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# Guidelines for diagnosis, prevention and treatment of hand eczema

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*The guidelines are expected to be valid until December 2017 at the latest.*

## Summary

The guidelines aim to provide advice on the management of hand eczema (HE), using an evidence- and consensus-based approach. The guidelines consider a systematic Cochrane review on interventions for HE, which is based on a systematic search of the published literature (including hand-searching). In addition to the evidence- and consensus-based recommendation on the treatment of HE, the guidelines cover mainly consensus-based diagnostic aspects and preventive measures (primary and secondary prevention). Treatment recommendations include non-pharmacological interventions, topical, physical and systemic treatments. Topical corticosteroids are recommended as first line treatment in the management of HE, however continuous long-term treatment beyond six weeks only when necessary and under careful medical supervision. Alitretinoin is recommended as a second line treatment (relative to topical corticosteroids) for patients with severe chronic HE. Randomized control trials (RCT) are missing for other used systemic treatments and comparison of systemic drugs in "head-to-head" RCTs are needed.

The guidelines development group is a working group of the European Society of Contact Dermatitis (ESCD) and has carefully tried to reconcile opposite views, define current optimal practice and provide specific recommendations, and meetings have been chaired by a professional moderator of the AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; Association of the Scientific Medical Societies in Germany).

No financial support was given by any medical company. The guidelines are expected to be valid until December 2017 at the latest.

## Introduction and methodology

### Scope and purpose

#### Overall objective(s) of the guidelines

Eczema is the most common of all inflammatory dermatoses. Eczema comprises a group of skin disorders exhibiting a common pattern of histological and clinical findings which vary depending on the stage of the disease. The terms eczema and dermatitis are often thought of as being synonymous. Eczema located on the hands is one of the most disabling skin conditions in terms of its impact on quality of life and occupation. Its treatment can be challenging. Hand eczema (HE) is not a homogeneous disease entity, and is associated with many different etiologies and morphologies. The severity of HE may range from very mild to severe and the course from acute to chronic, resulting in prolonged disability. Chronic HE is associated with a high health economic burden and significant loss of quality of life. Although numerous treatment options are available, the management of chronic HE is often difficult and unsatisfactory. There

 

is a lack of, and simultaneously a need for, well-designed randomized controlled trials (RCTs) in support of the efficacy of treatment modalities. The Guidelines aim to provide advice on the management of HE using an approach that is as evidence-based as possible, covering the classification, diagnosis, prevention and treatment aspects of HE.

### Target audience and patients to whom the guidelines are meant to apply

The guidelines specifically address dermatologists and occupational practitioners. However, the information provided might also be of interest to general practitioners and for health insurance purposes. The target population for the guidelines include all patients with HE, independently of age and gender, severity and whether the disease is occupationally related or not.

### Health questions covered by the guidelines

The guidelines cover preventive aspects as well as treatment of HE. Topical treatments, physical treatments and systemic treatments are included. Health related quality of life for HE patients is considered.

## Stakeholder involvement

The guidelines development group includes representatives of dermatologists and occupational physicians, thus representing the target audience. The guidelines working group is a working group on behalf of the European Society of Contact Dermatitis (ESCD), and members for the working group was called for by ESCD webpage. The aim of the work has been to produce systematically developed statements to assist dermatologists and, if necessary, other healthcare professionals and patients with decisions about appropriate health care for patients with HE. The guidelines assess the current comprehensive body of knowledge (evidence from clinical trials and clinical experience) and trades off the potential benefits, risks (and costs) of alternative interventions. The guidelines group has carefully tried to reconcile opposite views, define current optimal practice and provide specific recommendations. The guidelines group has had a total of four consensus meetings, the last three of which have been chaired by a professional moderator of the AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; Association of the Scientific Medical Societies in Germany), (ref. http://www.awmf.org/). In addition, peer review was sought by consultation of the ESCD membership (see section 6). The Guidelines have been approved by the executive committee of the ESCD.

**Table 1** Grades of Recommendation.

| Syntax | Grade of Recommendation | Symbol |
|---|---|---|
| "we recommend" | Strong | A |
| "we suggest" | Weak | B |
| "may be considered" | Open | o |

## Systematic review of the evidence

The Guidelines are considering the last draft of a systematic Cochrane review on interventions for HE [1], which are based on a systematic search of the published literature (including hand-searching) in the following data bases: The Cochrane Skin Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PASCAL, JICST-EPLUS, AMED. Details of the search on the therapeutic interventions are given in ref [1]. Selection criteria used were randomized controlled trials of interventions from 1977 to ultimo 2012 regardless of HE type and other affected localizations.

The guidelines of the German Society of Dermatology on the management of HE [2], the Canadian guidelines [3] and the Nice guidelines (Nice technology appraisal guidance 177, www.nice.org.uk) have also been considered.

## Grading of the quality of evidence and strength of recommendations

### Evidence

The levels of evidence were assigned according to the quality of trials that fulfilled the inclusion criteria (see chapter 3). Quality was assessed using the Cochrane risk of bias tool. Quality of evidence is given as: 1 = high (RCT with good quality), 2 = moderate (RCT with methodological limitations, e. g. no description of blinding), 3 = low and very low (RCT with serious methodological flaws). If no evidence from RCT was identified, this is stated in the text.

### Recommendations

Recommendations were formulated and graded as strong, weak or open, the latter expressing a high level of uncertainty (Table 1).

The grade of recommendation reflects not only the quality of the evidence but also considers the judgment of the experts in the Guideline Development Group with respect to the following aspects:

- relevance of outcomes and magnitude of effects
- balance of benefit and harm (burden)
- applicability of the evidence to the target population
- ethical, legal, economic considerations

Where relevant health questions could not be covered by systematic search and appraisal of the evidence, the working group decided to formulate recommendations based on expert opinion to provide guidance for the target audience. These are marked as *"consensus-based recommendation"*. Like evidence-based recommendations, consensus-based recommendations were discussed, graded and approved in a formal consensus process to reduce bias.

### Methods for formulating and approving the recommendations

Recommendations were discussed and approved by the working group following a formal consensus process moderated by an external, independent methodologist (Nominal Group Technique, NGT). The steps of the NGT were:

- introduction of the formal consensus technique by the Moderator
- silent work allowing each participant to make notes for specific changes and reasons based on the evidence and criteria for considered judgment
- registration of proposals of individual participants on a "round robin" basis by the Moderator, clarification and justification of alternative proposals
- preliminary vote on the first draft and all alternatives
- identifying areas of dissent and need for discussion
- debate and discussion
- final vote

Declaration of different opinions and minority votes with a substantial rationale was possible. The strength of consensus was determined for each recommendation: 75 %–95 % agreement is consensus; more than 95 % agreement is strong consensus.

### External review

While working with the guidelines, the manuscript draft was available on the internet between meetings, and on the ESCD webpage, where members could comment on the document. ESDC members were informed about this by email.

### Financial disclosure and management of conflicts of interest

No support was given by any medical company for development of this document. All costs for meetings (room, lunch and coffee) have been covered by the ESCD. Travel expenses and accommodation for the members of the guideline developing group was not reimbursed. All participants in the working group filled in a structured form to declare financial or nonfinancial conflicts of interest. Disclosures are given in the appendix.

