Guidelines for diagnosis, prevention, and treatment of hand eczema


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Abstract

Background: Hand eczema is a common inflammatory skin disorder. Health care providers need continuously updated information about the management of hand eczema to ensure best treatment for their patients.

Objectives: To update the European Society of Contact Dermatitis guideline on the diagnosis, prevention, and treatment of hand eczema.

Method: The Guideline Development Group (GDG) was established on behalf of the ESCD. A call for interest was launched via the ESCD website and via the ESCD members’ mailing list. Appraisal of the evidence for therapeutic and preventive interventions was applied and a structured method of developing consensus was used and moderated by an external methodologist. The final guideline was approved by the ESCD executive committee and was in external review on the ESCD webpage for 1 month.

Results: Consensus was achieved for several statements and management strategies.

Conclusion: The updated guideline should improve management of hand eczema.

KEYWORDS
allergic contact dermatitis, guideline, hand eczema, irritant contact dermatitis, prevention, treatment

1 | INTRODUCTION AND METHODOLOGY

1.1 | Scope and purpose

1.1.1 | Overall objective(s) of the guidelines

Eczema located on the hands, hand eczema (HE), is a disabling skin condition that strongly impacts the quality of life and occupational performance of affected individuals. HE should be considered an umbrella term as it covers different aetiologies and morphologies. Management can be challenging, as delay in adequate treatment and trigger avoidance increase the risk of chronic disease. 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.

1.1.2 | Target audience and patients to whom the guidelines are meant to apply

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

1.1.3 | Health questions covered by the guidelines

The Guidelines cover preventive aspects as well as diagnostic work-up and treatment of HE. Topical treatments, physical treatments and systemic treatments are included. Health-related quality of life (HR-QoL) for HE patients is considered.
1.2 | **Stakeholder involvement**

The Guideline Development Group (GDG) was established on behalf of the European Society of Contact Dermatitis (ESCD), with the aim of including representatives of the target population. The GDG includes representatives from dermatology, occupational and environmental medicine, and from a patient association.

1.3 | **Systematic review and grading of the evidence**

The Guidelines are founded on the Cochrane systematic reviews on interventions for hand eczema (HE)\(^1\) and on interventions for the primary prevention of occupational irritant hand dermatitis.\(^2\) Both systematic reviews were conducted according to the standard methodological procedures expected by Cochrane,\(^3\) which means a broad search in multiple databases, assessing the risk of bias of included studies using the Cochrane Collaboration’s domain based assessment tool,\(^3\) pooling data in a quantitative meta-analysis when heterogeneity allowed this, and grading the certainty of the evidence per outcome using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines\(^4\) (see Table 1). The literature searches were up to January 2018 and April 2018 respectively. The primary outcomes for treatment interventions were participant- and investigator-rated good/excellent control of signs and symptoms and adverse events. For primary prevention, these were signs and symptoms of occupational irritant hand eczema (OIHE) developed during the trials and frequency of treatment discontinuation due to adverse effects. For the current Guidelines the searches were updated up to April 2020, and it is clearly stated by intervention how and on which data the evidence was assessed. Further details on the methodology and data synthesis, such as the risks of bias and tables and forest plots of the GRADE summary of findings, can be found in the Cochrane reviews.\(^1,2\)

1.4 | **Strength of the recommendations**

To translate evidence into recommendations, the GDG used the GRADE Evidence to Recommendations framework (EtR).\(^4,5\) The strength of a recommendation reflects not only the certainty of the evidence, but also considers the judgment of the experts in the GDG with respect to relevance of outcomes and magnitude of effects, balance of benefit and harm (burden), applicability of the evidence to the target population and ethical, legal, and economic considerations. Recommendations were formulated and graded as strong, weak, or open, the latter expressing a high level of uncertainty (see Table 2). When health questions were not covered by a systematic search and appraisal of the evidence, the GDG decided to formulate recommendations based on expert opinion. These are marked as a ‘consensus-based recommendation.’ Both evidence-based recommendations and consensus-based recommendations were discussed, graded, and approved in a formal consensus process to reduce bias.

1.5 | **Methods for finalising and approving the recommendations**

Recommendations and Statements 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 as follows:

- Introduction of the formal consensus technique by the Moderator
- Silent work allowing each participant to make notes on specific changes and reasons, based on the evidence and criteria considered for judgment
- Registration of proposals by individual participants on a ‘round robin’ basis by the Moderator and 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

1.6 | **External review**

The manuscript draft was available before submission for publication on the ESCD webpage, where members could comment on the document. ESCD members were informed about this by email. The hearing period was 4 weeks, a total of seven comments were received. All comments and responses from the steering committee are available in the Supporting information.

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**Table 1** Assessment of the strength of evidence

<table>
<thead>
<tr>
<th>Syntax</th>
<th>Quality/certainty of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>We are very confident that the true effect lies close to that of the estimate of the effect</td>
<td>High</td>
</tr>
<tr>
<td>We are moderately confident in the effect estimate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Our confidence in the effect is limited; we have very little confidence in the effect estimate</td>
<td>Low and very low</td>
</tr>
</tbody>
</table>

**Table 2** Grades of recommendation

<table>
<thead>
<tr>
<th>Syntax</th>
<th>Grade of recommendation</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘We recommend’, ‘we do not recommend’</td>
<td>Strong</td>
<td>A</td>
</tr>
<tr>
<td>‘We suggest’, ‘we do not suggest’</td>
<td>Weak</td>
<td>B</td>
</tr>
<tr>
<td>‘May be considered’</td>
<td>Open</td>
<td>0</td>
</tr>
</tbody>
</table>
**1.7 | Financial disclosure and management of conflicts of interest**

No support was given by any medical company for development of this document. All meetings were virtual meetings, therefore there were no costs. All participants in the working group filled in a structured form to declare financial or non-financial interests. Disclosures are given in the Supporting information. The Guidelines were approved by the executive committee of the ESCD in October 2021.

