateral hands.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Observer-rated dyshidrotic eczema area and severity index (DASI) at week 2 and 4 (based on sum-score for severity 1=mild, 2=moderate, 3=severe for respectively vesicles, erythema, desquamation, itch multiplied by score for affected area).</td>
</tr>
</tbody>
</table>
### Table 3. Schnopp 2002\(^{22}\) (continued)

<table>
<thead>
<tr>
<th>Notes</th>
<th>Originally 20 patients with hand and/or foot involvement, of which 4 were excluded due to poor disease control during the trial-preceding wash-out phase. Study in 16 patients, of whom 12 had their hands involved. The limited data on 4 week post-treatment follow-period are difficult to interpret. Outcome scores at week 4 presented graphically, without exact numbers. Scoring of outcome (DASI) same as the study by Odia and Polderman.(^{39,46})</th>
</tr>
</thead>
<tbody>
<tr>
<td>All. conceal.</td>
<td>Unclear.</td>
</tr>
</tbody>
</table>

### Table 4. Granlund 1996\(^{23}\)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised parallel group design, with partial cross-over in 2(^{nd}) phase. Randomisation procedure unclear. Patients and outcome observer blinded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>41 Patients with hand eczema, continuously for 6 months, significant disability, inadequate response to conventional treatment, confirmation by histopathology. Dropouts: 6 in 1(^{st}) phase, 1 in 2(^{nd}) phase.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Oral ciclosporin 3 mg/kg/day and placebo cream for 6 weeks in 17/20 patients vs. topical betamethasone dipropionate 0.05% cream and placebo capsules in 19/21. At week 6, cross-over of those who had treatment failure in the first 6 week phase: 8 patients switched to betamethasone, and 6 to ciclosporin. In third phase a 24 week follow-up period without intervention. Own emollients allowed in both groups.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No primary outcome variable defined.</td>
</tr>
<tr>
<td>1.</td>
<td>Patient-rated overall assessment of efficacy (1=very good, 2=good, 3=moderate, 4=slight, 5=none).</td>
</tr>
<tr>
<td>2.</td>
<td>Observer-rated overall assessment of efficacy (1=very good, 2=good, 3=moderate, 4=slight, 5=none).</td>
</tr>
<tr>
<td>3.</td>
<td>Observer-rated disease activity score: grading 0-3 (0=none, 1=mild, 2=moderate, 3=severe) on erythema, scaling, infiltration, excoriation, crusting, vesicles.</td>
</tr>
<tr>
<td>4.</td>
<td>Observer-rated extent of disease.</td>
</tr>
<tr>
<td>5.</td>
<td>Use of emollients.</td>
</tr>
<tr>
<td>6.</td>
<td>Patient-rated itch and sleep disturbances for the final 2 weeks on a VAS). Treatment success, defined as decrease in disease activity score (see 1 above) to &lt;50% of baseline score.</td>
</tr>
</tbody>
</table>
### Table 4. Granlund 1996

**Notes**  
Study had 3 phases, which were partially overlapping. The 2\(^{nd}\) phase dealt with patients who had treatment failure in phase 1. In this 2\(^{nd}\) phase, patients were switched over to the alternative intervention. The 3\(^{rd}\) phase includes only patients who had treatment success in phase 1. This review deals only with phase 1 and phase 3. Paper is based on the same trial (same patients) as Granlund 1997.\(^{47}\)

**All. conceal.** Adequate.

### Table 5. Pigatto 1990

**Methods**  
Randomised parallel group (3 groups) design. Patients not blinded, observer of outcome blinded. Randomisation procedure unclear.

**Participants**  
24 Patients (3M, 21F) with dyshidrotic eczema (pompholyx) and positive patch-test to nickel, confirmed by reaction on oral challenge with nickel. Dropouts: see notes.

**Interventions**  
Low nickel diet for 3 months in 8 patients vs. oral disodiumcromoglycate (DSCG) 1500-2000 mg 3x daily for 3 months in 9 vs. no treatment in 7.

**Outcomes**  
No primary outcome parameter defined.

1. Observer-rated improvement/slight improvement/no improvement of degree of itching.
2. Observer-rated number of vesicles on an area (exact location not stated) of 2x2 cm.

**Notes**  
Unclear which of two is intervention and which is comparator. The third group consisted of patients who did not give consent to the interventions, and was observed without undergoing any treatment. Figures in table suggest dropout. Unclear how the outcome ‘degree of itching’ was assessed. In addition, there was an intestinal permeability study in 5 DSCG and 5 diet patients.

