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CHAPTER 3

HAND ECZEMA – THE EVIDENCE FOR TREATMENT QUESTIONS

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INTRODUCTION

Definition
The term ‘hand eczema’ implies an inflammation of the skin (dermatitis) that is confined to the hands. Clinically, the condition is characterised by signs of redness, vesicles (tiny blisters), papules, scaling, cracks and hyperkeratosis (callous-like thickening), all of which may be present at different points in time. Itch, sometimes severe, is a common feature. Microscopically, the disease is characterised by spongiosis with varying degrees of acanthosis, and a superficial perivascular infiltrate of lymphocytes and histiocytes.

Incidence and prevalence
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 on whether the disease definition includes more pronounced or mild cases. The prevalence may be higher in some countries. Recently, a decreased prevalence was stipulated, and attributed to decreased occupational exposure to irritants. Hand eczema is twice as common in women than in men, with the highest prevalence in young women. Reasons for this sex difference are unknown, although greater exposure of women to wet work is probably contributory. Reliable data on incidence are scarce, and are mainly confined to estimates in particular occupational groups. Estimates vary from 0.5 per 1000 in the general population to 7 per 1000 per year in high risk occupations such as bakers and hairdressers.

Aetiology
The aetiology is multifactorial. Contact irritants are the commonest external causes. Hand eczema caused by such irritants, or mild-toxic agents, is called irritant contact dermatitis. Causal factors that are less common than irritants are contact allergens. Hand eczema caused by skin contact with allergens is called allergic contact dermatitis. Ingested allergens (for example nickel) may also provoke hand eczema. Water is a contact irritant and thereby an external causal or contributing factor. Being atopic (a tendency to develop asthma, hay fever or eczema) is the major predisposing factor responsible for hand eczema. There are several types of hand eczema of which the cause or predisposing factor is unknown. These (partly overlapping) types are not precisely defined and are commonly described as: hyperkeratotic, tylotic, endogenous, dyshidrotic, pompholyx and nummular. In particular, dyshidrotic eczema is subject of debate: a hallmark is recurrent vesiculation, which may or may not be associated with factors such as nickel allergy, atopy and other factors. In many patients a combination of the abovementioned factors seems to play a role. The relevance of psychosomatic factors remains speculative.
Prognosis
When there is a single, easily avoidable contact allergic factor, the prognosis is good. Several studies, however, have suggested that hand eczema tends to run a long lasting and chronic relapsing course, probably because of the multifactorial origin.

Diagnostic tests
Diagnosis is mainly based on history and clinical signs; there are no standardised diagnostic criteria. Patients are patch-tested to detect or rule out a contact allergy. In addition, prick-tests are performed to detect atopy, and skin scrapings are performed to rule out a mycotic infection. In the majority of cases, no relevant contact allergy can be detected. Specific prick tests are of additional value in only very special cases (such as eczematised urticarial reactions).

Treatment
Treatment of hand eczema is aimed at reducing clinical symptoms (including the disabling itch), preventing relapses and reducing the burden of disease by allowing resumption of daily manual tasks. The outcome of this treatment can be assessed in different ways. Relevant outcome parameters are:
1. Percentage of patients with patient-stated good/excellent response
2. Percentage of patients with investigator-stated good/excellent response
3. Reduction in severity (patient and physician-rated scoring systems)
4. Dose reduction
5. Time until relapse.

OBJECTIVES
In daily clinical practice we often ask ourselves what treatment would be best for the patient with hand eczema sitting in front of us. These questions usually encompass a comparison between two treatment modalities. From this background, we formulated 14 clinically relevant questions.

Because of the tendency of hand eczema to develop a chronic or relapsing course, all questions dealt with chronic hand eczema. In the context of this chapter, chronicity can arbitrarily be defined as more than 6 months’ duration. Because prescription of topical corticosteroids is the most common treatment at present, they are the major comparator in the questions below.