The risk of bias due to conflicts of interest was assessed and discussed in the guideline developing group. It was felt that there was no substantial risk for undue influence on the guideline content since the following protective factors were applied:

- a systematic review and appraisal of the evidence for therapeutic interventions
- a structured, formal method of developing consensus moderated by an external methodologist without any financial conflicts of interest and no nonfinancial interests relevant to the guidelines content
- the composition of the guideline developing group including experts with different interests
- external review/consultation

### Update

The guidelines are expected to be valid until December 2017 at the latest. Depending on the availability of new evidence, the update process will be initiated earlier. The guideline developing group is aware that guidelines development groups should include diverse stakeholders. The guideline developing group of the 2012 guidelines included representatives of the a priori defined target audience (dermatologists and occupational physicians) and representatives with skills in evidence appraisal and synthesis. For an updated version of the guidelines, it is planned to address a broader audience and to invite representatives of other clinical fields as well as health care consumers/patients.

## Epidemiology

The estimated 1-year prevalence of HE in the general population in Sweden was 9.7 % in 1996 [4], although the occurrence of HE depends on the composition of the population in terms of age, gender and atopy. In school children the 1-year prevalence of HE was reported to be 7.3 % for children aged 12–16 years and 10.0 % for children aged 16–19 years, respectively [5, 6]. According to a review of studies performed between 1964 and 2007 the point prevalence of HE was around 4 %, the 1-year prevalence nearly 10 %, and the lifetime prevalence 15 % [7, 8]. Based on data from seven studies, [6, 9–14] the incidence rate was 5.5 cases per 1 000 person years (range 3.3–8.8) with a higher median incidence rate among women (9.6, range 4.6–11.4) than among men (4.0, range 1.4–7.4). A high incidence rate was associated with the female sex, contact allergy, atopic dermatitis, and wet work [15] (Table 2). Early onset of HE is frequent, and in around one third of cases occurs before the age of 20 [10]. The prevalence of HE in adults reporting moderate and severe atopic dermatitis in childhood was 25 % and 41 % respectively [16].

Table 2 Risk factors for development of HE.

| Risk factors | References |
|---|---|
| Previous episodes of HE | *[18]* |
| Atopic dermatitis | *[16, 29, 131]* |
| Contact allergy | *[19, 20, 131]* |
| Wet work | *[19]* |
| Early onset | *[131]* |

The importance of mucosal atopy for the development of HE is disputed, but it is a significantly lower risk factor than atopic dermatitis [10, 16–18]. Contact allergy, especially nickel allergy, has previously generally been accepted to be a risk factor for development of HE [19, 20], but evidence for this is changing, and the association is weakening [21]. The relationship between smoking, alcohol and HE has been investigated, and no clear association was found [22, 23].

### Impact and burden of the disease

HE has a substantial health economic and socio-medical impact, and skin disease has been the most commonly reported occupational disease for years [8]. Occupations at particularly high risk include hairdressers, bakers, butchers, florists, cashiers, electroplaters, dental technicians, machine operators, workers in metal surface processing, and healthcare workers [24, 25]. The annual incidence of new reports of occupational skin diseases is 0.7–0.8 per 1 000 employees [13, 26], yet the number of occupational skin conditions that go unreported is many times greater [27]. In a study conducted at 10 European centres, 28 % of HE patients were unfit for work, and disability persisted for longer than 12 weeks in 12 % of cases [28]. In this study the etiology was considered occupational in 52 % of the HE patients. In population based studies approximately 50 % of all patients with HE receive treatment for their disease [13], although this was 69 % in a Swedish study [29]. Amongst subjects who reported HE within the past 12 months, 67 % had consulted a general practitioner and 44 % a dermatologist in Denmark [30]. In this study the mean duration of sick leave was 18.9 weeks among those who reported any sick leave, and the mean total time on sick leave was highest among those individuals with allergic contact dermatitis (28.6 weeks) compared to those with irritant dermatitis (13.0 weeks) and atopic HE (11.8 weeks) in Sweden [29]. A total of 8 % reported changes of occupation because of HE. Josefson et al. [31] found that 15.5 % of Swedish women with HE had changed their job as a result of their skin condition.

The proportion of patients with HE seeking medical advice is estimated to be between 50 % and 70 % and the proportion of patients with severe chronic HE is estimated to range from 5 % to 10 % of all cases of HE [15, 32]. In a Danish study where participants self-rated the severity of their HE using a photographic guide, 23 % rated their HE as moderate to severe [30].

HE has been demonstrated to have a negative impact on health related quality of life to the same degree as psoriasis or asthma [22, 33], this negative impact is greater for females than for males [34]. The EQ-5D index for subjects with HE was similar to that of individuals with asthma and psoriasis [35]. In addition, psychological factors may have a significant impact on the disease [36], although no significant increase in frequency of depression has been reported [33].

## Terminology

*Eczema* and *dermatitis* are used as synonyms. Both terms are used interchangeably to describe a particular type of inflammatory disorder of the skin that targets the epidermis and the dermis. Clinically it is a polymorphic eruption. Among the primary lesions that may be observed are macules, papules and vesicles. Secondary lesions include oozing, crusting, scaling, lichenification, hyperkeratosis and fissuring. Pruritus is common in all types of eczema/dermatitis. There is both epidermal and dermal involvement with histological changes in the epidermis of intercellular oedema and spongiosis, acanthosis and parakeratosis, and in the upper dermis of a perivascular infiltrate of lymphocytes that migrate into the epidermis.

*Acute* and *subacute HE* can be defined as eczema, localized to the hands, that lasts for less than three months and does not occur more than once per year. In the acute stage vesicles will be present in most cases, although not always in irritant HE. Erythema, representing inflammation is pronounced in acute HE, as is oedema. A subjective sensation of burning and itching is present in most cases.

*Chronic HE* refers to an eczematous process that lasts for more than three months or relapses twice or more often per year. Scaling and fissures are found in most cases. Hyperkeratosis is present in chronic irritant and allergic HE, but is also found in the endogenous hyperkeratotic HE, and in other chronic cases.

*Location:* HE may be located anywhere on the hands and wrists. Involvement of a large area at onset of the disease indicates a bad prognosis [37]. Patch testing should be performed irrespective of location.

*Exogenous and endogenous HE:* Eczema is more commonly divided into two types: exogenous and endogenous (or constitutional).

*Exogenous HE* is caused by the interaction of the epidermis with the outside environment. This interaction includes factors that are chemical or physical, organic or inorganic,

allergens or irritants. Exogenous HE can be classified as *irritant* or *allergic*. There is no reliable connection between morphology and etiology, and all cases of HE should be fully investigated for possible allergy.

*Irritant HE* develops as a result of prolonged or repeated exposure to primary irritants, and depends on the duration and intensity of exposure to the potentially responsible agent(s). The diagnosis is based (a) on a documented exposure to an irritant that is quantitatively likely to cause contact dermatitis, and (b) on the absence of relevant contact allergy (no current exposure to allergens to which the patient has reacted positive in patch test, if any). An example of a well-defined irritant exposure likely to cause contact dermatitis is wet work: wet hands or wearing of gloves for two hours, or more than 20 hand washes daily. Relevance of the irritant exposure may be defined as either suspected or proven. The eczema in most cases remains limited to the sites of exposure and will rarely spread to unexposed skin areas. Irritant contact dermatitis (ICD) is commonly associated with wet work, and previous or current atopic dermatitis is an important endogenous co-factor [16]. ICD may set the scene for the development of allergic contact dermatitis (ACD), and combinations of irritant and allergic cases are common.