**All. conceal.** Unclear.

### Table 6. Bayerl 1999

**Methods**  

**Participants**  
48 Patients with chronic hand eczema (21 irritant, 18 allergic, 9 atopic), >3 months duration, more than 30% of the hands involved. All had occupation-related hand eczema: 41% were in wet occupation. Dropouts: 12.
### Table 6. Bayerl 1999

<table>
<thead>
<tr>
<th>Interventions</th>
<th>UVB-phototherapy 5 days/week for 8 weeks in 19/24 patients vs. no UVB in 17/24. Both groups non-specific creams/emollients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>No primary outcome variable defined. Other outcomes:</td>
</tr>
<tr>
<td></td>
<td>1. Observer-rated extent of hand eczema, and scoring 1-4 (1=absent, 2=mild, 3=moderate, 4=severe) on erythema, oedema, maceration, excoriation, lichenification, fissures, infection, scaling, itch.</td>
</tr>
<tr>
<td></td>
<td>2. Patient-rated VAS (0-10) on itching and restrictions in daily life.</td>
</tr>
<tr>
<td></td>
<td>3. Transepidermal water loss (TEWL) and Nitrazin yellow-test.</td>
</tr>
<tr>
<td>Notes</td>
<td>Authors rightly state that it is a pilot study. Only graphic presentation of a few components of some outcome parameters. Not clear, but assumed, that 24 were randomised to each group.</td>
</tr>
</tbody>
</table>

### Table 7. Rosén 1987

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised parallel group design, but with a within-patient comparison (left-right design) within each treatment group. Inadequate randomisation procedure. Patients not blinded, unclear if observers of outcome were blinded. Main unit of analysis is the treated hand.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>35 Patients (4M, 31F) with bilateral hand eczema of at least 6 months duration, previous treatment without benefit and interference of eczema with daily life. Dropouts: 5.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Oral PUVA 3x weekly until clearance in 14/18 hands vs. no treatment in 14/18 contralateral hands. UVB 3x weekly until clearance in 16/17 hands vs. no treatment on 16/17 contralateral hands. Emollients in all treatment groups.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No primary outcome defined.</td>
</tr>
<tr>
<td></td>
<td>1. Observer-rated sum of score 0-3 (0=none, 1=slight, 1=moderate, 3=severe) for erythema, desquamation, vesiculation, infiltration, fissures at 3, 6, 9 and 12 weeks.</td>
</tr>
<tr>
<td></td>
<td>2. Patient and observer-rated global evaluation (cleared, much improve, somewhat improved, unchanged/worse) when treatment completed.</td>
</tr>
<tr>
<td>Notes</td>
<td>In fact three studies on the same group of patients: two separate within-patient (left-right) studies in two groups of patients, whereby these two groups were also compared. No real randomisation, but allocation based on date of birth. Patient- and physician-rated global evaluation ‘coincided’. Graphic presentation of the results, but not clear on how many patients at each point in time it was based.</td>
</tr>
</tbody>
</table>

All. conceal: Inadequate.
Table 8. Sjövall 1987

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised parallel group (3 groups) design. Randomisation procedure unclear. Patients blinded for 2 groups (hands only vs. placebo). Unclear if observer of outcome blinded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>18 Patients (3M, 15F) with chronic hand eczema resistant to conventional therapy, of different aetiology (11 patch-test proven relevant allergy, 4 atopic, 3 endogenous). Dropouts: 3.</td>
</tr>
<tr>
<td>Interventions</td>
<td>UVB irradiation only on hands 4x week for 8 weeks in 5/6 patients vs. filtered light (placebo UVB) on the hands 4x week 8 week in 5/6 vs. hand UVB followed by whole body UVB + UVA 4x week 8 weeks in 5/6. Their ‘ordinary topical treatment’ was permitted in all groups.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No primary outcome defined. 1. Observer-rated scoring system (0=unchanged/worse, 1=improved, 2=cleared) after 4 weeks, if a patient cleared, or at 8 weeks. 2. Follow-up at 3 months after end of treatment, probably using above-mentioned scoring.</td>
</tr>
<tr>
<td>Notes</td>
<td>Small number of patients. Main table unclear: results at 8 weeks or 20 weeks? Follow-up at 3 months presented in a descriptive way, without exact details.</td>
</tr>
</tbody>
</table>

Table 9. Cartwright 1987

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>30 Patients with bilateral symmetric constitutional hand eczema, resistant to previous treatment. Dropouts: 12.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Superficial X-ray 300 Rad 10 kV 3x with 21 days interval in 18/30 hands vs. placebo-radiation in 18/30 contralateral hands.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No primary outcome variable defined. 1. Patient-rated severity score on scale 0-10. 2. Observer-rated score 1-4 (0=no eczema, 1=eczema, mild scaling, 2=erythema, scaling, fissures, 3=erythema, severe scaling, bleeding fissures, 4=active pompholyx).</td>
</tr>
<tr>
<td>Notes</td>
<td>Only graphic representation of outcome scores. High dropout: 12 out of 30. Reasons given for the 12 dropouts: unwilling to attend, mostly because eczema improved.</td>
</tr>
</tbody>
</table>