METHODS OF SEARCH
Controlled trials dating back to 1977 were located by searching the Cochrane Library, Medline, Embase, Pascal and Jicst-Eplus. In addition, a hand-search
was performed on any trial in major English, German, French, Italian and Dutch dermatology journals. Uncontrolled trials were discarded, unless on a specific subject systematic reviews and controlled trials were lacking. Also, papers studying different dermatoses and not specifically stating the results for the patients with hand eczema, were ignored. Prior to the search the questions were formulated; only papers pertaining to these questions were included.

The content of this chapter relies on an ongoing systematic review on interventions for hand eczema.\(^1\) An overview and quality appraisal of all trials on hand eczema between 1997 and 2003 has been published by the authors.\(^2\)

**QUESTION 1**

In adults with chronic hand eczema, do topical corticosteroids lead to better patient- or physician-rated reduction in symptom scores than topical coal tar preparations?

No systematic review was found, and no trial (controlled or uncontrolled) could be identified. Trials may be detected in older (pre-1977) literature.

**QUESTION 2**

In adults with chronic hand eczema, do short bursts of potent topical corticosteroids (class 3 or 4) lead to better patient- or physician-rated scores than continuous mild (class 1 or 2) topical corticosteroids?

We found no studies comparing the effect of short bursts of strong (class 3 or 4) topical corticosteroids (for example twice weekly, or weekends only) with continuous application of milder (class 1 or 2) topical corticosteroids. One randomised controlled trial (RCT) compared the three times weekly application versus weekend application of the same steroid, with limited evidence that the three times weekly application was better.

**Efficacy**

No systematic reviews were found.

**Three times weekly versus weekend application**

There is limited evidence of a preferential effect of three times weekly application of mometasone in an RCT of a 30-week maintenance phase (i.e. after induction of remission).\(^3\) The primary outcome variable was the number of recurrences of hand eczema.
Once-daily versus twice-daily application
Once daily halcinonide 0.1% versus twice daily betamethasone dipropionate 0.05% showed good efficacy in both groups. In half the patients once daily halcinonide 0.1% was superior.\textsuperscript{4}

Two different concentrations
One left-right RCT of 2 weeks’ duration comparing different concentrations of the same corticosteroid applied twice daily detected no difference.\textsuperscript{5}

Class 2 versus class 3 corticosteroids
One RCT compared short-term (3 weeks) application of fluprednuniene-21-acetate 0.1% cream (class 2) with betamethasone-17-valerate 0.1% cream (class 3), both in a once daily regimen.\textsuperscript{6} There was no difference in time to onset of effect nor in clinical efficacy.

Class 2 versus class 4 corticosteroids
In a double-blind left-right RCT more patients remained free from relapses with clobetasol propionate than with fluprednuniene acetate.\textsuperscript{7} In addition, time to relapse was longer with clobetasol propionate. Initial treatment and in case of recurrence was twice daily; in the maintenance phase application was twice weekly. Side effects between the two groups were comparable.

Drawbacks
Mild skin atrophy was reported in two studies.\textsuperscript{2,7}

Comment
Except for the study on three times weekly versus weekend application, all studies were of short duration. No study had tachyphylaxis or atrophy as outcome parameters. No uncontrolled trials were detected. Older (pre-1977) literature may give some insight into this issue.

Implications for clinical practice
The choice for an optimal topical steroid treatment schedule cannot be derived from the current literature on hand eczema trials. Evidence from studies on other eczematous diseases may have to be considered.

QUESTION 3
In adults with chronic hand eczema, are oral immunosuppressive agents (ciclosporin, methotrexate, mycophenolate mofetil) better in
maintaining a long-term (more than 6 months) reduction of patient- or physician-rated scores than topical corticosteroids?

Two RCTs were identified, one of which showed that ciclosporin was effective, but not better in terms of clinical signs. The other RCT, studying the same patients, also showed no comparative advantage of ciclosporin over topical corticosteroids in terms of quality of life.

**Efficacy**
No systematic review was found.

**Ciclosporin versus topical betamethasone**
One RCT compared ciclosporin with betamethasone dipropionate 0.05% twice daily.\(^8\) The study had three phases, none of which showed a comparative advantage in terms of clinical signs, global assessment or cumulative relapse rate. The first treatment phase was 6 weeks; the second and third amounted to 30 weeks.