*Allergic HE* is caused by a delayed-type reaction (type IV reaction) as an immunological response to contact with an allergen in a sensitized individual. The diagnosis is confirmed when there is a positive patch test reaction to a topical allergen or a cross-reacting allergen, and a relevant – either documented or suspected – current exposure to this allergen. Relevance may be defined as either suspected or proven. Early lesions appear at the sites of allergen contact, but spreading to adjacent and even distant areas may occur. Clinical manifestations of irritant and allergic HE may be highly variable, making it impossible to differentiate, clinically or histologically, between the two, although ACD tends to take a more acute course.

*Protein contact dermatitis* is a rare, distinct form of allergic or irritant HE in which IgE-mediated mechanisms or non-immunological mechanisms, give rise to clinical manifestations characterized by an initial urticarial phase followed by eczema. The most frequent triggers are latex and food allergens [38, 39].The diagnosis is based on exposure to proteins (food, latex and other biological material) and a positive prick test, or proven specific IgE, to suspected items. However, non-immunological forms also exist. A considerable proportion of patients with contact urticaria have atopic symptoms too.

*Endogenous HE* arises from a constitutional predisposition of the patient, as an exaggerated response to external stimuli, auto-antigens, as a result of a defective epidermal barrier, and possibly influenced by emotional factors. No obvious external cause for the disease is apparent, and there is usually a genetic influence.

*Atopic HE* occurs in individuals with previous or current atopic dermatitis, according to the U.K. criteria, and with no documented exposure likely to cause irritant contact dermatitis. There is little doubt that there is an epidermal barrier defect in atopic dermatitis that predisposes to the development of ICD. The evidence to support this comes from the enhanced transepidermal water loss, reduced irritancy threshold, increased percutaneous absorption, and dry appearance of lesional skin. Recently, with the identification of null-mutations within the gene encoding the key epidermal protein filaggrin, a breakthrough in the genetics of atopic eczema has been achieved [40]. Filaggrin is a structural protein of the cornified envelope and important for the formation of the epidermal skin barrier. A possible association between the variant alleles and chronic HE has been studied, but no clear conclusions have been reached except for the already well-established association between atopic dermatitis and HE [13, 15, 41, 42]. The cellular immunity in atopics is decreased, and ACD seems to occur in a smaller number of patients with a past or present atopic disease than in non-atopics [16, 43], although this point of view has recently been challenged [44]. Positive patch tests, often related to topical treatments, are commonly found in atopics, and patch testing should be performed as in other patients with HE.

*Pompholyx* is a recurrent HE with vesicular eruptions. While the term "vesicular HE" can be used for vesicular eruptions of chronic allergic or irritant contact, as well as endogenous vesicular dermatitis, the term pompholyx is used only for the endogenous form. No relevant contact allergy and no documented irritant exposure likely to cause dermatitis are present. Clinically pompholyx is by definition characterized by isolated vesicles on the palms of the hands, frequently also affecting the sides of the fingers, and accompanied by erythema of variable intensity and severe pruritus. Each episode classically lasts two to three weeks, resolves with desquamation and clears completely. Recurrences may be triggered by stress, systemic contact dermatitis, by dust mites [45] or by fungus infections elsewhere [46] and a relation to atopy and to nickel allergy has also been advocated. Histological and electron microscopy studies have revealed that there is no sweat gland involvement, and therefore the term "dyshidrotic" is confusing and should be avoided.

*Hyperkeratotic HE* is a chronic eczema with hyperkeratosis in palmar hands, or pulpitis, and no vesicles or pustules, also called hyperkeratotic dermatitis of the palmar hands [47]. No documented exposure to the involved skin areas likely to cause irritant exposure is present. It typically presents as sharply demarcated circumscribed hyperkeratotic and fissured lesions in the middle of the palms, and absence of vesicular lesions [47]. The causative factors of hyperkeratotic HE are still poorly understood.

Table 3 Definition of subtypes of hand eczema.

| | |
|---|---|
| Allergic contact dermatitis | HE caused by relevant contact allergens or cross-reactors identified by patch testing. Relevance means that there is a current exposure of the allergen to the hands. |
| Irritant contact dermatitis | HE with documented irritant exposure, which is quantitatively likely to cause dermatitis. No relevant contact allergy (no current exposure to allergens to which the patient has reacted positive in patch test). |
| Contact urticaria/ protein contact dermatitis | HE in patients exposed to proteins (food, latex and other biological material) with a positive prick test, or proven specific IgE, to suspected items. A considerable proportion of patients with contact urticaria will also have atopic symptoms. |
| Atopic hand eczema | HE in a patient with a medical history of atopic eczema, previous or current. No documented irritant exposure and/or relevant contact allergen likely to cause eczema. |
| Pompholyx | Recurrent HE with vesicular eruptions. No relevant contact allergy, no documented irritant exposure likely to cause dermatitis. |
| Hyperkeratotic eczema (hyperkeratotic dermatitis of the palms) | Chronic eczema with hyperkeratosis in the palms, or pulpitis, and no vesicles or pustules. No documented irritant exposure to the involved skin areas, likely to cause irritant exposure |

### Classification

- Evidence on classification is lacking and no specific recommendations can be made at the moment. However, in research and clinical trials we recommend that some kind of classification is applied. *Strong consensus-based recommendation (Grade A).*

Many different terms have been used to describe the skin affected by HE/dermatitis, and no generally agreed upon classification for HE exists. The pattern of the dermatitis is often polymorphic, and morphology is not at all related to etiology, which may sometimes be obscure. In the acute phase pruritus, erythema and vesiculation may be predominant, while the chronic phase is more dominated by scaling, infiltration, fissures and hyperkeratosis. The most common sub-diagnosis for HE is irritant HE, followed by allergic HE, and atopic HE, while other endogenous forms only constitute a minor group (for definitions see above or Table 3). Combined forms are common [28, 29, 41, 48, 49]. Hyperkeratotic phases are likely to occur in many patients with HE, while the term hyperkeratotic palmar HE describes the specific sub-classification of palmar, circumscribed infiltrated scaling plaques, which affect males more often than females, and with a later onset than other subtypes of HE [47, 50]. Classification of HE should always include the result of patch testing (see below). Omission of patch testing can never be justified, since the etiology of HE cannot be determined from the clinical manifestations alone [51, 52].

Classification is a major problem involving all studies on treatment of HE. Consensus on a classification is important in order to obtain a mutual understanding of sub-diagnoses. Classification of HE has been contentious, since the different subgroups are classified according to etiology as well as morphology. A system of classification is useful however, when conducting clinical trials and when communicating with patients and amongst professionals. Based on a recent study from ten different clinics in Europe it is suggested that the classification given in Table 3 may be used as a working tool. The diagnoses proposed are not exclusive, and each case may obtain more than one diagnosis.