All. conceal. Unclear.
### Table 10. Fairris 1984

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Within-patient (self-controlled, left-right hand) randomised design. Randomisation adequate. Patients and observer blinded.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>24 Patients with chronic constitutional therapy resistant hand eczema. Dropout: 1.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Ionising radiation 100 Rad 50 kV 3x with 31 days interval in 23/24 hands vs. placebo in 23/24 contralateral hands.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>No primary outcome parameter defined. 1. Patient-rated improvement yes/no. 2. Patient-rated score 0-10 on VAS. All three ratings at week 6, 9 and 18. 3. Observer-rated score (0=normal skin, 1=mild scaling+erythema, 2=moderate scaling+erythema+shallow fissures, 3=severe scaling+erythema+deep bleeding fissures, 4=active pompholyx).</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Only graphic presentation of scores with statistical significance given. All. conceal. Adequate.</td>
</tr>
</tbody>
</table>

### Table 11. Lindelöf 1987

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Within-patient (self-controlled, left-right hand) randomised study. Patient and outcome observer blinded. Adequate randomisation procedure.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>24 Patients with chronic hand eczema (13 allergic, 5 atopic, 3 irritant, 2 tyloitic, 1 pompholyx). Dropouts: 1.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Ionising radiation (Grenz-rays, 300 Rad) 1x weekly for 6 weeks in 23/24 hands vs. placebo radiation in 23/24 contralateral hands.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>No primary outcome parameter defined. 1. Observer-rated score (0=no symptoms, 4=very severe symptoms for erythema, scaling, itching, vesicles, fissures, area involved) at week 5 and week 10. 2. Comparison of number of patients who are better on the treated hand vs. number of patients who are better on the placebo hand.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Total scores are only graphically presented, without statistical analysis. All. conceal. Adequate.</td>
</tr>
</tbody>
</table>

### Table 12. Kucharekova 2003

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Randomised parallel group design. Unclear randomisation procedure. Patients not blinded, observer of outcome blinded.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>32 Patients with bilateral chronic hand eczema &gt;6 months, with mild to moderate severity and good response to topical corticosteroids. Dropouts: 6 or 7.</td>
</tr>
</tbody>
</table>
### Table 12. Kucharekova 2003\(^\text{31}\) (continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Emollient with ceramides 2x daily for 2 months in 13/17 patients vs. traditional pet-based emollient in 12/15. Both groups allowed to use triamcinolone ointment in case of active hand eczema.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>No primary outcome parameter defined. Many outcomes: 1. Patient-rated efficacy of response (worse, minimal, marked improvement). 2. Patient-rated cosmetic acceptability. 3. Patient-rated use of corticosteroids. 4. Observer-rated global assessment (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe, 5=very severe). 5. Observer-rated hand eczema area and severity score.</td>
</tr>
<tr>
<td>Notes</td>
<td>Unclear about 2 dropouts. Authors state that it is a pilot study. Analysis may have been ITT, but procedure unclear. Results presented graphically, without exact numbers.</td>
</tr>
</tbody>
</table>

| All. conceal. | Unclear. |

### Table 13. Bleeker 1989\(^\text{32}\)

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>76 Patients (22M, 54F, age 18-65) with different subtypes of hand eczema. Vesicular and infected dermatitis excluded. Dropouts: 1</td>
</tr>
<tr>
<td>Interventions</td>
<td>Flupredniden cream 1x daily in evening for 3 weeks in 37/38 patients vs. betamethasone cream 1x daily in evening for 3 weeks in 38/38. Both groups emollient (Unguentum Merck) if required.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome variable not stated. 1. Observer- and patient-rated general assessment of therapeutic result (0=healed, 1=improved, 2=unchanged, 3=worse). 2. Reduction in scoring based on symptoms (erythema, scaling, papules, vesicles, lichenification, fissures, excoriation, pruritus).</td>
</tr>
<tr>
<td>Notes</td>
<td>Unclear whether severity score as stated in methods was used in analysis. Aim was to study equivalency of treatment effect.</td>
</tr>
</tbody>
</table>

| All. conceal. | Unclear. |

### Table 14. Gupta 1993\(^\text{33}\)

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>58 Patients with corticosteroid responsive dermatitis limited to hands. Evaluable 54. Exact number of allocations to each intervention unclear. Dropouts: 6.</td>
</tr>
</tbody>
</table>
### Table 14. Gupta 1993<sup>33</sup> (continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Betamethasone dipropionate film-forming lotion in 28/29 patients daily for 7 days vs. betamethasone dipropionate thickened lotion in 26/29.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>No primary outcome defined.</td>
</tr>
<tr>
<td></td>
<td>1. Physician-rated overall severity of hand eczema (0=absent, 1=mild, 2=moderate, 3=severe).</td>
</tr>
<tr>
<td></td>
<td>2. Physician-rated scores (0=absent, 1=mild, 2=moderate, 3=severe) of pruritus, scaling, erythema, induration.</td>
</tr>
<tr>
<td></td>
<td>3. Physician global assessment of eczema-relief (-2 to +3).</td>
</tr>
<tr>
<td>Notes</td>
<td>Very short study of 7 days. Unclear about withdrawals in lotion group. Exact number allocated to each treatment not specified. Among the different outcomes, unclear how change in overall severity was calculated.</td>
</tr>
<tr>
<td>All. conceal.</td>
<td>Unclear.</td>
</tr>
</tbody>
</table>