**1.8 | Update**

The guidelines are expected to be valid until 2025, at the latest. The updated process will be initiated depending on the availability of new evidence.

**2 | TERMINOLOGY**

Eczema and dermatitis are used interchangeably to describe a particular type of inflammatory disorder of the skin that targets the epidermis as well as the dermis. It exhibits a specific pattern of histological and clinical findings, which vary depending on the stage of the disease. Among the primary acute lesions that may be observed are erythema, oedema, oozing, crusting, papules, and vesicles/bullae. Secondary chronic lesions include lichenification, hyperkeratosis, scaling, and fissures. Pruritus is the most common symptom in all types of eczema, whereas skin pain, burning, and stinging are increasingly appreciated as important symptoms as well. Histological changes depend on the stage of the disease, and include intercellular oedema and spongiosis, acanthosis, and parakeratosis in the epidermis, whereas perivascular infiltrate of lymphocytes is observed in the upper dermis, which, in turn, may migrate into the epidermis.

Acute and subacute HE can be defined as eczema, localized to the hands, which lasts for less than 3 months and does not occur more than once per year.

Chronic HE (CHE) refers to an eczematous process that lasts for more than 3 months or relapses twice or more often per year. HE may be located anywhere on the hands and wrists, sometimes it may be restricted to certain parts of the hands, for example the palms, interdigital spaces, or fingertips. Involvement of a large area at onset of the disease indicates a bad prognosis. According to a consensus-based recommendation, HE in this guideline is divided into the aetiological and clinical subtypes (see Table 3).

**3 | EPIDEMIOLOGY**

HE is a common skin disease with a 1-year prevalence of at least 9.1% in the general population (6.4% in men and 10.5% in women), including mild as well as severe cases. An incidence of 5.5 cases per 1000 person-years was found in adults, 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). Self-reported HE in women peaks at between age 19 and 29 years, and decreases with age, while in men the incidence increases gradually with age. A population-based study from Norway found that the self-reported prevalence of work-related HE was 4.8%. The higher prevalence in women is explained by a difference in distribution of exposure, domestically and occupationally. In Scandinavian school children, the 1-year prevalence of HE was 7.3% for children aged 12-16 years and 10.0% for adolescents aged 16-19 years.

**3.1 | Risk factors**

Table 4 summarizes the reported risk factors of HE. Environmental factors explain up to 59% of the aetiology of HE. Risk factors often associated with HE include atopic dermatitis (AD) in childhood, persistent/severe AD,19,20 previous HE, and low age at onset of HE,20 being contact allergic,17,20 being exposed to wet work,21,22 cold/dry weather conditions, and decreased indoor humidity22 as well as being active in certain occupations. The risk of developing HE is significantly related to the intensity of wet work, among females in particular, and in a dose-dependent manner. Moreover, lifestyle factors, including tobacco smoking, have been reported to influence the prognosis of occupational HE (OHE). In a recent register-based cohort study from Denmark, exercise was associated with increased prevalence of healing, while tobacco smoking and mental stress were factors associated with CHE.

It remains unclear whether HE is associated with asthma, rhinoconjunctivitis, elevated specific IgE, a parental history of atopy, body weight, alcohol consumption, educational level, and mental stress. Loss-of-function mutations in the filaggrin (FLG) gene do not seem to be associated with HE in adults without AD, whereas these mutations cause dry skin and predict early onset of HE and CHE in individuals with AD. Recently, FLG mutations were reported to be associated with incident HE among metal-worker apprentices.

**3.2 | Occupational HE**

Hand eczema has a substantial health economic and socio-medical impact due to considerable occupational, domestic, social, and psychological consequences. HE is the most common occupational skin disease with a prevalence up to 40% in high risk occupations, which include wet-work occupations (hairdressers, cleaners, health care workers, metal workers, dental technicians), but also occupations with more mixed exposures such as bakers, butchers, florists, cashiers, electroplaters, machine operators, and workers in metal surface processing. The adoption of common prevention standards, recently developed in a European consensus process, including aspects relevant for case definition, reporting and surveillance may contribute to better estimates for the occurrence of OHE.
3.3 Burden of the disease

Socioeconomically, the consequences of HE are mainly apparent in occupational settings, where the disease may cause a reduced work capacity. In a multicentre European study, 28% of HE patients were unfit for work, and disability persisted for longer than 12 weeks in 12% of cases.42 In population-based studies, approximately 50% of all patients with HE received treatment for their disease,43 although this was 69% in a Swedish study.44 In Denmark, amongst patients who reported HE within the past 12 months, 67% had consulted a general practitioner and 44% a dermatologist.45 In Sweden, 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 individuals with allergic contact dermatitis (ACD) (29 weeks) compared to those with irritant dermatitis (13 weeks) and atopic HE (12 weeks).44 In a Danish prospective study, 57% of