## Diagnosis, diagnostic procedures, examination

- We recommend a careful history taking as well as clinical examination of the location and morphology of the lesions. *Strong consensus-based recommendation (Grade A).*
- We recommend diagnostic patch tests be performed in all patients with HE with a duration of more than 3 months and/or relapse, to identify the role of contact allergens in the environment. *Strong consensus-based recommendation (Grade A).*
- We recommend patch testing with a baseline series which always should be supplemented with selected additional series/allergens depending on exposure. *Strong consensus-based recommendation (Grade A).*

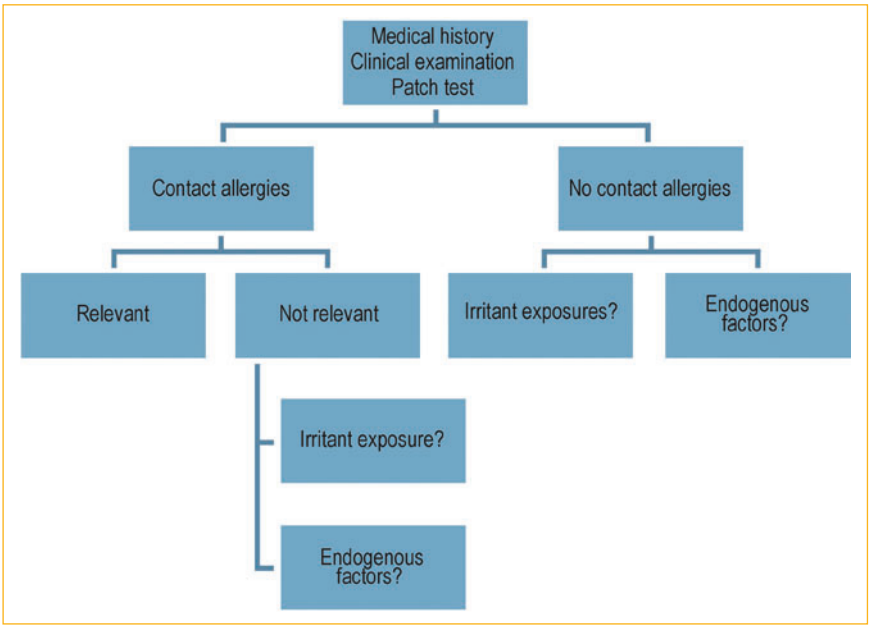


**Figure 1** Flow chart for diagnosis of HE. It is important to consider that the diagnoses are not exclusive, and that more than one diagnosis can exist. For patients with relevant contact allergies additional irritant exposures or endogenous factors should be considered. For patients with relevant irritant exposure additional endogenous factors should be considered.

A flow chart for diagnosis of hand eczema is given in Figure 1. In all areas of medicine, establishing a diagnosis is crucial, and this applies equally to HE, where many factors may contribute to the clinical presentation. A careful patient history, clinical examination and appropriate diagnostic procedures are all necessary and will yield important information. The history should be taken by guided interview and include a search for specific exposures related to the clinical features. This should include pattern of dermatitis, duration of dermatitis, exacerbations and remissions including relationship to work; the patient's own suspicions, the use of and response to skin care products and medicaments, the use of gloves, number of hand washings, hobbies and leisure activities, housework and occupational exposures. Information on previously documented allergies and test procedures should be collected, together with information about atopic status, including previous atopic dermatitis [2, 53].

Particular attention must be paid to exposures in the patient's home as well as occupational exposures, including the clinical course of HE during vacations, on weekends and during periods off work.

Apart from assessing the hands, the clinical examination should include an inspection of the entire skin, especially the feet. Palmar psoriasis is an important differential diagnosis to hyperkeratotic dermatitis of the palms. A careful inspection of clinical signs of dermatophytosis has always to be included.

Multiple diagnostic procedures may be needed in each individual case. These include diagnostic patch tests, skin prick tests, microbial tests and cutaneous biopsies.

## Diagnostic patch tests

Epicutaneous patch testing is the gold standard test for identifying type IV sensitization as the trigger of ACD. Diagnostic patch tests should be performed in all patients with HE of more than three months' duration to identify the role of contact allergens in the environment. It is important to emphasize that clinically relevant contact allergies cannot be estimated based on the pattern of dermatitis and/or its severity [2, 52].

Patch testing should be performed with a baseline series, which may vary depending on exposures that may differ according to geographic areas [54]. These will reflect dominant industries, use of topical medicaments and consumer habits. The European Society of Contact Dermatitis (ESCD), national and international research groups (such as the European and Environmental Contact Dermatitis Research Group or EECDRG) have recommended a baseline series comprising about 30 commonly occurring contact allergens [55]. The baseline series is dynamic and subject to modification at regular intervals depending on population exposures and the prevalence of contact allergy. The baseline series should always be supplemented with appropriate additional series and with relevant substances from work and home, including gloves, topical preparations and cosmetics. Detailed enquiries regarding skin exposures may identify specific allergens. Rare allergens may be obtained

for testing from commercial patch test material suppliers, or acquired from industry manufacturers, workplaces or from an Allergen Bank [55]. It is mandatory to carefully consider the choice of patch test concentration and vehicle when testing with materials that are not standardized [56–58]. The patch test technique may vary in detail from clinic to clinic depending on tradition and training. Several patch test systems are popular with their various proponents, and test application is usually two days with a subsequent reading at day 2–3 and an additional late reading on day 5–7 is highly recommended [59]. Scoring of patch test reactions should be done carefully according to the established recommendations of the International Contact Dermatitis Research Group (ICDRG) scoring scale [57, 59]. Reading and interpretation is subject to inter-individual variation depending on training and level of experience [60].

It is very important to assess the relevance of identified type IV allergens, and where occupational triggers have been identified the patient's workplace should be reviewed, along with the replacement of the causative allergen with a safe alternative. A negative patch test is not a definitive exclusion of an allergy since false negative results can occur. ACD will only clear if the triggering substance(s) is/are consistently avoided. Patients therefore need to be educated in detail about relevant allergens and where they are likely to be found. If specific ingredients of products have been identified as contact allergens, allergen-oriented counseling about skin protection and skin care is indispensable.

In summary, patch tests must be scored according to established recommendations, and the relevance for each positive reaction must be carefully assessed.

### Skin prick tests

HE patients may report immediate skin reactions, experiencing contact urticaria from use of natural rubber latex gloves or from contact with foodstuffs or certain animal proteins [61] with and without occupational relevance. Skin prick testing (SPT) is used to assess these reactions and should be performed using the most common inhalant allergens and specific occupational allergens where appropriate (e. g. latex or food allergens). When testing with fresh foods and plant material, prick-prick testing is the best technique [62], giving the more specific, accurate, fast and cheap results. IgE assays or radio-allergosorbent testing (RAST) may also be useful.

In the case of suspected protein contact dermatitis without systemic symptoms skin prick tests with fresh proteinaceous material (foods and plants) are a safe and important diagnostic tool. Evaluation of the test results must be done carefully due to risk of non-specific positive reactions. Testing of controls may be warranted. If the patient has had more generalized symptoms a risk of anaphylaxis should be considered and the test only performed with adrenalin available.