### Table 15. Möller 1983<sup>34</sup>

<table>
<thead>
<tr>
<th>Methods</th>
<th>Within-patient (self-controlled, left-right) randomised study. Patients blinded, unclear in observer of outcome. Randomisation procedure unclear.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>55 Patients with chronic symmetrical hand eczema &gt;6 months, who had been treated with clobetasol propionate 2x daily in a preceding 3 week healing phase. Uncler on status of 9 withdrawals.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Clobetasol propionate cream 2x weekly for unclear duration (55-193 days) in 46/55 hands vs. flupredniden acetate cream 2x weekly in 46/55 contralateral hands. Emollient on both hands. When relapse occurred during the maintenance phase, the cream allocated to that hand could be applied more frequently; if this failed, the cream of the other (best) hand could be used temporarily.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No primary outcome parameter defined.</td>
</tr>
<tr>
<td></td>
<td>1. Number of hands that relapsed and time of relapse.</td>
</tr>
<tr>
<td></td>
<td>2. Efficacy judgement (not specified) by dermatologist, at unknown point in time.</td>
</tr>
<tr>
<td>Notes</td>
<td>Study on maintenance therapy. Handling of dropouts unclear: 9 patients withdrawn because of unsatisfactory results (this could be an outcome). Study duration unclear. Difficult to interpret the results in patients with relapses. Unclear which of two treatments was intervention or comparator.</td>
</tr>
<tr>
<td>All. conceal.</td>
<td>Unclear.</td>
</tr>
</tbody>
</table>
### Table 16. Uggeldahl 1986

<table>
<thead>
<tr>
<th>Methods</th>
<th>Within-patient (self-controlled, left-right) randomised study. Patients and outcome observer blinded. Randomisation procedure unclear.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>46/50 Patients (1.5-70 years) with bilateral moderate hand, wrist, lower arm eczema, with left-right comparable severity. Dropouts: 2.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Desonide cream 0.1% 2x daily for 2 weeks in 44/46 hands vs. desonide cream 0.05% in 44/46 contralateral hands.</td>
</tr>
</tbody>
</table>
| Outcomes | No primary outcome defined.  
1. Observer-rated score 0-4 (0=absent and 4=maximum severity) for inflammation, infiltration, desquamation, lichenification, itching, tenderness, chapping, after 4-7 days and 11-14 days.  
2. Patient-rated therapeutic effect: both hands equal or one better than other hand. |
| Notes | In fact, 50 were randomised, but 4 excluded at the start. Not clear if inclusion criteria (hand/wrist/lower arm) stipulated that the hands had to be involved in all the patients. Youngest patient was 1.5 years old. Aim was to study equivalency, but this was not reflected in the analysis. |

### Table 17. Veien 1999

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel group (3 groups) study. Randomisation procedure unclear. Patients not blinded, unclear if outcome observer blinded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>106 Patients with hand eczema &gt;6 months (all patch-tested), who had cleared upon daily treatment for 9 weeks with mometasone furoate cream. Dropouts: none (see notes).</td>
</tr>
<tr>
<td>Interventions</td>
<td>Mometasone furoate cream 3x week (Sun/Tue/Thu) for 30 weeks in 35/35 patients vs. mometasone cream 2x week (Sat/Sun) in 37/37 vs. no corticosteroids in 34/34. Emollients (Essex cream and ointment) used in all groups. In case of recurrence, all groups were permitted to use mometasone daily for max 3 weeks on separate periods. Additional treatment permitted in all groups in case of bacterial infection.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome: number of recurrences of hand eczema and time at which recurrence occurred (recurrence defined as eczema score equal to or higher than initial score). Secondary: number and time of recurrence in subgroups. Data analysis by survival analysis.</td>
</tr>
</tbody>
</table>
### Chapter 4

#### Table 17. Veien 1999\(^{16}\) (continued)

| Notes | All randomised patients were supposed to be free of eczema due to preceding treatment (induction of remission) with mometasone, yet recurrence was defined as a score equal or higher than before this remission induction phase. In each group a few patients received additional treatment. Dropout defined as patient who had more than 2 recurrences. |
| All. conceal. | Unclear. |

#### Table 18. Van Coevorden 2004\(^{17}\)

| Methods | Randomised parallel group study. Patients and observer of outcome not blinded. |
| Participants | 158 Patients with chronic hand eczema of at least 1 year’s duration, at least 2 relapses of at least 3 weeks duration, moderate to severe, grade 6 on a hand eczema score at start of treatment. Dropouts: 33 during treatment, 8 during follow-up. |
| Interventions | Oral PUVA (methoxypsoralen) phototherapy at home on both hands 3x weekly for 10 weeks in 63/78 patients vs. topical bath PUVA (trioxsalen) 2x weekly in hospital for 10 weeks in 62/80. Emollients in both groups. |
| Outcomes | Primary outcome: Observer-rated score based on sum of scores 0-3 (0=none, 1=slight, 1=moderate, 3=severe) for erythema, desquamation, vesiculation, infiltration, fissures, itch, pain at week 10, i.e. at end of treatment. Secondary outcomes: 1. Observer-rated score (as described above) at week 18, i.e. 8 weeks after completion of treatment. 2. Patient-registered travel costs and time off work. 3. Nr. of patients improved at week 10. |
| Notes | Blinding of patients impossible. Observers of outcome not blinded. Analysis based on ITT principle. Scoring of eczema was similar to the scoring used by Rosén.\(^{26}\) Secondary outcome nr. 3 (number of patients improved at week 10) not specified in the methods. Authors mention adherence to CONSORT statement. |
| All. conceal. | Adequate. |
Interventions for hand eczema