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Classification of hand eczema (HE) including characteristics of subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Demographics</td>
</tr>
<tr>
<td>Aetiological subtypes</td>
<td></td>
</tr>
<tr>
<td>(a) Irritant contact dermatitis*</td>
<td>Most frequent form of HE; women &gt; men</td>
</tr>
<tr>
<td>(b) Allergic contact dermatitis*</td>
<td>Men &gt; women</td>
</tr>
<tr>
<td>(c) Atopic hand eczema</td>
<td>Onset at young age</td>
</tr>
<tr>
<td>(d) Protein contact dermatitis/contact urticaria</td>
<td>Relevant exposure to proteins. History of immediate skin reactions</td>
</tr>
</tbody>
</table>

Clinical subtypes

- Hyperkeratotic HE | Most common in men | No obvious exogenous or endogenous cause identifiable, neg. Patch test | Absence of vesicles. Little itch. Pain from fissures | Palms |
- Acute recurrent vesicular HE | | Cyclic eruptions | Many vesicles. Itch | Finger and palms |
- Nummular HE | | Patchy eczema, typically dorsal hands. Atopic dermatitis | Itch | Often xerotic skin in eczema lesions | Back of hands |
- Pulpitis | Relevant irritant exposure to allergens, positive patch test to culprit allergen(s) | Relevant irritant exposure to allergens, positive patch test to culprit allergen(s) | Little itch. Often atrophic skin. | Fingertips |

Note: Not infrequently two or more HE sub-diagnoses are required for HE characterization, and the sub-diagnoses may change with time (modified from references25,92,126,130,131).

*Phototoxic and photoallergic contact dermatitis are further subtypes belonging to the groups.

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Risk factors associated with hand eczema based on available evidence and expert consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors</td>
<td>References</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>15,16a</td>
</tr>
<tr>
<td>Low age at onset of hand eczema</td>
<td>20</td>
</tr>
<tr>
<td>Filaggrin gene mutations</td>
<td>38</td>
</tr>
<tr>
<td>Contact allergy</td>
<td>17,20</td>
</tr>
<tr>
<td>Wet work</td>
<td>21,22</td>
</tr>
<tr>
<td>Cold/dry weather conditions and decreased indoor humidity</td>
<td>23</td>
</tr>
<tr>
<td>Occupation</td>
<td>24,25</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>26–32,38</td>
</tr>
<tr>
<td>Lower educational level</td>
<td>34</td>
</tr>
<tr>
<td>Stress</td>
<td>30</td>
</tr>
</tbody>
</table>

*Persistent and severe atopic dermatitis.
patients with occupational skin disease had a sick-leave period due to HE in the past 12 months, 44% reported job change, 15% was on early retirement, and 72% suffered impairment of health-related quality of HR-QoL.56 Furthermore, severe OHE, age ≥40 years, and severe impairment of HR-QoL at baseline predicted long-term sick leave and unemployment.56

A cross-sectional, multicentre, Italian study found that 83.5% of patients had CHE, 21.3% had severe HE, with 62.0% of these patients being refractory to standard therapy. HE in occupational settings was most frequently associated with CHE.47

A systematic review, comparing the cost-of-illness of HE showed that the mean total yearly cost per patient varied between €1311 and €9792; more severe HE and OHE resulted in higher costs.48 Sickness absenteeism is a large contributing factor, but presenteeism (working while sick), although often overlooked, may have an even greater influence on costs, with a 1-year prevalence of 41% in HE patients.49

Hand eczema has a negative impact on HR-QoL to the same degree as psoriasis or asthma.50,51 This negative impact is greater for females than for males,52 with a higher occurrence of co-occurring depression among women53 as well as in metropolitan more than in non-metropolitan patients.54 A European multicentre study found that patients with HE reported significantly higher levels of distress, suicidal ideation, depression, and anxiety as compared to controls.52

4 | PREVENTION

- We recommend offering health education and training to individuals in high-risk groups, such as hairdressers, health care workers, metal workers etc., aiming to motivate adequate skin protection behaviour and to empower taking responsibility for one's own health. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).
- We suggest secondary prevention strategies be implemented as early as possible in already affected individuals, to prevent relapse or progress of HE. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).
- We recommend tertiary prevention in individuals with severe or CHE, to decrease the severity of the disease and adverse sequelae for better long-term control. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).

Prevention should aim at identification and subsequent reduction or elimination of occupational and non-occupational causative exposures as well as maintaining an intact skin barrier; but knowledge of endogenous and other individual risk factors should also be taken into account. Preventive measures differ between countries depending on the local economic and, especially, regulatory situation as well as the health care system.

Prevention comprises primary, secondary, and tertiary prevention strategies.55 Primary prevention addresses the healthy population and aims at decreasing the incidence (number of new cases) of HE. Secondary prevention in case of HE addresses patients in whom (mild) signs and symptoms of CHE are already present. Detection of initial skin changes is pursued to implement corrective measures as early as possible, to prevent a relapse or progress to a chronic or severe disease. Tertiary prevention targets patients with severe CHE in whom secondary prevention measures have failed. The aim is to reduce the severity of the disease and prevent development of adverse sequelae (e.g. by medical or occupational rehabilitation).