Quality of life was the outcome parameter in a study of the same design and of the same patients;\(^9\) this parameter showed no comparative advantage.

**Methotrexate**
We identified no controlled trials.

**Mycophenolate mofetil**
We identified no controlled trials.

**Drawbacks**
Paraesthesia (‘tingling’), dizziness, insomnia and increase in serum creatinine were reported.

**Comment**
The comparator in the ciclosporin studies was a relatively strong corticosteroid.

**Implications for clinical practice**
Ciclosporin may be useful to obtain short-term control, but cannot be recommended for maintenance therapy.
QUESTION 4

In adults with chronic hand eczema, does treatment with ionising radiation (X-rays) lengthen the time to relapse compared with topical corticosteroids?

We identified six RCTs, all of which had a left-right design (i.e. the contralateral hand of each patient served as control). Two RCTs found no evidence that X-rays were superior to conventional topical medication. None of the trials had a follow-up time longer than 6 months; therefore, there was no evidence that ionising radiation induced a longer remission period than conventional topical medication.

Efficacy
No systematic reviews were found.

Versus topical medication
One 18-week study of Grenz-rays using a grading system as outcome parameter,\textsuperscript{10} and one study of superficial radiotherapy, using (nearly) clearing as outcome parameter,\textsuperscript{11} found no beneficial effect. One 10-week RCT of Grenz-rays,\textsuperscript{12} and one 18 week RCT of superficial X-rays found a beneficial effect.\textsuperscript{13}

Versus topical PUVA
One trial found at 6 weeks a superior effect of radiotherapy at 6 weeks, but after 18 weeks follow up there was no difference in reduction of severity scores.\textsuperscript{14}

Superficial X-rays versus Grenz rays
One study of 18 weeks’ duration found a superior effect of conventional X-rays from the doctor’s point of view, but the patients’ rating showed no difference.\textsuperscript{15}

Drawbacks
Three trials mentioned the absence of adverse reactions during treatment.\textsuperscript{12,13,15} No study could assess the possible long-term harmful effects of the radiotherapy.

Comment
No trial used time until relapse as outcome variable. No study gave a rationale for the sample size; sizes varied between 15 and 30 patients. None of the trials stated explicitly which conventional topical therapy was the comparator; at the most it was described as corticosteroids and/or tar. Overall, the studies did not explicitly describe the types of hand eczema of the patients: four studies
Chapter 3

specified the type of eczema as constitutional, the other two gave only a very partial results among some types of hand eczema. Older literature may give an indication about possible long-term harm.

Implications for clinical practice
Given the uncertainties about the long-term effects of this treatment modality, and the very limited evidence of a short-term effect, radiotherapy cannot be recommended.

QUESTION 5

Does the daily application of a bland emollient lead to dose and/or frequency reduction of topical corticosteroids in adults with chronic hand eczema?

No RCTs addressing this issue could be identified. Only one controlled study compared an emollient with two different topical corticosteroids.

Efficacy
No systematic review was found.

Emollient versus topical corticosteroids
One controlled trial indicated a beneficial effect of a camomile-extract-containing cream over a cream with 0.25% hydrocortisone, but not in comparison with 0.75% fluocortin butylester cream. Uncontrolled studies noted a reduction in steroid use in patients treated with a moisturising cream and in patients treated with a protective foam.

Versus each other
In one left-right RCT, using patient preference as outcome parameter, there was limited evidence in favour of Aquacare HP over Calmurid, both of which contained 10% urea.

One controlled clinical trial (CCT) with a left-right design did not detect an advantage of a urea cream over an aqueous cream.

An RCT confirmed that the frequent application of emollients resulted in better hand eczema scores. However, a superior effect of emollient with ceramides could not be demonstrated. This RCT showed that an emollient with ceramides could reduce the use of topical corticosteroids.