### Microbial tests

Clinical examination of hand dermatitis may give rise to suspicion of secondary infection as an aggravating factor, particularly in atopic dermatitis patients, and skin swabs may be used to obtain information about antibiotic resistance [63]. Furthermore, scabies should be excluded as a differential diagnosis, and dermatophyte infection should also be considered by taking skin scrapings for microscopy and culture. A careful inspection of clinical signs of dermatophytosis has always to be included. As mentioned, it is essential to inspect the feet for possible dermatophytosis as a trigger factor for HE.

### Cutaneous biopsy

Cutaneous biopsy may be useful for differential diagnosis. The various types of dermatitis rarely present a histologic picture sufficiently diagnostic to allow their differentiation. Diseases that can show the non-specific histologic picture of chronic dermatitis include psoriasis, lichen planus and pityriasis rubra pilaris. A chronic dermatitis may simulate the histologic picture of psoriasis through the presence of evenly elongated rete ridges. Biopsy does not allow for conclusions regarding the etiology of HE, especially for the distinction between allergy and irritancy. Immunostaining methods have not turned out to be useful.

### Exposure assessment

Exposure assessment is an important step in the diagnosis of contact dermatitis. Whenever positive reactions to patch test are found, exposure to the allergen(s) should carefully be looked for. Spot tests, like the dimethyl-glyoxime test for nickel release, applied on metal objects in contact with skin, is a simple test that can be performed by the patient himself/herself.

Material Safety Data Sheets should be examined carefully and extra suspected allergens added to the patch test procedure when possible and feasible.

In case of suspected allergy to botanical material, direct exposure as well as exposure through cosmetic products should be examined. With respect to irritant exposure it is important to assess not only the quality of the exposure, but also the exposure time, as well as the body part being exposed in relation to the location of the eczema.

## Prevention

- We recommend primary prevention to decrease the incidence of HE. *Strong consensus-based recommendation (Grade A)*
- We suggest secondary prevention strategies whenever skin manifestations are already present on the hands. *Strong consensus-based recommendation (Grade B)*
- Skin protection education and training are an important part of secondary prevention, they aim to motivate people to use adequate skin protection, and to foster a feeling of empowerment in terms of taking responsibility for one's own health and we suggest to develop it for high risk groups like hairdressers, health care workers, metal workers etc. *Strong consensus-based recommendation (Grade B).*

Since HE is a disease that may often become chronic, is a burden for the patient and is a great cost to society, prevention is an essential element in the management of HE. Prevention should aim mainly at exposure, but knowledge about endogenous risk factors/skin barrier defects should also be taken into account. A distinction is made between primary, secondary, and tertiary prevention strategies.

### Primary prevention

The aim of primary prevention is to decrease the incidence of HE, and the target is the healthy population. Regulation of allergen exposure either by legislation on threshold values or regulations on precautions in handling of allergenic products reduces allergen exposure and subsequently reduces the frequency of ACD, however randomized controlled trials are missing [64, 65]. Examples of legislation changing the frequency of contact allergy and contact dermatitis within special working groups or in the population as a whole are regulations on chromate in cement and on nickel in jewelry and in private items [21, 66]. Previous or current atopic dermatitis is, as already mentioned, a significant endogenous risk factor for development of HE, and counselling about avoiding wet and soiled occupations should be given to atopics in childhood. General Practitioners as well as health care personnel at schools should actively participate in this. Exposure to wet work is a particular risk factor for development of HE, and preventive efforts should aim at reducing wet exposure. Educational programs directed at the general population are attractive, but have never been scientifically evaluated (*www.dguv.de/content/prevention/campaigns/documents/campaign_skin.pdf*). The implementation of a "skin-healthy" occupational environment was evaluated in an intervention study in the health care sector, and its effectiveness was statistically confirmed [67]. Implementation of an evidence based prevention program among gut cleaners was also found to have a significant positive effect on occupational eczema [68].

Protection of the hands is essential for the prevention of HE and is a fundamental aspect of the treatment of HE. Effectiveness of protective measures such as use of moisturizers and gloves has mostly been documented in laboratory studies with experimentally damaged skin [69]. In a prospective four-arm intervention study with a 12-month follow up, the effectiveness of skin care and skin protection measures was assessed in metal workers [70]. The largest and most significant improvement was noted in the group following the skin protection program as it was generally recommended (skin care + protection) followed by skin protection alone as second best. Use of gloves in wet work has generally been recommended and accepted as an important preventive measure. Compliance with this recommendation is good in some, but not all occupations [71]. Gloves may also sometimes be the cause of HE, since protective rubber gloves may cause ICD from heat and sweating, or ACD from contact sensitization to rubber additives or contact urticaria caused by immediate allergy to natural rubber latex [72–74]. The choice of the glove material may play an important role in minimizing glove-induced irritation [75].

### Secondary prevention

Secondary prevention strategies are indicated when eczema is already present on the hands. The objective of secondary prevention is to spot early skin changes in order to rapidly implement corrective measures. Based on experimental research a skin care program for prevention of HE in wet work occupations has been suggested (Table 4) [67].

If occupational HE is suspected, the authorities should immediately be notified in some countries (e. g. Denmark, Germany, UK and France).

Outpatient skin protection seminars have been established for healthcare workers, hairdressers, cooks, caterers and other food handlers, cleaners, and other occupations at risk [76–78]. Skin protection seminars are based on the methodological principles and procedures of adult education and provide theoretical background knowledge and "hands-on" training in the selection and use of adequate skin protection strategies. They are aimed at helping people to keep working in their occupation. The seminars also aim to motivate people to use adequate skin protection, and to foster a feeling of empowerment in terms of taking responsibility for one's own health [79]. The results of secondary and tertiary prevention are

Table 4 Skin protection program based on evidence from clinical and experimental studies (modified from: [132]).

- Use gloves when performing wet work.
- Protective gloves should be used appropriately but for as short a time as possible.
- Protective gloves should be intact, clean and dry inside.
- When protective gloves are used for more than 10 minutes, cotton gloves should be worn underneath.
- Wash hands in lukewarm, not hot, water. Rinse and dry hands thoroughly after washing.
- Hand washing with soaps should be substituted with alcohol disinfection when hands are not visibly dirty.
- Do not wear finger rings at work.
- Apply moisturizers on your hands during the working day but especially after work and before bedtime. It may be reasonable to use a lighter moisturizing lotion during the day and a greasier fragrance-free, lipid rich moisturizer before bedtime.
- Moisturizers should be applied all over the hands, including the webs, finger tips and dorsal aspects.
- Take care when doing domestic work. Use protective gloves for dish washing and insulating gloves in the winter.

very promising, and the effect was recently documented in a RCT study including almost 400 health care workers [80, 81].

### Tertiary prevention

Strategies for tertiary prevention are basically the same as for secondary prevention, but the focus for tertiary prevention strategies are patients with severe and/or chronic HE in which outpatient secondary prevention strategies have been ineffective [82]. Tertiary prevention strategies in (occupational) HE comprise concerted (in/outpatient) and interdisciplinary (occupational dermatology, industrial health, health educational, occupational therapeutic, psychological, and trade association-administrative) interventions with the aim of improving the affected individual's clinical condition and where possible, allowing them to keep working in their occupation in the long run.