**Table 19. Grattan 1991**

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>15 Patients with vesicular hand eczema for at least 6 months. Dropouts: 3.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Topical PUVA 3x weekly for 8 weeks on 12/15 hands vs. UVA (with placebo psoralen paint) on 12/15 contralateral hands. Both hands moisturisers, and both hands a small fraction of UVB from the UVA lamps.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No primary outcome variable defined.</td>
</tr>
<tr>
<td>1.</td>
<td>Observer-rated global rating 1-5 (0=clear, 1=minimal, 2=mild, 3=moderate, 4=severe).</td>
</tr>
<tr>
<td>2.</td>
<td>Patient-rated VAS to indicate improvement.</td>
</tr>
<tr>
<td>3.</td>
<td>Observer-rated T-120 scores: multiplying surface area involved with severity scores (0-4) for erythema and scaling.</td>
</tr>
<tr>
<td>4.</td>
<td>Questionnaire after completion of the study.</td>
</tr>
<tr>
<td>Notes</td>
<td>Small number of patients. Exact figures for main outcomes not given: instead, there are graphic presentations. Questionnaire assessment after completion of the study, but duration of follow-up in this questionnaire assessment unclear.</td>
</tr>
</tbody>
</table>

**Table 20. Polderman 2003**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised, parallel group design. Patients and observer of outcome blinded. Randomisation procedure not clear, probably adequate (according to a lottery system).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>28 Patients with dyshidrotic hand eczema, of 4 months to 34 years duration. Dropouts: 3.</td>
</tr>
<tr>
<td>Interventions</td>
<td>UVA1 irradiation 40 J/cm² on the hands in 15/15 patients 5x weekly for 3 weeks vs. placebo (simulated blue light) in 10/13. Probably emollients in both groups</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome: Observer-rated dyshidrotic eczema area and severity index (DASI, based on sum-score for severity 1=mild, 2=moderate, 3=severe for respectively vesicles, erythema, desquamation, itch multiplied by score for affected area); time point not specified.</td>
</tr>
<tr>
<td>Secondary outcome:</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>VAS for itch (probably patient-rated).</td>
</tr>
<tr>
<td>2.</td>
<td>Observer-rated separate items of DASI.</td>
</tr>
</tbody>
</table>
**Chapter 4**

Table 20. Polderman 2003\(^{39}\) (continued)

| Notes | Primary outcome probably at week 3, i.e. at end of treatment. There was a follow-up 6 weeks after treatment, but only summary data given for the treatment group. Scoring of outcome (DASI) the same as in the study by Odia and Schnopp.\(^{22,46}\) All. conceal. Adequate. |

Table 21. King 1984\(^{40}\)

| Methods | Within-patient (self-controlled, left-right) randomised design. Randomisation procedure unclear. Patients and observer of outcome blinded. |
| Participants | 20 Patients with chronic palmar eczema. Evaluable 15 (8 hyperkeratotic, 7 pompholyx). Dropouts: 5. |
| Interventions | Superficial ionising radiation fractionated 100 Rad, at 45 kV, 1x weekly 3 weeks, total dose 300 Rad in 15/20 hands vs. placebo radiation 1x weekly 3 weeks in 15/20 contralateral hands. Topical medication continued unchanged. |
| Outcomes | No primary outcome defined. |
| Notes | Outcome 2 (photographs) was not used in the presentation of results. All. conceal. Unclear. |

Table 22. Fairris 1985\(^{41}\)

| Methods | Within-patient (self-controlled, left-right hand) randomised design. Randomisation adequate. Patients and observer blinded. |
| Participants | 25 Patients with chronic constitutional therapy resistant hand eczema. Dropouts: 5. |
| Interventions | Superficial X-ray 300 Rad 10 kV 3x with 21 days interval in 20/25 hands vs. 100 Rad 50 kV 3x with 21 days interval in 20/25 contralateral hands. |
### Table 22. Fairris 1985

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No primary outcome parameter defined.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Patient rating improvement yes/no.</td>
</tr>
<tr>
<td></td>
<td>2. Patient-rated score 0-10 on VAS. All three ratings at week 6, 9 and 18.</td>
</tr>
<tr>
<td></td>
<td>3. Observer-rated score (0=normal skin, 1=mild scaling+erythema, 2=moderate scaling+erythema+shallow fissures, 3=severe scaling+erythema+deep bleeding fissures, 4=active pompholyx).</td>
</tr>
</tbody>
</table>