4.1 | Legal regulations

Legal regulations of exposure to irritants or allergens, for example, by prohibition, threshold values or precautions in handling of hazardous products, are implemented on the level of primary prevention. Regulations target specific groups (e.g. members of a professional group) or the population as a whole. Examples are EU regulations on occupational safety and health56 or on exposures to contact allergens such as chromium in cement and leather, or nickel in jewellery and other personal items,57–60 and methylisothiazolinone in personal hygiene products and cosmetics.61

4.2 | Risk assessment and hierarchy of prevention measures

Conducting a risk assessment is essential for detecting and subsequently minimizing harmful skin exposures, particularly in workplaces.40 The substitution/elimination technological measures, organizational measures, and personal protective equipment (STOP) principle describes the suggested hierarchy of prevention measures (Table 5). Harmful activities or exposure to hazardous

<table>
<thead>
<tr>
<th>Measure</th>
<th>Examples</th>
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<tbody>
<tr>
<td>1. S</td>
<td>Substitution/elimination</td>
</tr>
<tr>
<td>2. T</td>
<td>Technological measures</td>
</tr>
<tr>
<td>3. O</td>
<td>Organizational measures</td>
</tr>
<tr>
<td>4. P</td>
<td>Personal protective equipment</td>
</tr>
</tbody>
</table>

TABLE 5 | Hierarchy of preventive measures according to the ‘STOP’ principle to reduce hazardous exposures |
substances should be eliminated or replaced whenever possible. A good example is the replacement of products containing allergens relevant to the individual HE (e.g. protective gloves, emollients, or specific products from the workplace, such as metal-working fluids or disinfectants); sometimes, reduction of detrimental exposures may be sufficient. Accordingly, healing and improvement of OHE is achieved by decreasing the amount of wet work showing an inverse dose-response relationship. Technological measures (e.g. automation of work processes, shielding) minimize the exposure to dangerous substances, while organizational measures reduce the number of exposed individuals and/or the duration and intensity of individual exposure. If complete elimination of exposure to hazardous substances is not possible, personal protective equipment (PPE) should be utilized after careful selection and risk assessment and should comply with the necessary safety standards. Known allergies must be respected. For example, protective gloves may contain rubber additives leading to ACD, or natural rubber latex causing contact urticaria and/or protein contact dermatitis. Inadequate equipment or failure in usage of adequate equipment may lead to the development or worsening of HE, therefore, instruction for the correct usage of PPE and protective behaviour should be provided. Practical literature-based recommendations referring to this are summarized in Table 6. Regarding barrier creams, evidence for their efficacy is limited. They may only be effective against certain irritants and may sometimes even intensify the irritant skin response. Barrier creams are not well defined: they vary in composition and there is no specific difference between barrier creams and emollients. In a large, prospective intervention study of 1020 metalworkers with a 12-months follow-up, the use of both skin barrier cream and after-work emollient was associated with the strongest improvement of HE, followed by skin barrier cream alone. A recent Cochrane review found that emollients used alone or in combination with barrier creams may result in a clinically important protective effect, either in the long- or short-term, for the primary prevention of irritant OHE. The authors concluded that, at present, there is insufficient evidence to confidently assess the effectiveness of interventions in the primary prevention of irritant OHE based on the use of barrier creams, emollients, or health education.

### 4.3 Health education

Raising awareness and performing education on the pathogenesis of HE as well as on the use of PPE are important strategies to improve

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**TABLE 6** Practical recommendations for use of personal protective equipment and protective behaviour to prevent hand eczema

<table>
<thead>
<tr>
<th>Protective gloves</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use protective gloves for wet work and work with hand contact to hazardous substances, both at home and at work.</td>
<td>38,40,74,192-195</td>
</tr>
<tr>
<td>When choosing protective gloves, permeation rates and degradation of glove materials must be respected.</td>
<td>196,197</td>
</tr>
<tr>
<td>Protective gloves should be intact, clean and dry inside.</td>
<td>38,40,195,198</td>
</tr>
<tr>
<td>Protective gloves should be used when necessary, but for as short a time as possible because friction, sweating, and heat caused by wearing of gloves may result in irritant contact dermatitis, particularly in case of prolonged usage or skin pre-irritated e.g. by detergents.</td>
<td>38,40,192,195,198-202</td>
</tr>
<tr>
<td>When protective gloves are used for more than 10 minutes, cotton gloves should be worn underneath and changed regularly to reduce occlusive effects.</td>
<td>38,40,195,198</td>
</tr>
<tr>
<td>Single use gloves should be worn only once.</td>
<td>40,74,194</td>
</tr>
<tr>
<td>Use insulating gloves in the winter or when working in the cold.</td>
<td>38,74,195,203</td>
</tr>
</tbody>
</table>

**Hand cleaning**

Hand washing is important to remove hazardous substances from the skin. However, frequent hand washing is associated with development of HE and should be avoided.

- Wash hands in lukewarm, not hot water. | 38,56,195,205 |
- Use of crude brushes and abrasives or even organic solvents to clean the skin should be abandoned. | 200 |
- Rinse and dry hands thoroughly after washing. | 38,40 |
- Hand washing with soaps should be substituted with alcohol disinfection when hands are not visibly dirty (particularly in healthcare or food handling) as alcohol is less irritating than hand washing with soap. | 200,202,206 |

**Emollients/barrier creams**

- Apply emollients on your hands during the working day but especially after work and before bedtime. | 38,66,71,192,195,207,208 |
- It may be reasonable to use a lighter emollients lotion during the day and a greasier, preferably fragrance-free, lipid rich moisturizer before bedtime. | 38,74,195 |
- If barrier creams are used, apply them before work and again after hand washing before continuing work. | 66,192 |
- Emollients and barrier creams should be applied all over the hands, including the webs, fingertips and dorsal aspects. | 38,40,195 |