## Treatment

- Acute HE should be treated quickly and vigorously to avoid the development of chronic HE. *Strong consensus-based recommendation (Grade A)*[3].
- We recommend identification and avoidance of causative exogenous factors. *Strong consensus-based recommendation (Grade A).*
- We recommend moisturizers/emollients be used in all HE patients. *Evidence level 2 (moderate quality) (Grade A)*[1, 3, 69, 83]. The choice of emollient should be individualized according to exposure and skin condition. *Strong consensus-based recommendation.*
- The guideline development group considers that the evidence base is too weak for recommendations on specific moisturizers or emollients. *Strong consensus-based recommendation.*

A wide range of approaches is available for the management of acute and chronic HE (Table 5). In the systematic Cochrane review "Interventions for hand eczema" [1], 49 RCTs have been identified, in which a total of 4 208 participants were enrolled. These studies covered a large variety in treatments and reporting outcomes; however there was substantial heterogeneity in interventions, outcome measures and timing of the outcome assessments. There are very few studies about the role of lifestyle changes and a lack of directly comparative trials of different treatments for HE. According to the Cochrane review only four studies compared two different classes of interventions [1]. The efficacy of available treatments cannot be directly compared because differences in the eligibility and exclusion criteria for published trials have resulted in the recruitment of different patient populations.

### General principles of treatment

The treatment of HE must take into account the general principles of treatment of stage-appropriate therapy, disease etiology (atopic, allergic, irritant), acuteness (acute vs. chronic eczema), morphology (redness, scaling, lichenification, blistering, hyperkeratosis, rhagades, etc.) and location (dorsal aspects of hands, interdigital spaces, palms). Successful therapy requires identification and avoidance of causal exogenous factors (e. g. allergens, irritants). Despite extensive clinical experience with various therapies that have been used for years, RCTs are still lacking.

Acute HE should be treated quickly and consequently to avoid the development of chronic HE. Topical corticosteroids, together with emollients, are the most effective treatment to control an acute flare of HE. As full functional regeneration of the epidermal barrier takes several weeks after the eczema subsides, patients must avoid re-exposing the skin to irritants or allergens.

Table 5 Treatment options for chronic HE.

| Skin protection program | Topical therapies | Systemic therapies (in alphabetic order) | Physical therapies |
|---|---|---|---|
| ▸ Education<br>▸ Avoidance and substitution<br>▸ Protection | ▸ Emollients<br>▸ Topical steroids<br>▸ Topical calcineurin inhibitors (tacrolimus, pimecrolimus)<br>▸ *Other topical treatment* (iontophoresis, tar, potassium permanganate, aluminium acetate) | ▸ Acitretin<br>▸ Alitretinoin<br>▸ Azathioprine<br>▸ Cyclosporine<br>▸ Corticosteroids<br>▸ Methotrexate | ▸ UVB<br>▸ PUVA |

Chronic HE is difficult to treat and requires complex management strategies, taking into account etiology, morphological features, and site of the lesions. A prerequisite for successful therapy is identification and avoidance of causative exogenous factors. Treatments for chronic HE and the panel's assessment of their efficacy, are discussed below. Recommendations are based on a review of the clinical evidence, but in many cases evidence was limited.

## Non-pharmacological interventions

Lifestyle change is recommended for all patients. This involves avoidance of identified allergens and irritants, substituting alternatives where possible, use of hand protection, and avoiding wet work and mechanical irritation (Table 4). A skin protection program should be tailored to individual need; this should include education about HE with the aim of giving the patient realistic expectations of treatment outcomes, as HE is not always curable. Cases associated with occupational exposure should be notified to the appropriate authority. Management should include not only the patient but the family too, taking into account psychological issues, occupation and the history of the condition and its treatment. Educational programs should promote alcoholic disinfection as a procedure with good efficiency and skin tolerability to reduce the number of hand washes [64, 84].

## Topical treatments

### Emollients

Emollients are traditionally used in all kinds of skin diseases involving epidermal pathology and barrier dysfunction, and in occupational settings emollients are used both for treatment and prevention of skin disease. Although emollients are very widely used and recommended by physicians, evidence for efficacy is sparse, and depends on the substances included in the specific product. [85]. An overwhelming number of formulations are available [86], and words such as emollients, moisturizers, lotions, skin care products or barrier creams may be used interchangeably. Most emollients improve the hydration state of normal skin/stratum corneum, and are effective for treatment of contact eczema [87, 88]. They may help prevent itching, reduce the frequency of flares, and act to restore the lipid balance of the skin. Emollients with high lipid content accelerate the healing after experimental damage to the skin [89]. Emollients, including humectants, may sometimes improve barrier function, mainly by increasing the hydration of the stratum corneum and in some products also by anti-irritant capacity [90]. No good evidence exists as to whether emollients with physiological lipids are more effective than those with other lipids [91]. The guidelines development group considers the evidence base for specific recommendations on which moisturizers or emollients should be used too weak to give recommendations.

There is a risk that use of emollients may be associated with increased penetration of allergens and irritants, especially when applied during working hours [89, 92]. Facilitated penetration may lead to sensitization or elicitation of allergic contact dermatitis, or it may induce irritant reactions in the skin. However, the skin barrier is often impaired after working hours in occupations with wet work or other exposures to irritants, and in such cases the application of emollients will facilitate healing of the barrier. In general, emollients should be recommended when there is an impaired skin barrier function, and used prophylactically after working hours. Adherence to treatment is important, and this may be optimized when patients chose emollient that they like to use. Nurse instruction in the use of emollients (when, how, which one to choose) may be necessary.

### Topical corticosteroids

- Topical corticosteroids play an essential role in the management of HE, and there is a significant body of evidence for their efficacy. *Evidence level 1 (high quality)*[1]. We recommend topical corticosteroids as first line treatment in the management of HE. *Strong consensus-based recommendation (Grade A).*
- They are very effective in the short term, but they inhibit repair of the stratum corneum and cause skin atrophy, and interfere with recovery in the long-term. *Evidence level 1 (high quality).*
- Development of side effects depends on the potency, the amount applied, the duration of treatment, frequency of use and the anatomical site. *Strong consensus-based statement.*
- Therefore we recommend continuous long-term treatment beyond six weeks be performed only when necessary and under careful medical supervision. *Strong consensus-based recommendation (Grade A).*
- There is limited evidence of efficacy for long-term intermittent use as maintenance therapy. *Evidence level 2 (moderate quality)*[1, 93].

Along with emollients the local treatment of choice is a topical corticosteroid. These agents are very effective in the short term, but they inhibit repair of the stratum corneum [94, 95] and may cause skin atrophy [96], and interfere with recovery in the long-term. Once daily treatment is sufficient and may even be superior to twice daily application [97]. Effectiveness of topical corticosteroids for ICD in experimental settings is low or non-existent [98, 99].

In clinical studies there is evidence of efficacy for long-term intermittent monotherapy with mometasone furoate cream for HE [93]; the risk of recurrence is reduced by use of a very potent steroid (clobetasol propionate) compared with a moderately potent preparation [100].