**Notes**
- Only graphic presentation of scores with statistical significance given.
- All. conceal. Adequate.

### Table 23. Belsito 2004

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>294 Patients with mild to moderate chronic hand eczema (117 irritant, 94 endogenous, 32 irritant+endogenous, 32 irritant+allergic, 9 allergic, 4 allergic+endogenous, 4 irritant+allergic+endogenous). Duration more than 6 weeks. Dropouts: 22.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Pimecrolimus 1% cream 2x daily with 6 hr glove occlusion evenings for 3 weeks in 140/151 patients vs. vehicle 2x daily with 6 hr glove occlusion evenings in 132/143. Both groups barrier creams or emollients allowed, if applied more than 1 hr before study cream.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome variable: Investigator global assessment (IGA) on 5 point scale: ranging from 0=clear to 4=severe. Efficacy measured as proportion of treatment successes at end of study (day 22) in each group; treatment success is IGA 0 (clear) or 1 (almost clear).</td>
</tr>
<tr>
<td>Notes</td>
<td>ITT analysis. Overall efficacy (proportion of treatment successes) for both groups at end of study presented as graph (bar-chart), exact figures not given. In separate table exact figures for treatment successes, but strata of selected groups are overlapping (“to identify groups highly responsive”).</td>
</tr>
</tbody>
</table>
- All. conceal. Unclear.

### Table 24. Cherill 2000

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised parallel group (4 groups) design. Patients blinded, unclear on blinding of outcome observer. Randomisation procedure unclear.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>48 Adult patients with chronic irritant hand eczema of moderate severity. No dropouts.</td>
</tr>
</tbody>
</table>
### Table 24. Cherill 2000<sup>43</sup> (continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Pimecrolimus 1% cream 2x daily 6 weeks in 12 patients vs. pimecrolimus 1% under occlusion 2x daily 6 weeks in 12 vs. vehicle 2x daily 6 weeks in 12 vs. vehicle under occlusion in 12 patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Primary efficacy parameter: Observer-rated (?) total key sign/symptom score (0-3 for erythema, excoriation, oedema/papulation, pruritus) at day 8, 15, 22, 29, 36, and 43.</td>
</tr>
<tr>
<td>Notes</td>
<td>Study is published as conference abstract, therefore limited information on quality issues. Authors were contacted by e-mail. Similar abstract published in J Eur Acad Dermatol Venereol 2000; 14: 128.</td>
</tr>
<tr>
<td>All. conceal.</td>
<td>Unclear.</td>
</tr>
</tbody>
</table>

### Table 25. Hill 1998<sup>44</sup>

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>116 Patients with diagnosis of eczema on one or both hands, and with suspected or confirmed infection. Originally 120 patients, but 4 violated inclusion criteria. Patients were enrolled in 16 centres. Dropouts: 6.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Betamethasone valerate 0.1% + clioquinol 3% cream 2x daily 4 weeks in 57/61 patients vs. betamethasone valerate 0.1% + fusidic acid 2% cream in 53/55.</td>
</tr>
</tbody>
</table>
| Outcomes      | Primary outcome: Observer-rated proportion of patients with satisfactory (i.e. good or excellent) response at the last on-treatment visit (based on global rating: excellent, good, fair or poor). Secondary outcomes:  
1. Patient-rated response to treatment: excellent, good, fair, or poor.  
2. Observer-rated changes in scores for erythema, pruritus, induration, dryness/scaling, cracking/fissuring, clinical signs of infection (for each: 0=absent, 1=mild, 2=moderate, 3=severe) at week 1, 2 and 4.  
3. Patient-rated severity of itching: 0=absent, 1=mild, 2=moderate, 3=severe.  
4. Patient’s assessment of treatment acceptability.  
5. Bacterial culture at entry and at end of treatment: successful if pre-treatment pathogen, if present, was eradicated. |
| Notes         | Primary outcome assessed at last on-treatment visit: probably for most patients at week 4, but unclear how much earlier for dropouts (graph suggests after week 4). Not clear if data for secondary outcome nr. 2 (patient-rated response) are presented. |
Table 25. Hill 1998\textsuperscript{44} (continued)

| All. conceal. | Unclear. |

Table 26. Hanifin 2004\textsuperscript{45}

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>55 Patients with chronic severe hand eczema (32 atopic, 18 irritant, 5 dyshidrotic or other), duration at least 6 months and severity score 3 or 4. Evaluable 42; dropouts 13.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Bexarotene 1% gel escalated stepwise from 1x every other day to 3x daily in 28 for 22 weeks vs. bexarotene gel stepwise plus mometasone furoate 0.1% ointment 2x daily in 13 vs. bexarotene gel stepwise plus hydrocortisone 1% ointment 2x daily in 14. In all 3 groups daily use of emollients.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome: Observer-rated treatment success defined by 90% or better clearance using a physician assessment score (not exactly defined). Secondary outcome: Observer-rated percentage improvement of HEASI (adaptation of EASI for the hands) score. The HEASI equals (sum of severity scores for signs) x (involved hand area integer), whereby this integer is 1=10% involvement, 2=10-29%, 3=30-49%, 4=50-69%, 5=70-89%, 6\geq90%. Severity score of signs is 0=none, 1=mild, 2=moderate, 3=moderately severe, 4=severe for respectively erythema, scaling, oedema, lichenification, vesiculation, fissuring. Tertiary outcomes: 1. Observer-rated clinically significant response, defined by 50% improvement using a physician assessment score (not exactly defined). 2. Patient-rated pruritus on a scale from 0=none to 4=severe.</td>
</tr>
<tr>
<td>Notes</td>
<td>Phase I-II open label study. ITT principle not stated, but the proportion of patients with treatment success is based on the number of all patients that were enrolled in each treatment group. Of the 12 dropouts/withdrawals, it is unknown to which treatment group they belong.</td>
</tr>
<tr>
<td>All. conceal.</td>
<td>Inadequate.</td>
</tr>
</tbody>
</table>
Table 27. Oedia 1996