**General**

- Do not wear rings or any other jewellery on the hands when performing wet work. | 38,74,195 |
We recommend diagnostic patch tests be performed in all patients. We recommend a careful history taking including a search for per-
care workers, hairdressers, food handlers, or cleaners.82 especially in those working in occupations at risk, including health
care workers, hairdressers, food handlers, or cleaners.82 However, from others we have learned that face-to-face education is a particularly
effective secondary prevention strategy in patients with HE.50,81 especially in those working in occupations at risk, including health care
workers, hairdressers, food handlers, or cleaners.82,84 Nevertheless, recent data indicate that health care workers may not ben-
fit from standard information and may need education on a different level.79 ‘Hands-on’ skin protection seminars on adequate
skin protection behaviour has in some places become an effective standard procedure in management of individuals with OHE, show-
ing good short- and long-term results regarding decrease of disease severity and ability to continue in the profession.85–87 These inter-
ventions are more effective for mild to moderate HE than for severe cases, highlighting the importance of early interventions in
the initial stages of the disease.81,86 For those in whom secondary prevention fails, more intensified strategies are indicated. In
Germany, a tertiary individual prevention program (TIP) is offered to patients with severe and recalcitrant OHE (Osnabrueck
Model).88 The TIP is based on a 3-week inpatient phase in a special-
ized centre providing intensified diagnostics and treatment as well as health education and psychological counselling, followed by a
3-week outpatient phase allowing the skin barrier to recover before returning to work. The TIP is associated with sustained improve-
ments in terms of disease severity, ability to work, quality of life, and prognosis.89–91

5 | MEDICAL HISTORY, EXAMINATIONS
AND DIAGNOSTIC PROCEDURES

- We recommend a careful history taking including a search for per-
sonal and occupational exposures along with clinical examination
of the hands and the entire skin integument. Consensus-based rec-
ommendation (first round 100% [12/12], second round 100% [22/22]).
- We recommend diagnostic patch tests be performed in all patients
with HE of more than 3 months’ duration or who are non-
responsive to adequate treatment, or clinical suspicion of contact
allergy. Consensus-based recommendation (first round 100%
[12/12], second round 100% [22/22]).
- We recommend patch testing with a baseline series, extended by
selected additional series/allergens, depending on exposure. Consensus-based recommendation (first round 100% [12/12], sec-
ond round 100% [22/22]).

The diagnosis of HE is based on medical history, clinical examina-
tion, and performance of skin tests. If necessary, the diagnostic
spectrum may be further extended by histopathology examination
and microbiology tests. A diagnostic work-up for HE is shown in
Figure 1.

5.1 | Medical history and clinical examination

The medical history should be taken by a structured interview and
contain detailed information on the current signs and symptoms, dura-
tion and course of disease, exacerbations and remissions in relation to
work-related activities, personal and family history of AD, previous
and concurrent skin or systemic diseases, regular use of medications,
and smoking habits. Information on previously documented allergic
sensitizations and test procedures should be collected, together with
information on the use and response to topical medications and skin
products, wet work as well as current and previous occupational,
household, and recreational exposure to known contact allergens and
irritants.92,93

The clinical examination requires inspection of the hands, and
when judged relevant, inspection of the entire skin integument,
including the feet. Involvement of the feet in HE patients is present in
up to 20% of all cases and not restricted to endogenous eczema.94
The clinical manifestations of HE show similarities to a broad spec-
trum of dermatoses of different aetiology that should be excluded
(Table 7).93,95 Genital involvement may occur in ACD cases, and here
it may be worth asking the patient specifically about such
involvement.

5.2 | Epicutaneous patch testing

Epicutaneous patch testing is the gold standard to diagnose contact
allergy. Patch tests should be performed in all patients with HE of more
than 3 months’ duration or who are non-responsive to adequate treat-
ment as well as clinical suspicion of contact allergy. Clinically relevant
contact allergies cannot be estimated based on the pattern of dermatitis
and/or its severity, but should be based on exposure, location of derma-
titis, and often with vesicular morphology supporting an aetiology.95,96

The indication for patch testing and the spectrum of substances to
be tested must be carefully considered in view of patient history
and occupational and private exposure, including recreational expo-
sures.97,99 The ESCD guidelines on epicutaneous patch testing
describe in detail how patch testing is practically planned and
performed.99
Any positive patch test reaction requires a careful evaluation. It is important to mention that a negative patch test is not an absolute exclusion of a contact sensitization since false negative results may occur, or there can be a missed allergen. If needed, other less standardized techniques, such as an open, semi-open or repeated open application test (ROAT), could be useful to rule out contact allergy and should be undertaken in experienced clinicians.99–101

5.3 Skin prick tests and specific IgE measurement

HE patients may report immediate skin reactions, such as contact urticaria, after exposure to natural rubber latex gloves or proteins from plant or animal foods,102 with or without occupational relevance.102–107 If exposure to proteins is continuous or repeated, eczematous reactions may occur, referred to as protein contact dermatitis. Skin-prick testing (SPT) is a first-line approach to assess these reactions because of its generally good safety profile, sensitivity, specificity, rapidity of performance, and low cost. SPT should be performed according to the recommendations of the published guidelines, and the wash-out periods for topical and systemic medications must be respected.108

Prick-to-prick testing is the method of choice when considering a test with fresh foods of plant or animal origin, given its more specific and accurate results, including the possibility of detecting an underlying immediate type sensitization to allergen components underrepresented in the commercially available test solutions. In cases of suspected protein contact dermatitis without systemic symptoms, the prick-to-prick test with fresh proteinaceous material (foods and plants) is a safe and important diagnostic tool. Alternatively, an approximately 20-minute direct exposure to fish or meat on the finger where protein contact dermatitis occurs may lead to wheals and even vesicles that support the diagnosis. If, however, the patient has had generalized symptoms in the past, the risk of anaphylaxis should always be considered, and the test be performed only if emergency medication is available. The evaluation
Table 7: Differential diagnoses of hand eczema