The disadvantages of topical corticosteroids include cutaneous adverse effects (skin atrophy), tachyphylaxis (theoretically) and adrenal suppression after systemic absorption (very infrequent). Atrophy of the epidermis has been reported as a consequence of topical corticosteroids, and should especially be considered when long-term treatment is used [94].Corticosteroids have even been reported to cause eczema craquelé [101]. Allergic contact dermatitis caused by topical corticosteroids is not uncommon, and should be considered when HE does not respond to treatment [102].

Anecdotal experience suggests that intermittent dosing may reduce the risk of adverse effects, but there is no scientific data to support this at the moment. Clinical experience suggests that alternating or combining a topical corticosteroid with a topical calcineurin inhibitor may be considered in order to reduce adverse effects, although randomized clinical trials are missing and the long-term safety of this approach is unknown.

### Topical calcineurin inhibitors

- Topical calcineurin inhibitors may be considered for HE patients with long-term need for treatment, although evidence for their efficacy is limited *(Evidence level 2, moderate quality). Strong consensus-based recommendation (Grade 0).* Doctors and patients need to be aware that this is an off-label treatment except for patients with HE on an atopic basis.

The topical calcineurin inhibitors tacrolimus and pimecrolimus are licensed for the treatment of atopic dermatitis when topical corticosteroids have failed or not been tolerated. Tacrolimus has been shown to be as effective as mometasone furoate, whereas pimecrolimus appears to be non-inferior to a mildly potent topical steroid [103–105]. Adverse effects include transient stinging, flushing with alcohol ingestion, and skin infection; despite concerns about the long-term effects of topical immunomodulators, observational data suggests that these agents are not associated with lymphoma [106–109].

### Other topical treatments

Other topical treatment procedures are available in various countries depending on traditions or clinical experiences. The guideline development group cannot recommend in favor or against these treatments.

## Physical therapies

### Photo-therapy

- In adult patients with chronic HE refractory to first line treatment (relative to topical corticosteroids) we suggest photo-therapy of the hands. *Evidence level 2, moderate quality. Strong consensus-based recommendation (Grade B).*
- Long-term use of photo-therapy may increase the risk of skin malignancy [110]. *Strong consensus-based statement.*

Small trials have shown that UVB may improve chronic HE over a period of ten weeks [111]. PUVA treatment is an alternative, which has been reported to be superior in some, but not in all studies [112, 113]. Oral as well as bath or paint PUVA are used in some countries [114]. UVA1 may also be effective [115], although in most places availability is limited. Side effects of UV-treatment, especially bath and paint PUVA, are erythema and burning of the skin.

Grenz ray treatment is variably used in different countries, but side effects with development of skin cancer may occur, so this is not used anymore since these side effects developing many years after therapy, have induced some concern [116, 117]. Based on the perceived balance of benefit and harm the GDG cannot recommend this treatment.

## Systemic treatment

- *Alitretinoin* has a strong evidence base in the systemic treatment of chronic HE and is approved for use in treating severe, chronic HE that does not respond, or responds inadequately, to topical corticosteroids. Pregnancy prevention measures are required with alitretinoin. *(Evidence level 1, high quality)*. We recommend alitretinoin as second line treatment (relative to topical corticosteroids) for patients with severe chronic HE. *Consensus-based recommendation (Grade A)*.
- *Systemic corticosteroids* can be effective symptomatic treatment in acute HE or acute flares of chronic HE, but chronic use is not recommended due to potentially serious long-term side effects. *Strong consensus-based recommendation (Grade A)*.
- There is moderate evidence for the efficacy of *cyclosporine*. *Evidence level 2 (moderate; no benefit compared to first line treatment)*. Cyclosporine may be considered for HE patients with long-term need for treatment if first and second line therapy has been insufficient or contra-indicated. *Strong consensus-based recommendation (Grade 0)*. Doctors and patients need to be aware that this is an off-label treatment except for patients with HE on an atopic basis.
- We did not identify any evidence for the efficacy of *azathioprine* for the treatment of HE, but traditionally this treatment has been used over the years and may be considered for HE patients; especially those with atopic HE, with long-term need for treatment if first and second line therapy has been insufficient or contra-indicated. *Strong consensus-based recommendation (Grade 0)*. Doctors and patients need to be aware that this is an off-label treatment.
- We did not identify any evidence for the efficacy of methotrexate for the treatment of HE, but traditionally this treatment has been used over the years and may be considered if first and second line therapy has been insufficient or contra-indicated. Strong consensus-based recommendation (Grade 0), Doctors and patients need to be aware that this is an off-label treatment.
- There is low evidence for the efficacy of *acitretin*. *Evidence level 3 (low quality, tested in hyperkeratotic eczema of the palm only)*. Acitretin may be considered for hyperkeratotic eczema of the palm, if first and second line therapy has been insufficient or contra-indicated. *Strong consensus-based recommendation (Grade 0)*. Doctors and patients need to be aware that this is an off-label treatment.
- We have not identified any evidence for the efficacy of *antihistamines*. We do not recommend systemic antihistamines for treatment of HE. *Strong consensus-based recommendation (Grade A)*.

For a new drug to be licensed for a specific disease today, well performed RCTs are required, and evidence for efficacy needs to be provided. As compared to this, older drugs that have traditionally been used for treatment of HE are not submitted to RCTs, since such studies are expensive, and require financial support. This should be taken into consideration when discussing evidence for efficacy. Another important issue to consider is the side effects, given that for new drugs long-term safety data is missing, although surveyed.

The systemic therapies most widely used in the treatment of HE are summarized in Table 6 [118–124]. With the exception of alitretinoin no other systemic treatments are licensed for the treatment of HE and strong evidence of efficacy is lacking (no RCTs). Since alitretinoin is a new drug only recently available on the market, it has been evaluated in a large non-interventional study, and was found to be effective [125]. However, clinical experience with alitretinoin is as yet limited, the cost is significantly higher than for other retinoid products, and no "head-to-head" trial with comparison to the traditionally used systemic drugs is available yet.

### Systemic corticosteroids

Systemic corticosteroids can be used briefly to treat acute severe HE (generally for a maximum of three weeks). Systemic corticosteroids are not appropriate for use in the chronic phases of HE, as they are associated with well-known long-term side effects such as osteoporosis, osteonecrosis, glaucoma, cataracts, hypothalamic-pituitary-adrenal axis suppression, hyperglycemia, hypertension, and immunosuppression.

