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TOPICAL TREATMENT WITH MEDIUM-POTENCY CORTICOSTEROIDS COMPARED TO PUVA (ORAL AND TOPICAL PSORALEN PLUS ULTRAVIOLET A) IN THE MANAGEMENT OF POMPHOLYX IN ADULT PATIENTS.

TESIS

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Background/Objectives

Dyshidrosis or pompholyx is a chronic disease characterized by the formation of vesicles and blisters on the palms, soles and lateral faces of fingers, which causes pruritus and intense burning. The aim of this review was to evaluate the treatment of dyshidrosis with mid-potency topical corticosteroid vs. PUVA (psoralen and ultraviolet A) therapy.

Methods

We conducted a systematic review of the existing literature for studies on the treatment of dyshidrosis on PubMed, SCOPUS and OVID from inception to May 2019. We used the key words 'pompholyx', 'dyshidrosis', 'dyshidrotic eczema', 'topical steroids', 'mometasone' and 'phototherapy'.

Results

We identified 329 studies and two met inclusion criteria with a total of 43 patients. The interventions included mometasone cream and PUVA therapy. Topical steroids proved to be the most effective treatment of pompholyx. The main adverse events of both treatments tend to be mild.

Conclusions

Medium-potency topical corticosteroids along with emollients are recommended as first-line treatment. PUVA therapy and topical calcineurin inhibitors are indicated as rotational therapy due to the recalcitrant nature of the entity. Longer follow-up studies and randomized controlled clinical trials are needed to establish the optimal treatment for dyshidrosis and to measure the impact on quality life, which was not evaluated in these studies.

Introduction.

Dyshidrosis or pompholyx is an infrequent disease with a chronic and recurrent course.[1] Its prevalence is calculated to be between 0.05 and 10.6% in the adult population.[2,3] Most cases are sporadic, although an autosomal dominant pattern has been described in some.[4,5] It is characterized by vesicles and/or blisters on the palms, soles and lateral faces of the fingers, which cause pruritus, intense burning sensation and pain.[1,6,7] Some of its differential diagnoses are palmoplantar pustulosis (PPP), acropustulosis of infancy, dyshidrosiform pemphigus, among others.[7,8] There are several diseases associated with dyshidrosis, such as nickel allergy, contact dermatitis, atopic dermatitis and tinea pedis.[2,4,9,10,11] Exacerbating factors such as seasonal changes, water, solvents, detergents, prolonged use of gloves, smoking, stress and hyperhidrosis have been described.[4,9,11,12,13]

The goals of treatment are to eliminate the blisters and inflammation, to decrease pruritus, and to prevent superimposed infections.[4,11] The most efficient and frequently used topical treatment is mometasone, however, the effect of topical treatments is limited by the thickness of the corneal layer and the density of eccrine sweat glands in the palmoplantar area.[11] Other therapies include topical calcineurin inhibitors (TCI), bexarotene gel, systemic corticosteroids, immunosuppressants such as azathioprine, methotrexate, mofetil mycophenolate and cyclosporine A, either alone or in combination with systemic corticosteroids.[11,13,14] UVA1 radiation is a therapeutic option for mild pompholyx cases Dyshidrotic Eczema Area and Severity Index (DASI 4-15) or maintenance therapy. In severe cases of dyshidrosis, treatment with both oral and topical psoralen plus UVA radiation (PUVA) has been described as effective,

however, it has the disadvantage of local side effects. [11,14,15,16] It should be noted, that the use of emollients should be considered as an adjuvant with any of the therapies.[4,12]

Pompholyx does not have a clear pathophysiological mechanism and lacks a specific treatment algorithm, thus the importance to establish the efficacy of available therapeutic options. The objective of our study was to evaluate topical treatment with mid-potency corticosteroids compared to PUVA therapy for the management of dyshidrosis in adult patients.

Material and methods.

(1) Search strategy

We conducted a systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. This study was registered in PROSPERO (CRD42019123659). We performed the literature search on the electronic databases of PubMed, SCOPUS, and Ovid of all existing records until May 2019 with the following terms: 'pompholyx', 'dyshidrosis', 'dyshidrotic eczema', 'topical steroids', 'mometasone', and 'phototherapy'.

(2) Selection criteria

Randomized and non-randomized clinical trials were included in this study. Studies evaluating an intervention with mid-potency topical corticosteroids and/or PUVA therapy were included in our study. Articles written in a language other than English, articles that did not provide a clinical outcome, meta-analyses, case reports, and case series were excluded.