- Psoriasis
- Dyshidrosis lamellosa sicca/keratolysis exfoliativa
- Dermatophyte infection (tinea manuum)
- Scabies
- Bullous impetigo
- Lichen planus
- Pityriasis rubra pilaris
- Cutaneous T cell lymphoma
- Porphyria cutanea tarda
- Hand-foot-and-mouth disease
- Fixed drug eruption
- Friction blisters
- Chemotherapy-associated hand-foot syndrome
- Palmoplantar keratodermas
- Bowen’s disease
- Acrokeratosis paraneoplastica (Bazex syndrome)
- Secondary syphilis

of the results of a prick-to-prick test with fresh materials must be done carefully because of the risk of non-specific positive (irritant) reactions. Testing of controls may be warranted. In addition to SPT, the measurement of specific IgE may provide complementary information on the individual sensitization profile and so facilitate the diagnosis of immediate type hypersensitivity in a patient with HE.

5.4 | Microbiology tests

The clinical examination may give rise to suspicion of a secondary infection, primarily driven by Staphylococcus aureus (S aureus), as a concomitant or aggravating factor of HE, particularly in atopic patients. In such cases, skin swabs may be used to obtain information about the causative microorganism and antibiotic resistance, but signs of clinical infection should be the main driver for prescription of antibiotic treatment. The possibility of a dermatophyte infection (tinea) should be considered. In unilateral cases of HE, in particular, skin scrapings for microscopy and culture or polymerase chain reaction tests should be taken. Dermatophytosis on the feet may cause dermatophytid reactions on the hands, as a concomitant disease or co-factor in HE. Furthermore, scabies should be excluded as a differential diagnosis. In rare cases, if vesicles are present typically on one finger, herpes simplex infection should be considered.

5.5 | Skin biopsy examination

Skin biopsies are only recommended to rule out differential diagnoses (e.g. psoriasis, lichen planus, lymphoma).

6 | EXPOSURE ASSESSMENT

6.1 | Exposure assessment

- We recommend that exposure assessment, using all available sources, such as ingredient labels and safety data sheets, be performed prior to patch and skin-prick testing, to identify potential allergens in the environment for inclusion in testing. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).
- We recommend that following any positive patch test or skin-prick test, qualitative and, if possible, quantitative assessment of exposure to said allergen be performed, including use of relevant spot tests. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).
- Exposure assessment can assist in identifying an aetiological cause of HE and plays a substantial role in implementation of specific preventive measures. Consensus-based statement (first round 100% [12/12], second round 100% [22/22]).

6.1.1 | General principles

Assessment of exposure is a prerequisite for planning patch and skin-prick testing in patients with HE. It is also a tool for making an aetiological diagnosis of ACD, protein contact dermatitis and/or ICD, for determining work-relation and for effective prevention.

Taking the medical history with great care is fundamental in any exposure assessment. This should detail both occupational and domestic exposures including the use and type of protective equipment as well as products used for skin care, personal hygiene, and medical and alternative therapy. Ingredient labelling is mandatory on cosmetic products in the European Union including those used in the workplace and is a tool for identifying contact allergens, which may be of relevance for the HE. Safety data sheets should be retrieved from the workplace to assist in identifying potential allergens prior to patch testing. Many allergens encountered in the workplace may not be picked up by testing with the baseline series alone. Importantly, both allergens and irritants may be in a product without it being documented in the safety data sheet as there are concentration limits for warning and declaration of an ingredient. Often the manufacturer must be contacted to retrieve additional information on the product. Metal composition is rarely reported with regards to metal tools, ingredient lists may be incomplete or inaccurate, and organic exposures, such as plants, lack ingredient lists. In these situations, physical exposure assessments for allergens may be appropriate. Exposure to common irritants, such as water, needs to be quantified.

It is easy to overlook exposures, which is why a systematic approach should be employed. A stepwise approach has been suggested. These principles are illustrated in Figure 2.

After patch testing, exposure analysis should be repeated in the case of negative or unexpected positive results. For certain allergens, more advanced methods exist to identify or even quantify exposures (see below). The final step in the exposure analysis is to determine if current exposures to allergens and/or irritants have caused the present dermatitis and to suggest preventive measures, if relevant. Common European standards on prevention and management of work-related skin disease have been developed; these include minimum requirements for workplace exposure assessment.
6.2.1 | Contact allergens

Allergic contact dermatitis can play a significant role in HE, both as a single aetiological cause or by worsening existing irritant or atopic HE. If patch testing leads to identification of relevant contact allergies, avoidance of said allergens is crucial to improve the chances of resolution.

6.2.2 | Metal allergens

In the case of metal allergens, there are three primary techniques for direct exposure assessment: spot tests, release tests in artificial sweat, and elemental analysis. Spot tests are fast, easy to use, inexpensive, non-destructive, colorimetric, semi-qualitative tests that can be used to assess for metal ion release from metallic objects. The most common of these is the dimethylglyoxime spot test to assess for nickel release, although spot tests for cobalt and chromium release have also been developed. These tests assess for metal ion release, not chemical composition, a clear advantage, but they cannot reliably be used on non-metallic items such as make-up or leather. A special advantage of the dimethylglyoxime test is that it can be used to demonstrate deposition of nickel directly on the hands, for example, by employing it before and after work in cases suspected of occupational allergic contact dermatitis to nickel. More advanced methods for measuring skin deposition of nickel, chromium, and cobalt have been developed but have until now mostly been used in experimental and research settings.