The beneficial effect of emollients on hand eczema was also seen in a CCT comparing two bland emollients. There was a decrease in transepidermal
water loss, as well as an improvement in physician- and patient-rated severity scores.

**Drawbacks**
No major side effects were reported. Burning and worsening of the pre-existing hand eczema were reported. Patients were concerned with greasiness of their hands, and with staining of objects they handled.

**Comments**
Several poor-quality uncontrolled studies were also identified, none of which had steroid dose reduction as the outcome parameter.

**Implications for clinical practice**
Despite their widespread use, there is only little evidence of any steroid-sparing or additive effect in the treatment of hand eczema. In general, there seems to be no harm either, apart from the occasional contact allergy to an ingredient.

**QUESTION 6**
Is treatment of chronic hand eczema with local PUVA or UVB irradiation better in reducing patient- and physician-rated scores than topical corticosteroids?

We identified no trial explicitly comparing PUVA or UVB therapy with topical corticosteroids; only one RCT had ordinary topical treatment with emollients as comparator. A further six controlled trials were identified that compared the efficacy of PUVA, UVB or UVA1 therapy with a control group or using a left-right design. There is insufficient evidence that PUVA or UVB therapy is more effective than the conventional topical corticosteroids therapy.

**Efficacy**
No systematic reviews were found.

**Topical PUVA**
In a double-blind randomised within-patient trial of 15 patients with chronically relapsing vesicular hand eczema, topical PUVA and UVA treatment showed improvement of the severity score over the 8-week treatment period, but no statistical difference between the treated hands at any stage. In a CCT with a left-right design, topical cream PUVA was compared with UVA1. The study comprised 27 patients with bilateral dyshidrotic hand eczema. Almost all patients showed a good response to both treatments, with a
reduction of physician-rated scores of 50%. There was no statistical significant difference between the left and the right hand.

In a left-right design, there was little difference between topical 8-methoxypsoralen (8-MOP) bath PUVA and topical 8-MOP lotion PUVA therapy in 24 patients with chronic hand or foot eczema patients; there was greater than 80% clearing with both modalities. After 1 month the most successful treatment was continued on both sides until lesions cleared; there was no difference in the length of the relapse-free period.

An open label RCT showed that oral PUVA at home was equally effective as topical bath PUVA in the hospital. In addition, it appeared to result in lower costs and less time off work for the 158 patients.

**UVA1**
In a double-blind RCT with 28 patients with dyshidrotic hand eczema five times weekly irradiation with UVA1 was compared with placebo. After one week treatment a significant difference between the two groups was seen, with a greater efficacy of UVA1. Minor erythema was the only side effect observed.

**UVB**
Eighteen patients with chronic hand eczema resistant to conventional topical therapy with potent corticosteroids were randomly divided into three treatment groups: UVB of the hands only, placebo irradiation, and whole body UVB irradiation. Local UVB irradiation of the hands was significantly better than placebo; whole body UVB irradiation with additional irradiation of the hands significantly better than the continuing local treatment alone (not specified) according to a simple clinical grading (cleared, improved, unchanged/worse). A three months follow-up demonstrated the fast relapse of hand eczema.

In an RCT with 48 patients with occupational hand eczema the combination of UVB at home was compared with emollients alone. Physician-rated scores and transepidermal water loss improved in both groups, although the improvement did not reach statistical significance for most parameters.

**Drawbacks**
PUVA treatment can cause side effects such as burning episodes, subacute eczema and acute exacerbation of eczema. UV-therapy may also induce skin cancer as a long-term effect.

**Comment**
In some studies patients continued their topical medication or emollients. There is no study comparing PUVA, UVA1 or UVB therapy with the conventional
topical corticosteroids therapy. There is also no evidence that UV-therapy is the most effective for hand eczema (see the next question).

Implications for clinical practice

PUVA and UVB are effective; UVA1 seems to be also effective. The choice for these treatment options is guided by considerations other than proven clinical superiority over other modalities.