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>20 Patients with bilateral dyshidrotic hand eczema (13M, 7F). Atopic 7, and 9 with nickel allergy (4/9 also atopic). No dropouts.</td>
</tr>
<tr>
<td>Interventions</td>
<td>One hand pulsed direct current iontophoresis, 20x of 15 minutes each during 3 weeks in 20 hands vs. no iontophoresis on 20 contralateral hands. Both hands received corticosteroid-free tar solution and zinc paste.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Decrease in authors’ special (investigator-rated) score: sum of score points on vesicles, erythema, desquamation, itching, multiplied by size of affected area.</td>
</tr>
<tr>
<td>Notes</td>
<td>Unclear at which point in time outcome was assessed. Same scoring (DASI) was used in the studies by Polderman and by Schnopp.</td>
</tr>
<tr>
<td>All. conceal.</td>
<td>Inadequate.</td>
</tr>
</tbody>
</table>
### Table 29. Thstrup-Pedersen 2001

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised parallel group study. Patients not blinded, observer of outcome probably blinded, but unclear. Randomisation procedure probably adequate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>29 Patients (21M, 8F) with hyperkeratotic eczema on palms, patch-test negative or irrelevant. No dropouts.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Acitretin orally 30 mg daily for 8 weeks in 14/14 patients vs. placebo capsules in 15/15. Both groups topical emollients.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No primary outcome defined.</td>
</tr>
<tr>
<td></td>
<td>1. Mean observer-rated scores (0=absent, 1=slight, 2=moderate, 3=severe) for each of the signs: hyperkeratosis, fissures, scaling, itch, redness, vesicles at week 4 and week 8.</td>
</tr>
<tr>
<td></td>
<td>2. Change in biochemical parameters (haemoglobin, hepatic function, cholesterol, triglyceride).</td>
</tr>
<tr>
<td>Notes</td>
<td>Randomisation unclear from the paper, but was confirmed after writing to the 1st author. No overall scores presented as outcome. Details of biochemical parameters not given.</td>
</tr>
<tr>
<td>All. conceal.</td>
<td>Unclear.</td>
</tr>
</tbody>
</table>

---

### Table 30. Ruzicka 2004

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised parallel group design of one placebo group and three treatment groups of different doses of same (oral) medicament. Randomisation procedure correct. Patients and observers of outcome blinded. Multicentre study in 43 clinics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>319 Patients (235M, 84F) with moderate or severe chronic hand eczema of at least 3 months duration and refractory to standard therapy. All types of hand eczema. Dropouts: 75.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Oral alitretinoin 10 mg/day for 12 weeks in 62/80 vs. oral alitretinoin 20 mg/day in 67/80 vs. oral alitretinoin 40 mg/day in 63/81 vs. placebo capsules in 62/78. Standard emollient in all treatment groups.</td>
</tr>
</tbody>
</table>
Table 30. Ruzicka 2004\textsuperscript{49} (continued)

| Outcomes | Primary outcome: Responders according to physician global assessment of overall severity, whereby physician global assessment is categorised in clear, almost clear, mild, moderate, severe. Responders are defined as clear or almost clear at week 12 or last evaluation. Secondary outcomes:  
1. Observer-rated total lesion symptom score: sum of scores (0=absent, 1=mild, 2=moderate, 3=severe) for erythema, oedema, vesicles, desquamation, hyperkeratosis, fissures, pruritus/pain.  
2. Patient-rated global assessment: clearing or almost clearing (>90% clearing of signs and symptoms compared with baseline), marked improvement (>75%), moderate improvement (>50%), mild improvement (>25%), no change, worsening.  
3. Observer-rated extent of the disease: total percentage involvement of palms and dorsa of both hands.  
4. Dermatology life quality index (DLQI). |
| Notes | Largest study thus far. No other active treatment as comparator. Study included a safety assessment by careful medical and laboratory monitoring. Analysis based on intention-to-treat principle. More males enrolled because of exclusion of women of childbearing potential. Of the 127 responders 117 were followed-up for another 12 weeks after end of treatment; only summary data about this extra follow-up are presented. |
| All. conceal. | Adequate. |