6.2.3 | Non-metal allergens

Analysis of ingredient labels of products and safety data sheets is the most common and straightforward method for identification of non-metal allergens. Direct exposure assessment for non-metal allergens is less well established and, in most cases, difficult. One exception is formaldehyde. Formaldehyde release can be assessed using a colorimetric test, based on either acetylacetone or chromotropic acid, both of which change colour when in contact with formaldehyde.

6.2.4 | Proteins

Skin exposure to proteins may cause a type I allergic reaction, which classically presents as urticaria, but if skin exposure occurs continuously or repeatedly, protein contact dermatitis may develop and HE. Exposure assessment to proteins is relevant to those in occupations handling food as well as in those in occupations handling insects or animals, such as zookeepers, assistants in animal experiments, and veterinarians. Generally, the only method to investigate exposures in such cases is by taking a careful history and/or visiting the workplace.

It is important to explore the use of protective equipment, especially gloves and glove materials, which may contain latex protein, a well-known cause of type I allergy. Skin-prick testing is key for the diagnosis.

6.2.5 | Irritants

Irritant contact dermatitis is the clinical manifestation of an inflammatory skin reaction due to irritants, exogenous agents causing damage to keratinocytes and other skin cells. A wide array of chemicals can potentially cause ICD and the disease is usually multifactorial. Irritant reactions are non-specific, meaning that most people exposed to an irritant would react similarly, albeit with varying inflammatory reactions, depending on the intensity and duration of exposure and individual skin resistance level. The effects of different irritants can compound skin damage and the resulting disease may be sustained by various and alternating factors. Wet work is the main cause, and the risk is positively correlated with duration and frequency of exposure. It is important to quantify exposures to irritants by taking a careful history including the number of hand washes, hours of wet hands per day, use of occlusive gloves, use of skin cleansers, and contact to solvents or detergents. Physical factors should also be addressed, including repeated trauma and skin abrasion as well as desiccation in dry ambient air and thermal damage (both cold and heat). Chemical factors causing skin damage include corrosive substances (acids, alkalis) or cellular toxins. Contact to irritant chemicals can, in some cases, be identified by the safety data sheet, but often these are not of great help.

To summarize, in cases of HE, assessment of exposure to contact allergens, proteins and irritants, qualitatively and quantitatively is obligatory, to plan skin test strategies, make a correct diagnosis, and design preventive measures and create treatment plans.

7 | CLASSIFICATION

- We recommend the following classification of HE. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).
Hand eczema is a multifactorial disease with a polymorphic clinical picture. Histology and morphology rarely allow for definitive conclusions about the underlying aetiology of the individual patient’s HE, and for the same aetiology the clinical morphology may change with evolution. Often more than one aetiological factor is found to play a role in the development of the disease, for example ICD is often found together with ACD and atopic HE. This further complicates the classification of HE.

Clear classification is desirable for multiple reasons: establishing consensus on HE subtypes would facilitate the comparison of clinical trial results as well as interpretation of research findings. Understanding the HE subtype of each patient provides guidance relevant for treatment and counselling. This is particularly important as different morphologies requiring different galenic formulations for topical therapy and recommendations for skin care and patient education vary between subtypes.

Classification of HE has been historically controversial, and no clear consensus has been reached in favour of one approach. Recent publications, however, share similarities in their approach, though varying slightly in the details of their classification systems. It is generally more common to classify according to the underlying aetiology than according to morphology, chronicity, and anatomical location, though the clinical picture is used as an additional feature when aetiological factors remain unclear. Some examples of recent classification approaches can be found in previous publications.

Irritant contact dermatitis is an exclusion diagnosis, and it is a prerequisite that other aetiologies, especially ACD, have been ruled out, and that the patient has been exposed to skin irritants. Combination with other aetiologial HE subtypes is frequent. With respect to ACD, identifying contact allergy does not automatically explain the cause or the complete cause of HE. A diagnosis of ACD requires identification of relevant allergen exposure and contact allergy to the culprit allergen. Atopic HE may be associated with inherent skin barrier impairment (e.g. filaggrin deficiency, due to common loss-of-function), but is often diagnosed based on the dorsal location of eczema and sparse palmar involvement. HE due to protein contact dermatitis is uncommon but is diagnosed based on a positive skin-prick test, and a history of immediate skin reaction to a source of protein, typically meat, fish, vegetables, and fruit in food handlers. Regarding hyperkeratotic HE, it has been suggested that this might have to be considered an entity on its own, maybe even distinct from HE, but is characterized based on involvement of the central palmar area. Hyperkeratotic HE is not attributable to the other categories, it is more common in men than in women, and an association with tobacco smoking has been indicated that seems to be stronger than for the other subtypes. Acute recurrent vesicular HE (previously called dyshidrotic endogenous eczema or pompholyx) has been described as a separate entity in most proposed classifications, and poses challenges with regard to diagnosis and treatment. The term acute recurrent vesicular HE describes the clinical course and morphology but not the aetiology and may, therefore, be observed in the context of several aetiologies. A comprehensive understanding of the molecular pathogenesis of HE is still lacking, though more and more details are emerging. It is likely that future classification systems will have to take the molecular subtyping into account and urge us to reconsider the current classification concepts.