**QUESTION 7**

In adults with chronic hand eczema, does treatment with PUVA irradiation (oral or topical psoralen) lead to better reduction in patient- and physician-rated scores and remission periods than UVB irradiation?

We identified one RCT on oral PUVA and two CCTs on oral/topical PUVA. The controlled trial on topical bath PUVA demonstrated no comparative advantage, whereas the RCT on oral PUVA showed an effect in favour of PUVA.

*Efficacy*

No systematic review was found.

*Topical bath PUVA versus UVB*

A 6-week left-right design CCT of 13 patients showed that, though effective, topical bath PUVA was not better than UVB.\(^{30}\)

*Oral PUVA versus UVB*

The only RCT we found, a three month study of 35 patients, showed an effect in favour of oral PUVA.\(^{31}\) In this study, only one hand was treated, but in most patients the untreated hand also improved.

A CCT comparing UVB used at home with PUVA at the clinic showed no comparative advantage.\(^{32}\)

*Drawbacks*

Nausea caused by the oral psoralen was reported. Pain, burning, itching and redness was reported with both therapies, but slightly more from PUVA irradiation.
Comment
Long-term adverse effects could not be assessed. Improvement of the untreated hand may be the result of compliance with topical emollients. More than 17 uncontrolled studies were identified, claiming a beneficial effect of UV treatment (PUVA or UVB), but there was no comparator in any of the studies.

Implications for clinical practice
PUVA or UVB is effective in treating hand eczema. The question of which modality is better is unsolved.

QUESTION 8
In adults with chronic hand eczema, is oral treatment with retinoids better in terms of patient- and physician-rated scores, than topical corticosteroids?

We identified four trials on the use of retinoids in hand eczema; no trial compared oral retinoids against corticosteroids. Both topical and oral treatment with retinoids appeared to be effective.

Efficacy
No systematic reviews were found.

Topical retinoid versus topical corticosteroids
In a symmetrical double-blind non-randomised study the efficacy of triamcinolone acetonide 0.1% cream was compared with the same cream containing, in addition, 0.25% retinoic acid. The study involved 18 subjects with different types of eczema (12 atopic dermatitis, 4 allergic contact dermatitis, 1 nummular eczema, 1 dyshidrosis); the palms and soles were involved in only five patients. The duration of treatment was planned for 2 weeks with the option to extend treatment to 3 weeks. No statistically significant difference between the treatments was observed.

An open-label RCT with 55 patients compared bexarotene gel monotherapy (ligand for retinoid X receptors) with the same gel in combination with either mometasone furoate 0.1% ointment or with hydrocortisone acetonide 1% ointment. The steroids were applied twice daily, whereas bexarotene gel was applied in an increasing regimen, starting at once every other day up to three times daily, unless adjustment was needed because of irritation. All groups showed a meaningful decrease in physician-rated scores, without significant differences between the group. Side effects were reported in half the patients in all three groups, without significant differences between the
groups, with the exception of stinging and burning, which had a greater incidence in the combination treatment arms.

**Oral retinoids**

An RCT with 29 patients compared once daily 30 mg acitretin (regardless of weight) with placebo. A significant improvement compared with the placebo group was seen on hyperkeratosis, fissures and scaling, but not on itch, redness and vesicles. The improvement occurred in the first four weeks, with no additional effect seen in the following four weeks. No information was given on subjective side effects.

A large multicentre double-blind RCT assessed the efficacy of three different dosages of 9-cis-retinoic acid and placebo. The 319 patients were equally randomised over four groups: oral alitretinoin 10 mg/day, 20 mg/day, 40 mg/day and placebo. Alitretinoin led to a significant and dose-dependent improvement in physician-rated score. Side effects were also dose-dependent; the most frequently reported were headache (14%), dry lips (5%) and flushing (3%).

**Drawbacks**

Topical use of retinoid acid plus corticosteroids is reported to cause significantly more subjective irritation than topical corticosteroids without retinoid acid. We have no information on subjective side effects of oral acitretin; it appeared to cause no changes in serum biochemistry in a small trial. Oral 9-cis-retinioic acid showed few and mild side effects.