(3) Data extraction

Two of the authors independently extracted data using an extraction form. A third author was consulted to resolve any disagreement. The articles were screened by title and abstract; those considered relevant were reviewed in full text and selected or rejected according to the inclusion and exclusion criteria.

Data for the following items were extracted: study design, patient characteristics (number of patients, age and sex), intervention, and outcomes.

(4) Outcomes

The primary outcome was to determine the therapeutic efficacy of topical corticosteroids and PUVA (oral and topical psoralen and ultraviolet A) according to the DASI (Dyshidrotic Eczema Area and Severity Index). DASI is based on the number of vesicles per square centimeter, erythema, desquamation, itching and the extension of the affected area. Each element is assigned a point on a scale of 0-3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe) with a maximum score of 60: mild (0-15), moderate (16-30) and severe (31-60).

(5) Assessment of risk of bias

In the randomized controlled trials (RCT), the risk of bias was evaluated using the Cochrane risk-of-bias tool.

Results.

Study characteristics

A total of 329 studies were screened by abstract and title. Twenty one

articles were read in full text and two fulfilled inclusion criteria Fig. 1. During the full text review, the reviewers discussed and resolved five conflicts. The characteristics of the included studies are described in Table 1. Excluded studies are shown in Table 2.

The included studies correspond to single-center clinical trials with a duration of 3 to 8 weeks. Each study reviewed the data collection in two centers in the Department of Dermatology and Allergy in Germany. A total of forty-three patients were included in the two studies, 11 were men and 32 women. In the Petering et al. study, the reported mean age was 39 years (range 20–77), while in the Schnopp et al. study, the reported mean age was 43 years (range 23-54). The race and ethnicity of the patients were not reported. Petering et al. included patients with phototype I and II, while Schnopp et al., did not consider phototype as a variable. There was no loss of patients reported on neither study.

The predominant topography in both studies was the palms. Petering et al. reported the duration of the disease with a range from 6 months to 5 years, while Schnopp et al. reported a mean duration of 38.6 months (range 2 to 184 months).

A history of atopic dermatitis, nickel allergy, and nickel sensitization was reported in 48.1% of the patients by Petering et al. and 37.5% of the patients by Schnnop et al.; one study (Petering et al.) reported the use of nicotine as an associated factor.

Efficacy

Patients included by Petering et al. received PUVA therapy for 6 weeks,

while patients by Schnopp et al. were managed with topical tacrolimus vs. mometasone furoate.

To evaluate treatment efficacy, both studies used the Dyshidrotic Eczema Area and Severity Index (DASI). In the study of Schnopp et al., DASI decreased approximately 50% from its baseline value after 2 weeks of active treatment with topical tacrolimus and mometasone furoate. In the study of Petering et al, at the third week of treatment in the two study branches, there was a reduction in DASI (>50%). However, the reduction in DASI score did not reach statistical significance in any of the studies.

Regarding application of topical tacrolimus on palms in the study by Schnnop et al., patients had a baseline DASI score of 18, at the second week a reduction was obtained from the initial score of 6.6 (64%), and at the fourth week there was an increase from the baseline score of 9 (50%). In the group treated with mometasone furoate on palms: the baseline DASI score was 18.4 with a reduction of 7 points (62%) two weeks later, and an increase in the score 4 weeks later from the baseline of 7.4 (59.8 %). Regarding application of topical tacrolimus on soles: baseline DASI score of 30 with a 2-week reduction of 29.59 (1.36%) and increase from the baseline score to 32.91 (8.33%) after 4 weeks. Compared with the group treated with mometasone furoate, their baseline DASI score was 35.82 and decreased at the second and fourth weeks to 26.23 (26.7%) and 24.59 (31.35%), respectively.

Petering et al. reported that in the case of palms treated with PUVA, patients began therapy with a DASI score of 10.23 that decreased from baseline at 3 and 6 weeks to 5 (51.12%) and 4.11 (59.8%), respectively. In the group

treated with UVA1 in the same topography, the baseline DASI was 11.38 and decreased at 3 and 6 weeks to 5.43 (52.28%) and 4.52 points (60.28%). On the soles treated with PUVA, the initial DASI score was 12.5 and decreased at 3 and 6 weeks to 5.69 (54.48%) and 5 (60%), respectively. In comparison with the group with the same topography and treated with UVA1, the baseline DASI was 15 and decreased at 3 and 6 weeks to 8.42 (43.86%) and 6.6 (55.93%), respectively.