Table 31. Burrows 1986\textsuperscript{50}

| Participants | 23 Patients with chronic eczema on palms or dorsa and with positive patch-test to nickel. Dropouts: 3. |
| Interventions | Triethylenetetramine (Trientine) 300 mg daily for 6 weeks in patients (number unknown) vs. placebo. Cross-over after 4 week wash-out. |
| Outcomes | No primary outcome defined.  
1. Improvement (yes/no) based on decision by physician and patient.  
2. Urinary nickel and copper excretion. |
| Notes | Trial was terminated due to literature report on potential side effects (teratogenicity). Study based on patients entered before termination. Results table difficult to interpret in view of the cross-over; based on 20 patients? |
| All. conceal. | Unclear. |
Table 32. Kaaber 1983

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised parallel group design, with adequate randomisation procedure. Patients blinded, unclear if observer of outcome blinded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>30 Female patients with pompholyx more than 6 months, and positive patch-test to nickel. Dropouts: 6.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Oral tetrathiomol (TETDS) 50 mg/day first week, increasing to 200 mg/day for at least 6 weeks in 11/15 patients vs. placebo tablets in 13/15. Both groups desoxymethasone ointment and emollient.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No primary outcome parameter defined.</td>
</tr>
<tr>
<td></td>
<td>1. Patient-rated (?) number of flares at each 2-3 week visit.</td>
</tr>
<tr>
<td></td>
<td>2. Observer-rated score (area involved 0-4, erythema 0-3, number of vesicles 0-1, scaling 0-3).</td>
</tr>
<tr>
<td></td>
<td>3. Number of patients healed (not specified in methods).</td>
</tr>
<tr>
<td></td>
<td>4. Amount of corticosteroid ointment used since last visit.</td>
</tr>
<tr>
<td>Notes</td>
<td>Study duration unclear. Timing of outcome assessments not clear. Comparison based on slopes of linear regression of scores.</td>
</tr>
<tr>
<td>All. conceal.</td>
<td>Adequate.</td>
</tr>
</tbody>
</table>

Table 33. Whitaker 1996

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel group design. Randomisation procedure unclear. Patients blinded, unclear if outcome observer blinded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>39 Patients with chronic stable hand eczema with &gt;12 months duration. Dropouts: 5.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Gamma linolenic acid (GLA) 50 mg (in 500 mg evening primrose oil capsules) daily 16 weeks in 19/20 patients vs. gelatine capsules with 500 mg sunflower oil daily 16 weeks in 15/19.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No primary outcome variable defined.</td>
</tr>
<tr>
<td></td>
<td>1. Observer-rated clinical evaluations (using a 100 mm visual analogue scale to evaluate dryness, redness, itch, cracking, vesiculation, oedema, and overall impression) at 4 week intervals, up to 24 weeks, of which the score decreases (improvements) from baseline at week 16 and week 24 are analysed.</td>
</tr>
<tr>
<td></td>
<td>2. Change in epidermal GLA content.</td>
</tr>
<tr>
<td></td>
<td>3. Decrease in corticosteroid usage.</td>
</tr>
<tr>
<td>Notes</td>
<td>Part of the study was a laboratory investigation in 10 matched healthy controls. At the beginning of the study, all patients had blood taken for laboratory parameters, and biopsies for histology and electron microscopy. No patient-rated outcome.</td>
</tr>
<tr>
<td>All. conceal.</td>
<td>Unclear.</td>
</tr>
</tbody>
</table>
**Table 34. Veien 1995**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel group study in 47 patients. Randomisation procedure unclear. Probably adequate blinding of patients and outcome observer, but procedure not described.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>47 (11M, 36F) with hand eczema of at least 6 months duration. All had or previously had atopic dermatitis. All without positive reaction to standard patch-test series. Dropouts: 9.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Oral ranitidine 300 mg 2x daily (21/23 patients) vs. placebo tablets (17/24 patients). Duration of treatment not stated, probably it was 16 weeks. Both groups received betamethasone cream/ointment and emollient.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No primary outcome variable defined. 1. Observer-rated scoring based on scoring (0=absent, 1=mild, 2=moderate, 3=severe) for erythema, vesicles, scaling, pruritus, fissures, and 1-3 score for area involved. 2. Patient-rated treatment result: 0=unchanged/aggravated, 1=slight improvement, 2=marked improvement, 3=clear. 3. Observer-rated treatment result: same scoring. 4. Patient and physician-rated (combined?) overall result: successful (marked alleviation or clear) or failed (unchanged/aggravated). 5. Scores of separate items in outcome 1.</td>
</tr>
<tr>
<td>Notes</td>
<td>Published as brief communication. In results section unclear whether the outcome was based on the patients’ or the physicians’ scores or a combination of these. Analysis according to ITT, but no details given.</td>
</tr>
</tbody>
</table>

**Table 35. Larsen 2003**

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<tbody>
<tr>
<td>Participants</td>
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<tr>
<td>Interventions</td>
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<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td>Conference abstract presenting same data as Ruzicka 2004.</td>
</tr>
<tr>
<td>All. conceal.</td>
<td>Not used.</td>
</tr>
</tbody>
</table>