**Comment**

Oral 9-cis-retinioic acid seems to be a promising option, but evidence of a comparative advantage to conventional therapy is absent. It has to be demonstrated that this new drug with fewer side effects is more effective than conventional topical corticosteroids or UVB/PUVA therapy.

**Implications for clinical practice**

Oral retinoids appear to be effective in hand eczema. However, as there is no comparison with conventional therapy, it is unclear if it should be therapy of choice.

**QUESTION 9**

In adults with dyshidrotic hand eczema, does iontophoresis or botulinum toxin injections lead to an improvement of patient- and
physician-rated scores, when compared with topical corticosteroids or UVB/PUVA irradiation?

We identified only one RCT using iontophoresis in patients with dyshidrotic hand eczema. This trial showed a significant improvement of the iontophoresis–treated side compared with the non-treated side. No trial has compared iontophoresis with topical corticosteroids or UVB/PUVA therapy. We identified two CCTs dealing with the successful treatment of hand eczema with botulinum toxin injections.

**Efficacy**
No systematic reviews were found.

**Iontophoresis versus no treatment**
In a randomised one-sided comparison, the effects of tap-water iontophoresis in addition to steroid-free topical therapy was investigated in 20 patients with dyshidrotic hand eczema. After 3 weeks (20 iontophoresis applications) the parameters ‘itching’ and ‘vesicle formations’ scored significantly better on the iontophoresis-treated side than on the non-iontophoresis treated side, but redness and desquamation did not differ significantly.

In an open study of 54 patients with hyperhidrosis, 20 patients with palmoplantar eczema who continued the iontophoresis treatment at home for at least 6 months were compared with a historical sex- and age-matched control group of eczema patients without iontophoresis. The relapse-free interval, but not the time needed for clearing, was significantly improved in the iontophoresis-treated group.

**Botulinum toxin**
One CCT compared the additive effect of botulinum toxin in patients with dyshidrotic hand eczema. The study, with eight patients, had a left-right comparison design, with topical corticosteroids on both hands, and botulinum toxin on the more severely affected hand. It showed an improvement on physician-rated score with a reduction of itch and relapses.

Another CCT, with ten patients, also had an intrapersonal comparison. However, one hand was treated with botulinum injections, the other was left untreated. No topical corticosteroids were used. Both physician- and patient-rated scores improved.
**Drawbacks**
Tap-water iontophoresis was always connected with subjective sensations like stinging and discrete paraesthesia (‘tingling’). No severe side effects or possible harmful effects were reported.

Injection with botulinum toxin is painful and has only a temporary effect; repeated injections every few months is needed.

**Comment**
No trial showed sufficient evidence for the benefit of additional iontophoresis therapy compared with conventional corticosteroid or UVB/PUVA therapy. The open study that compared the long-term effects of iontophoresis in patients with non-specified hand eczema with historical controls had insufficient evidence to show whether iontophoresis prolongs the relapse-free interval in dyshidrotic hand eczema. Only one study describes the types of dyshidrotic hand eczema of the patients.

Botulinum toxin appears to be effective as adjuvant to topical corticosteroids in patients with hand eczema. However, the two CCTs included only 18 patients in total. There were no studies on the effect of iontophoresis.

**Implications for clinical practice**
Iontophoresis and botulinum toxin injections seem harmless, but are not proven to be effective.

**QUESTION 10**
In adults with hyperkeratotic hand eczema, does dithranol lead to an improvement in patient- and physician-rated scores, and longer remission periods upon clearance, when compared with topical corticosteroids?

No systematic review was found, and no trial (controlled or uncontrolled) of dithranol for any type of hand eczema could be identified. Trials may be detected in older (pre-1977) literature.