Safety

The Petering et al. study described that phototherapy was well tolerated and no adverse effects such as erythema, persistent hypopigmentation or hyperpigmentation, or the presence of vesicles were observed. In the case of tacrolimus and mometasone study, no side effects were reported.

Risk of bias

The estimation of risk of bias of included studies is shown on Table 3 and of excluded studies on Table 4.

GRADE

The GRADE of the first study (Holger Petering, et al.) was determined to be low and that of the second (Christina Schnopp, et al.) was calculated as moderate.

Quality of life

None of the studies evaluated quality of life.

Conclusions

A comparison between topical treatment with mid-potency corticosteroids and PUVA therapy for the management of dyshidrosis in adult patients, which was considered the main objective of this work, was not performed due to the heterogeneous characteristics of the included studies. We found no studies directly comparing PUVA with topical steroids.

Mometasone furoate 0.1% has been evaluated in palmoplantar dyshidrosis over the years and several clinical reports have reported successful treatment of dyshidrosis with mid-potency steroids (Wollinaa et al.).[4,12] The Schnopp et al. study demonstrated a 50% improvement in the DASI scale, a result similar to others reports, such as that of Veiene N.K et al., that showed the similar result in hand eczema when using mometasone furoate, and the one by Volden G. et al., using clobetasol propionate, which supports the use of medium to high-potency topical corticosteroids as first-line therapy.[4,17,18] However, it is still not considered the treatment of choice due to the low number of existing studies. Corticosteroids are accessible, inexpensive, and have a rapid onset of action, characteristics that allow greater adherence by patients and eventually a better control of the disease. On the other hand, adverse effects such as cutaneous atrophy, telangiectasias, persistent erythema, striae, tinea incognito, hypopigmentation, and photosensitivity, limit their long-term or continuous use, making management of dyshidrosis difficult.[19,20]

Due to the limitations of corticosteroid use and the recalcitrant course of the disease, the search for different therapeutic options is needed. PUVA therapy could be a treatment option for severe and recalcitrant dyshidrosis. PUVA is a

treatment that induces lymphocyte apoptosis and promotes the release of anti-inflammatory cytokines, thus decreasing erythema, burning sensation and itching. Its effectivity on palms, as reported by Petering et al., was 51.12% and 59.8%, at 3 and 6 weeks respectively, and 54.48% and 60% at 3 and 6 weeks on soles. Grundmann-Kollmann M et al. evaluated improvement in 12 patients with severe and recalcitrant dermatitis of the hands and reported a 50% improvement by evaluating the treatment response in a scale from 0-4. Grattan CE et al. compared UVA and PUVA treatment in patients with chronic hand eczema, without finding statistically significant differences.[21,22] However, PUVA therapy is limited by its accessibility, cost, and the fact that the patient cannot perform the treatment at home. Another disadvantage of topical psoralens is the photosensiblity they may cause; it is essential to adequately explain correct application to patients in order to avoid adverse effects such as burns derived from its improper use. In previous studies, PUVA therapy was found to harbor important local and gastrointestinal side effects such as nausea when administered orally as 8-MOP, therefore its use was limited. Currently, several studies have reported lower rates of these side effects, so its use can be considered in selected patients.[4,18,23]

Topical calcineurin inhibitors, approved for the treatment of atopic dermatitis and considered as steroid sparing agents, have been studied for palmar dyshidrosis.[11,23] Schürmeyer-Horst et al. reported the case of a patient with dyshidrotic eczema that was initially treated with clobetasol, followed by occlusive treatment with pimecrolimus cream 1% twice a week with good response.[24,25] Belsito et al. conducted a randomized clinical trial in patients with chronic eczema of the hands, pimecrolimus cream 1% vs. placebo was

applied followed by occlusion, once a day for 3 weeks, reporting a statistically significant improvement.[26] On patients with prolonged or maintenance steroid use, topical calcineurin inhibitors could be an appropriate rotational therapy, with long-term benefits. However, patients with fissures may not be candidates for this treatment due to the burning sensation produced by pimecrolimus; also, alternative therapy may be considered in patients whose soles are mainly affected due to the milder effect of topical calcineurin inhibitors in this topography.