Table 6 Systemic therapies for chronic HE (in alphabetic order).

| Systemic treatment | Level of evidence | Grade of recommendation | Licensed for HE | Benefit (Pros) | Harm (Cons) | References |
|---|---|---|---|---|---|---|
| Acitretin | 3 | 0 | No | One small trial demonstrated efficacy in hyperkeratotic dermatitis of the palms. | Safety profile overall consistent with retinoid class. Teratogenic, must be avoided during pregnancy. | [123] Reduction in severity, doctor-rated scoring: In the acitretin group a 51 % reduction in overall score, and in the placebo group. 9 %. Patients with psoriasis were not excluded from this study. |
| Alitretinoin | 1 | A | Yes | Three randomized controlled trials including chronic HE demonstrated efficacy. | Safety profile overall consistent with retinoid class. Teratogenic, must be avoided during pregnancy. | [124, 133]: 47.7 % of participants on alitretinoin were assessed "clear" or "almost clear", as compared to 16.6 % in placebo group<br>[126]: 39 participants who were re-treated with 30 mg alitretinoin were rated as "clear" or "almost clear" compared to 2 participants in the control group. |
| Azathioprine | No evidence | Consensus | No | No specific evidence in HE, though effective in atopic dermatitis. | Hepatotoxicity, bone marrow suppression, increased toxicity in patients with thiopurine methyltransferase deficiency. Immuno-suppression. | No RCT |
| Cyclosporine | 2 | 0 | No | Equivalent efficacy to betamethasone dipropionate. 12 months' remission achieved at a dose of 3 mg/kg. | Nephrotoxicity, hypertension, adverse effects on skin. Immunosuppression. | [120, 121]: Overall assessment of efficacy good/very good in the cyclosporine group 60 %, and 48 % in the betamethasone group; the difference was not statistically significant. |
| Corticosteroids | No evidence | Continuous use disrecommended Consensus | No | Few convincing studies in HE | Adrenal suppression, upper gastrointestinal symptoms, hypertension, increased risk of diabetes and osteoporosis | No RCT |
| Methotrexate | No evidence | Consensus | No | Demonstrated efficacy in small uncontrolled trials | Liver toxicity; blood marrow depression | No RCT |

### Alitretinoin

Alitretinoin is approved for use in treating severe, chronic HE that does not respond, or responds inadequately, to topical corticosteroids. Alitretinoin is an agonist of both types of retinoid receptors (RAR and RXR). The precise mode of action is unknown; its main mechanism of action is thought to be immunomodulatory and anti-inflammatory. Its safety profile is consistent with retinoid class. Side effects with respect to mucosal drying seem to be less pronounced, however, a comparative study to other retinoids has not been performed. Treatment should be stopped if no effect has occurred after three months. In 1 032 patients with severe refractory HE, 48 % of randomized patients treated with alitretinoin were clear or almost clear within 12–24 weeks compared with 17 % assigned to placebo [124]. Patients had been deemed "refractory" if they had had little response to topical corticosteroids, appropriate skin care and had avoided irritants and allergens. Conditions mimicking HE had been excluded. The most common adverse effect was headache, reported by 11 % and 20 % of patients at doses of 10 and 30 mg/day compared with 6 % with placebo. In this study differentiation between the following subgroups of HE was made: hyperkeratotic, fingertip eczema, pompholyx and others and the drug was effective for all groups. However, no differentiation was made with respect to etiology. Intermittent long-term treatment has been reported to be successful [126]. The effect of alitretinoin on HE has recently been re-evaluated and confirmed in an observational study including patients with moderate and severe HE [125]. Retreatment with alitretinoin in patients with relapsed chronic HE was studied in a randomized controlled study including 117 patients [126], and a positive response was observed in 80 % in the treatment group as compared to 8 % in the control group. Alitretinoin is associated with an increase in plasma cholesterol and triglyceride levels, and a decrease in thyroid function parameters and these should be monitored during therapy [127]. The long term health risk related to changes in plasma cholesterol and triglycerides in patients (repeatedly) treated with alitretinoin is unknown and should be considered. Like all retinoic acid derivatives, alitretinoin is teratogenic. Pregnancy prevention one month before, during, and for one month after cessation of treatment, is therefore required in women of child-bearing potential.

### Acitretin

Acitretin is currently not licensed for the treatment of HE. There is limited data on its efficacy, but a small, open-label study of 29 patients with hyperkeratotic dermatitis of the palms, 30 mg/d for four weeks was associated with a 51 % reduction of all symptoms, compared to only 9 % in a placebo control group. In this study patients with psoriasis were included in the data analysis, and the statistical efficacy of the drug may have been driven by inclusion of these patients. No further improvement was seen with four additional weeks of treatment [123].

Being a retinoid, acitretin is teratogenic and therefore pregnancy prevention measures are indicated during treatment, and for acitretin for at least 2–3 years after discontinuation of the drug, depending on the country where it is prescribed. In combination with alcohol, acitretin has been associated with the formation of etretinate, which increases the duration of teratogenic potential for female patients [123]. Overall its safety profile is consistent with retinoid class.

### Cyclosporine

Cyclosporine has been used to treat severe chronic HE that has proven unresponsive to all other available treatments. In a double-blind study of 41 patients randomized to either oral cyclosporine (3 mg/kg/d) or 0.05 % betamethasone dipropionate cream, disease activity decreased by 50 %, compared to 32 % in the steroid group, which was not a statistically significant difference. The relapse rate for both groups was 50 % after two weeks of follow up [120]. In a second, open label study, 75 patients treated for six weeks with oral cyclosporine 3 mg/kg/d, showed one-year success rates of 79 %, and 74 % for atopic and chronic HE, respectively [121]. A recent meta-analysis suggested that the efficacy of cyclosporine after 6–8 weeks of treatment was 55 % in atopic eczema [115].

The use of cyclosporine requires careful monitoring, as treatment can be associated with potentially serious adverse events including nephrotoxicity, risk of malignancy, increased blood pressure and increased risk of infection. If the patient fails to respond within eight weeks, cyclosporine should be discontinued.

### Azathioprine

Although not registered for this specific purpose, azathioprine has been used to effectively treat airborne allergic contact dermatitis caused by sesquiterpene lactones from the weed *Parthenium*[128], and has been reported to improve atopic eczema and pompholyx [129].

Patients on azathioprine require regular blood monitoring, as it can cause a serious lowering of blood cell counts. Measurement of blood levels of thiopurine methyltransferase (TPMT) before initiating therapy is helpful to find the suitable dose for the individual patient.

### Methotrexate

Case reports have shown that low doses of methotrexate (MTX) led to improvement or clearing of HE, together with a decreased need for concomitant systemic corticosteroids [130].

Long-term use of methotrexate is associated with significant potential for side effects including hepatitis, liver cirrhosis, pancytopenia, pulmonary fibrosis and teratogenicity, but these can be minimized if it is appropriately dosed and patients are selected and monitored carefully.

### Further systemic treatments

RCTs are lacking for other, occasionally used therapies (off-label) such as interferon, intravenous immunoglobulins and, infliximab. The use of systemic anti-histamines may be appropriate in some patients for the symptomatic relief of itching and redness, but they have not been shown to alter the overall course of HE. Topical antihistamines should be avoided, as they can sensitize the skin.

## Future research

The most important area for future research in the area of systemic treatment of HE would be comparison of systemic drugs in "head-to-head" RCTs. However, this would require full scale dose finding assessment for each comparator and a dose form that would allow blinding a randomization, and such studies would be very expensive. However, continuous research in already available drugs for HE is necessary to optimize doses, treatment regime and combinations of drugs. Financial support to independent studies would be preferable to industry-initiated clinical trials.

An individualized approach to treatment is another focus for future research. The etiology and morphology of HE may vary extensively between patients, and more knowledge about the response of different subgroups of HE to different types of drugs would optimize treatment. At the moment there is no consensus about classification of HE and more studies are needed within this area.

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# Appendix

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