**QUESTION 11**
In adults with relapsing vesicular hand eczema based on contact allergy to nickel, does dietary intervention or oral therapy with chelating agents lead to an improvement of patient and physician-rated scores, when compared with topical corticosteroids?
We identified three trials: two RCTs and one CCT. All studies were small, performed in nickel-sensitive patients with hand eczema. Two studies used a nickel-chelating compound and one a low-nickel diet. None of the studies compared the intervention with topical corticosteroids. One multicentre RCT on triethylenetetramine found no significant improvement of hand eczema. The other RCT on tetraethylthiuramdisulphide (disulfiram) found only very limited evidence in favour of this treatment. One controlled trial found no evidence that a low-nickel diet improves dyshidrotic hand eczema.

Efficacy
No systematic reviews were found.

Oral therapy with a nickel chelating compound
In a multicentre, randomised, double-blind, cross-over study oral treatment with triethylenetetramine 300 mg daily for a 6-week period, or a lactose-containing placebo was given to 23 nickel-positive patients with chronic hand eczema after a 4-week rest period before cross-over. No significant improvement occurred in hand eczema on the basis of either the patients’ or the doctor’s evaluation. 41

In a double-blind, placebo-controlled RCT, tetraethylthiuramdisulphide with a gradually increased dose was given for at least 6 weeks after having reached the full dosage of 200 mg. 42 Hand eczema was graded according to a semi-quantitative scoring system. During the treatment period, the hand eczema healed in five out of the 11 tetraethylthiuramdisulphide-treated patients compared with two out of 13 in the placebo group (not significant). Using the semi-quantitative scoring system, results in favour of tetraethylthiuramdisulphide were statistically significant for scaling and frequency of flares but not for the sum of parameters.

Low nickel diet
In a non-randomised trial of 24 patients with dyshidrotic hand eczema caused by nickel, the effects of a low-nickel diet for 3 months (eight patients) were compared with oral disodium chromoglycate for 3 months (nine patients) and with seven patients who did not give consent to the study and did not receive any treatment. 43 All 24 patients were evaluated blind for itching and number of vesicles. The low-nickel diet did not improve these patients, but those treated with disodium chromoglycate improved significantly and had significantly fewer vesicles than the controls and the patients treated by diet.

Drawbacks
In one RCT, one patient treated with disulfiram had toxic hepatitis after 8 weeks of treatment and two patients out of 30 patients showed signs of hepatic
toxicity. One RCT mentioned the absence of adverse reactions during the treatment with triethylenetetramine, 300 mg daily for a 6-week period. No study using a low-nickel diet could assess possible harmful effects.

**Comment**

No trial showed sufficient evidence for the benefit of either a low-nickel diet or a nickel-chelating compound. Only two RCTs with a small number of patients (23 and 11) were performed. On the basis of the harm and the possible side effects, oral treatment with a nickel-chelating compound cannot be recommended. None of the trials compared treatments with conventional topical medication (for example corticosteroids).

**Implications for clinical practice**

Given the side effects and the lack of efficacy, oral therapy with a nickel-chelating compound cannot be recommended. There is no evidence that a low-nickel diet improves pompholyx-type hand eczema.

**QUESTION 12**

In adults with chronic clinically active hand eczema, do protective or occlusive gloves, barrier-creams, avoidance of allergens and irritants, and other non-pharmacological interventions lead to better patient- or physician-rated scores than topical corticosteroids?

Information on avoidance of allergens or irritants on a case-by-case basis can be found in the major textbooks on contact dermatitis. The effect of emollients was covered in the fifth question above.

**Efficacy**

No systematic reviews were found. There is, however, one systematic review being prepared on interventions to prevent occupational hand dermatitis. A number of issues in connection with this question will be dealt with in this review. Information on avoidance of allergens or irritants on a case-by-case basis can be found in the major textbooks on contact dermatitis. The effect of emollients was covered in the fifth question above.

No controlled trials on gloves or protective creams were found. We found a few uncontrolled rather descriptive studies indicating some benefit of gloves and/or barrier creams, one study having a within-patient left-right design.
QUESTION 13
Does addition of a topical antibacterial agent to topical corticosteroids result in better patient- or physician-rated scores than topical corticosteroids alone?

No trials compared the additional effect of topical antibacterial agents to topical corticosteroids alone. Only one RCT comparing betamethasone cream with the addition of either fusidic acid or clioquinol was found, showing a similar effect on clinical severity.