In the past few years, increasing importance has been given to the quality of life in patients with dermatological conditions, reason why the Dermatology Life Quality Index (DLQI) questionnaire was developed.[27] Ruiz M.A et al. validated an abridged questionnaire with 17 items to establish the quality of life of patients with hand eczema.[28] In a retrospective study by Bretterklieber A et al., patients with long-standing chronic palmoplantar dermatosis treated with PUVA reported a subjective decrease in their ability to engage in their personal activities; other studies have also demonstrated that it is a cause of occupational disability.[1,2,29] Despite the availability of tools for assessing quality of life and previous reports supporting the fact that hand eczema may have an impact on quality of life, none of the included studies evaluated this outcome.

The most important limitation of our study is the inclusion of only two studies in our analysis. Reports and case series predominate in the literature; however, our inclusion criteria only allowed clinical trials. The prevalence of the disease, its bivalent course, the low number of patients that seek medical attention, availability of drugs, and long-term costs, limits the recruitment of patients and the may explain the few number of clinical trials we found in the literature.

Other treatments are under study for the treatment of this dermatosis, including botulinum toxin for the management of associated hyperhidrosis; currently, only intradermal repeated injections are available, further studies with a topical formulation could prove as a good adjuvant to treatment. [9,12,30] In summary, PUVA therapy may be a valuable therapeutic alternative given the recalcitrance of this dermatosis. Further clinical trials that compare treatment efficacy between PUVA and corticosteroids are needed. Likewise, quality of life and time to recurrence of disease should be consider in study outcomes in order to thoroughly study both treatments. Multicenter clinical trials could aid in the recruitment of a larger number of patients and may create a more diverse population in the study.

The current evidence on the treatment of dyshidrosis is limited. Based on the available data, the use of mid-potency topical corticosteroids is the most effective approach, without disregarding the use of emollients. PUVA therapy and topical calcineurin inhibitors are alternative therapeutic options alone or as rotational therapy with steroids. However, further studies and randomized clinical trials are needed to evaluate the efficacy of treatments for dyshidrosis. Paragraph: use this for the first paragraph in a section, or to continue after an extract.

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[Tables]

Table 1. Characteristics of the studies included in the analysis.

(a)	(b)	(c)	(d)	(e)	(f)	(g)
Article ID	**Author**	**Year of Publication**	**Patients included (n)**	**Intervention**	**Duration of intervention**	**Outcome**
PMID: 14699368	Petering *et al.*	2004	27 patients (PUVA = 27) (UVA1 = 27)	• Compared effects of localized radiation with high UVA1 *vs* PUVA doses in treatment of dyshidrosis	• 3-6 weeks	• Efficacy: Statistically significant decrease in baseline DASI when compared at the end of treatment (week 6) with both treatments. But no statistically significant differences between patients treated with UVA1 *vs* PUVA • Safety: Erythema, persistent hypopigmentation or hyperpigmentation and

						blister formation were observed • Quality of life: not evaluated • Non-statistically significant decrease in DASI.
PMID: 11756949	Schnopp *et al.*	2002	16 patients (Mometasone cream =16) (Tacrolimus=16)	• Compared the efficacy of 1% tacrolimus (FK506) ointment and 0.1% mometasone furoate in the treatment of palmoplantar dyshidrotic eczema	• 4-8 weeks	• Palms: decrease in DASI from 18 (SD 12.68) to 6.6 (SD 6.18; p = .008 and from 18.5 (SD 14.09) to 6.9 (SD 7.7; p = .010) in FK506 and with mometasone furoate, respectively • Adverse effects: not reported • Quality of life: not evaluated

PUVA (oral and topical psoralen and ultraviolet A), DASI (Dyshidrotic Eczema Area and Severity Index).

Table 2. Characteristics of experimental studies, not included in in the analysis.

(a)	(b)	(c)	(d)	(e)	(f)
No.	**Study**	**Author**	**Year plublication**	**Study design**	**Patients (n)**
1	A double-blind placebo-controlled trial of UVA-1 in the treatment of dyshidrotic eczema PMID: 14616819	Polderman *et al.*	2003	Quasi-experimental	28
2	The Dyshidrotic Eczema Area and Severity Index - A score developed for the assessment of dyshidrotic eczema ISSN Linking: 1018-8665	Vocks *et al.*	1999	Quasi-experimental	12
3	Disodium cromoglycate versus diet in the treatment and prevention of nickel-positive pompholyx PMID: 2138953	Piggato *et al.*	1990	Quasi-experimental	24

4	Treatment of chronic palmoplantar eczema with local bath-PUVA therapy	Schempp *et al.*	1997	Quasi-experimental	28
5	Oral vs. bath PUVA using 8-methoxypsoralen for chronic palmoplantar eczema PMID: 19292787	Tzaneva *et al.*	2009	Quasi-experimental	29
6	Adjuvant botulinum toxin A in dyshidrotic hand eczema: a controlled prospective pilot study with left-right comparison PMID: 11952288	Wollina and Karamfilov.	2002	Quasi-experimental	8
7	PUVA-gel vs. PUVA-bath therapy for severe recalcitrant palmoplantar dermatoses. A randomized, single-blinded prospective study PMID: 15752122	Schiener *et al.*	2005	Quasi-experimental	20

8	PUVA-bath photochemotherapy (PUVA-soak therapy) of recalcitrant dermatoses of the palms and soles PMID: 10321515	Behrens *et al.*	1999	Quasi-experimental	30
9	Medium-dose-UVA-1 irradiation - and topical PUVA - Therapy in chronic dyshidrotic hand dermatitis - A prospective randomized study	Adams *et al.*	2007	Quasi-experimental	15
10	Efficacy and tolerability of a Chinese herbal medicine concoction for treatment of atopic dermatitis: A randomized, double-blind, placebo-controlled study PMID: 17501956	K.L.E. Hon *et al.*	2007	Quasi-experimental	85 children
11	Local narrowband UVB phototherapy vs. local PUVA in the treatment of chronic hand eczema PMID: 17254029	Sezer & Etikan.	2007	Quasi-experimental	15

12	Oral methoxsalen photochemotherapy of recalcitrant dermatoses of the palms and soles PMID: 708596	Morison *et al.*	1978	Quasi-experimental	20
13	Ultraviolet-free phototherapy PMID: 15752121	Krutmann *et al.*	2005	Quasi-experimental	10
14	Clobetasone 17-butyrate, lotion scalp fluid. Results of a clinical trial in the treatment of steroid-sensitive dermatitis ISSN: 00099325	Fallica *et al.*	1989	Quasi-experimental	40
15	Comparison of topical PUVA with UVA for chronic vesicular hand eczema PMID: 1675518 ISSN: 00015555	Grattan *et al.*	1989	Quasi-experimental	15
16	Comparison of local bath-PUVA with steroid treatment in palmoplantar pustular psoriasis and dyshidrotic eczema	Kim *et al.*	2000	Quasi-experimental	44

17	Long-term results of radiotherapy in patients with chronic palmo-plantar eczema or psoriasis 18398587	Sumila *et al.*	2008	Quasi-experimental	28
18	[Therapy of hyperhidrosis with tap water iontophoresis. Positive effect on healing time and lack of recurrence in hand-foot eczema]	Wollina *et al.*	1998	Quasi-experimental	54
19	The effect of hyperthermia on some allergodermatoses PMID: 4244440	Csaba *et al.*	1970	Quasi-experimental	58

Table 3. Bias Risk of the articles included for evaluation: Heldinger *et al*, and Schnopp *et al.*

(a)	(b)	(c)
Bias risk, Cochrane tool	PUVA Study (Ptering *et al.*)	Tacrolimus/Mometasone study (Schnopp *et al.*)

Selection bias		
Sequence generation	Unclear risk of bias	Low bias risk
Allocation concealment	Unclear risk of bias	High bias risk
Blinding of participants and staff (bias of realization)	Unclear risk of bias	Low bias risk
Blinding of assessors (detection bias) (results reported by the patient)	Low bias risk	Low bias risk
Blinding of assessors (detection bias) (mortality)	Low bias risk	Low bias risk
Management of incomplete outcome data (attrition bias) (short-term outcomes) [2 to 6 weeks]	Low bias risk	Low bias risk
Management of incomplete outcome data (attrition bias) (longer term outcomes) [> 6 weeks]	High bias risk	Low bias risk
Selective notification (notification bias)	Low bias risk	Low bias risk

Table 4. Bias Risk of the articles not included for evaluation.

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)
Study	**Sequence generation**	**Allocation concealment**	**Blinding of participants and staff (bias of realization)**	**Blinding of assessors (detection bias) (results reported by the patient)**	**Blinding of assessors (detection bias) (mortality)**	**Management of incomplete outcome data (attrition bias) (short-term outcomes) [2 to 6 weeks]**	**Management of incomplete outcome data (attrition bias) (longer term outcomes) [> 6 weeks]**	**Selective notification (notification bias)**
1 A double-blind placebo-controlled trial of UVA-1 in the treatment of dyshidrotic eczema PMID: 14616819	Low bias risk	Low bias risk	Low bias risk	Low bias risk	Low bias risk	Low bias risk	High bias risk	Low bias risk
2 The Dyshidrotic Eczema Area and Severity Index - A	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low bias risk