Efficacy
No systematic reviews were found.

Addition of fusidic acid or clioquinol to betamethasone
In a multicentre open label RCT with 120 patients 4 weeks twice daily application of betamethasone 0.1% clioquinol 3% cream was compared with betamethasone 0.1% fusidic acid 2% cream.\(^47\) The two preparations were equally effective in reducing observer-rated score. However, the combination of betamethasone cream and fusidic acid gave a better bacteriological response.

Drawbacks
Betamethasone 0.1% fusidic acid 2% cream was considered more cosmetically acceptable than the preparation with clioquinol. This difference was highly statically significant. Staining of the skin and clothing were the major problems.

Comment
Staphylococcal superantigens in infected areas elsewhere on the body, although the study protocol allowed them to be treated, could have had an effect on the hands.

Implications for clinical practice
There was no comparison of a corticosteroid versus a combination of corticosteroid and antibacterial agent. The evidence of an additional effect of such an antibacterial agent in patients with hand eczema is still lacking.

QUESTION 14
Is treatment of chronic hand eczema with calcineurin-inhibitors better in reducing patient- and physician-rated scores than topical corticosteroids?
Only one RCT was found which compared the efficacy of topical tacrolimus with mometasone furoate, which appeared to be equal. One RCT compared topical pimecrolimus with vehicle.

**Efficacy**
No systematic reviews were found.

**Tacrolimus**
Sixteen patients were included in an RCT with intrapersonal comparison, comparing topical tacrolimus 0.1% ointment with mometasone furoate 0.1% ointment (a class III corticosteroid). The treatment period was 4 weeks, with a follow-up period of up to 8 weeks. Both treatments gave a statistically significant decrease in clinical severity, without a significant difference between the two groups. Also, in the follow-up period there was equal efficacy.

**Pimecrolimus**
In a multicentre RCT 294 patients with hand eczema were allocated to up to 3 weeks treatment with pimecrolimus 1% cream or to vehicle. The twice daily application of the study creams (evening application under occlusion) was continued until clearance or completion of 3 weeks treatment. The efficacy of pimecrolimus 1% cream increased over time, and that of the vehicle plateaued after the second week. There was no statistical significant difference between the two groups, except for those patients where palmar involvement was present: then pimecrolimus 1% cream was superior.

**Drawbacks**
Tacrolimus 0.1% ointment gave stinging upon application; with pimecrolimus 1% cream however, this was uncommon (0.7% vs. 2.1% in the vehicle group).

**Comment**
The comparative effect of pimecrolimus 1% cream to vehicle might have attained significance when the follow-up period would have been longer, as the efficacy of pimecrolimus 1% cream increased over time. Both studies did not look at patient-rated scores.

**Implications for clinical practice**
Topical calcineurin-inhibitors are at best equally effective as topical corticosteroids. With the present evidence they may be used for rotational therapy with topical corticosteroids, with potent corticosteroids for (severe) exacerbations and topical calcineurin-inhibitors in the maintenance phase and mild exacerbations.
KEY POINTS

1. There is insufficient evidence for a choice between short bursts of potent topical corticosteroids versus continuous application of mild corticosteroids.

2. There is insufficient evidence for oral immunosuppressants as maintenance therapy.

3. There is insufficient evidence for a comparative advantage of radiotherapy (X-rays).

4. Although widely prescribed, there is not much evidence of a steroid-sparing effect of emollients.

5. PUVA and UVB are effective, but there is no evidence of a clinical advantage of one modality over the other.

6. Oral retinoids appear to be effective in hand eczema.

7. There is insufficient evidence of an additive effect of iontophoresis or botulinum injections.

8. There is insufficient evidence for low-nickel diet or chelating agents in hand eczema accompanied by nickel allergy.

9. There is insufficient evidence of an additive effect of topical antibacterial agents.

10. There is insufficient evidence of superiority of topical calcineurin-inhibitors to topical corticosteroids.

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