score developed for the assessment of dyshidrotic eczema ISSN: 1018-8665								
3 Disodium cromoglycate versus diet in the treatment and prevention of nickel-positive pompholyx PMID: 2138953	High bias risk	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low bias risk	Low bias risk	Low bias risk
4 Treatment of chronic palmoplantar eczema with local bath-PUVA therapy	High bias risk	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low bias risk	Low bias risk	Low bias risk
5 Oral vs. bath PUVA using 8-methoxypsoralen for chronic palmoplantar eczema PMID: 19292787	Low bias risk	Low bias risk	Unclear risk of bias	Low bias risk	Low bias risk	Low bias risk	Low bias risk	Low bias risk
6 Adjuvant botulinum toxin A in dyshidrotic hand eczema: a controlled prospective	High bias risk	High bias risk	High bias risk	Unclear risk of bias	Unclear risk of bias	Low bias risk	Low bias risk	Low bias risk

pilot study with left-right comparison PMID: 11952288								
7 PUVA-gel vs. PUVA-bath therapy for severe recalcitrant palmoplantar dermatoses. A randomized, single-blinded prospective study PMID: 15752122	Low bias risk	Unclear risk of bias	Low bias risk	Low bias risk	Low bias risk	Low bias risk	High bias risk	High bias risk
8 PUVA-bath photochemotherapy (PUVA-soak therapy) of recalcitrant dermatoses of the palms and soles PMID: 10321515	Unclear risk of bias	Unclear risk of bias	Low bias risk	High bias risk	High bias risk	Low bias risk	Low bias risk	Low bias risk
9 Medium-dose-UVA-1 irradiation - and topical PUVA - Therapy in chronic dyshidrotic hand dermatitis - A prospective randomized study	Low bias risk	Low bias risk	High bias risk	High bias risk	High bias risk	Low bias risk	Unclear risk of bias	Low bias risk

10 Efficacy and tolerability of a Chinese herbal medicine concoction for treatment of atopic dermatitis: A randomized, double-blind, placebo-controlled study PMID: 17501956	Low bias risk	Low bias risk	Low bias risk	Low bias risk	Low bias risk.	Low bias risk	Low bias risk	Low bias risk
11 Local narrowband UVB phototherapy vs. local PUVA in the treatment of chronic hand eczema PMID: 17254029	Low bias risk	Low bias risk	High bias risk	High bias risk	High bias risk	Low bias risk	Low bias risk	Low bias risk
12 Oral methoxsalen photochemotherapy of recalcitrant dermatoses of the palms and soles PMID: 708596	High bias risk	High bias risk	High bias risk	Unclear risk of bias	Unclear risk of bias	Low bias risk	Low bias risk	Low bias risk
13 Ultraviolet-free phototherapy PMID: 15752121	High bias risk	High bias risk	Unclear risk of bias	High bias risk	High bias risk	Low bias risk	Low bias risk	Low bias risk

14 Clobetasone 17-butyrate, lotion scalp fluid. Results of a clinical trial in the treatment of steroid-sensitive dermatitis ISSN: 00099325	High bias risk	High bias risk	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low bias risk	High bias risk	High bias risk
15 Comparison of topical PUVA with UVA for chronic vesicular hand eczema PMID: 1675518 ISSN: 00015555	High bias risk	High bias risk	Unclear risk of bias	Low bias risk	Low bias risk	Unclear risk of bias	Low bias risk	High bias risk
16 Comparison of local bath-PUVA with steroid treatment in palmoplantar pustular psoriasis and dyshidrotic eczema	Low bias risk	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low bias risk	Low bias risk	Low bias risk
17 Long-term results of radiotherapy in patients with chronic palmo-plantar eczema or psoriasis 18398587	Unclear risk of bias	Unclear risk of bias.	Unclear risk of bias	High bias risk	High bias risk	Unclear risk of bias	Low bias risk	Low bias risk

18 [Therapy of hyperhidrosis with tap water iontophoresis. Positive effect on healing time and lack of recurrence in hand-foot eczema]	High bias risk	High bias risk	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low bias risk	High bias risk	High bias risk
19 The effect of hyperthermia on some allergodermatoses PMID: 4244440	Unclear risk of bias	Unclear risk of bias	High bias risk	Unclear risk of bias	Unclear risk of bias	High bias risk	High bias risk	High bias risk

Legends

Figure 1. PRISMA Flow Diagram