Nummular eczema is characterized by coin-shaped, sometimes very itchy lesions often manifest on the backs of the hands. A significant number of patients have an underlying ACD. A recent publication has confirmed the role of formaldehyde and formaldehyde releasers in nummular eczema and its results support patch testing in this patient group. Fingertip eczema is hand eczema localized to the tips of the fingers. The most common underlying aetiology is chronic skin irritation, but it can also be seen in the context of AD or ACD. The term pulpitis sicca is used to describe a subtype of AD with painful fissures on the fingers (and toes) as the predominant clinical feature.

Concomitant eczema on the feet may be present in all subtypes of HE, however, more often in hyperkeratotic HE and in ACD; however even in HE categorized as ICD, concomitant eczema on the feet is found in 20% of all cases.

An open question remains why some cases of HE heals after counselling and topical treatment, whereas other cases progress into CHE, which may last for many years. Some patients may even develop a hardening phenomenon following irritant exposure. In some cases of CHE, a classification referring to the original aetiological causative factors is less helpful, since eliciting factors (e.g. allergens or irritants) should have been eliminated, and since a long time may have passed since onset of the disease.

In conclusion, HE classification is important and current approaches share many similarities, with new details emerging due to an improved understanding of the disease’s pathogenesis. Still, evidence is limited and, therefore, it is premature to provide specific recommendations.

### 8 | Treatment

A wide range of approaches is available for the management of acute HE and CHE. In the Cochrane review on which this section is based, 60 RCTs were identified, with a total of 5469 adult participants. There was substantial heterogeneity in treatments and outcome measures, limiting pooling and quantitative meta-analyses. The duration of treatment was short, generally up to 4 months. Only 24 studies included a follow-up period. Few studies performed head-to-head comparisons of different interventions. An overview of treatment recommendations can be found in Table 8. Regarding recommendations
on health education, primary, secondary and tertiary prevention see the section on Prevention.

8.1  General principles of treatment

- We recommend identification and avoidance of causative exogenous factors. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).

The treatment of HE must consider the general treatment principles of disease-stage appropriate therapy, disease aetiology, acute-ness, morphology, comorbidities, and location. Successful therapy requires identification and avoidance of causal exogenous factors (e.g. allergens, irritants, and proteins).

Acute HE should be classified and treated quickly and rigorously to avoid the development of CHE. Topical anti-inflammatory agents, together with emollients, are effective treatment to control an acute flare-up of HE in most patients. As full, functional regeneration of the epidermal barrier takes several weeks or months after the eczema subsides, patients must avoid re-exposing the skin before complete healing of the skin barrier as well as prolonged exposure to potent topical corticosteroids that may further disrupt the skin barrier. A prerequisite for successful therapy is identification and avoidance of causative exogenous factors.

8.2  Topical treatments

8.2.1  Emollients and moisturizers

- We recommend that emollients/moisturizers are frequently used in all HE patients. Consensus-based recommendation (first round 100% [8/8], second round 100% [21/21]).
- We recommend that the choice of emollient should be individual-ized according to skin condition, patients’ preference, and existing (contact) allergies. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).

Emollients/moisturizers are traditionally used for the treatment of HE, yet evidence of their efficacy is limited. The Cochrane review from 2018 identified three studies on the protective effects of moisturizers in primary prevention of OIHD. Meta-analysis showed a possibly important protective effect with the use of moisturizers: in the intervention groups, 13% of participants developed symptoms of OIHD compared to 19% of the controls (RR 0.71, 95% CI 0.46 to 1.09). The Cochrane review from 2019 could only include two small studies on emollients.1 These studies could not be assessed with GRADE and no conclusions were drawn on efficacy. These two studies140,141 and three that were additionally identified,142–144 showed that emollients may reduce severity and itch and may reduce time to next flare-up. There is no evidence that supports use of any specific moisturizers in HE.1,145,146

However, the Guidelines working group recommends that emol-lients be used in HE to maintain and/or improve skin barrier function. The preference of the patient and existing (contact) allergies are key factors for the choice of emollient(s). To optimize use and adherence, health care provider instruction (when, how, which one to choose) may be necessary. In practice, sometimes emollients with 10% urea - or other keratolytics - are used in hyperkeratotic HE, but there is no evidence to recommend this.

8.2.2  Topical corticosteroids

- We recommend topical corticosteroids as short-term first-line treatment in the management of HE. Quality of evidence: moderate. Grade of recommendation: A. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).
- Long-term intermittent use of topical corticosteroids as mainte-nance therapy may be considered, although the evidence for its efficacy is limited. Quality of the evidence: low. Grade of
recommendation: 0. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).

- Development of side effects of topical corticosteroids depends on the potency, the amount applied, the duration of treatment, frequency of use and the anatomical site. Consensus-based recommendation (only one round: 100% [22/22]).

Along with emollients, the local treatment of choice for HE is a topical corticosteroid, although there is a paucity of long-term evidence. The 2019 Cochrane review on HE included nine studies on topical corticosteroids.\(^1\) Six studies were very short in duration (≤3 weeks) and mostly compared two corticosteroids, or compared the same corticosteroid in different vehicles, or with different dosages or application frequencies. All showed a reduction in disease severity, although the certainty of the evidence was not assessed with GRADE. Two studies compared a topical corticosteroid vs vehicle or no treatment and were assessed with GRADE. In a 1-day study, clobetasol foam yielded favourable participant-rated disease control vs vehicle after 15 days, but not in investigator-rated control (both moderate certainty evidence).\(^1\) The only study with a longer duration (36 weeks), assessed after having reached remission, disease control with mometasone two times per week vs three times per week vs no mometasone.\(^1\) Three times a week mometasone may have worked slightly better than two times per week (low certainty evidence), but led to slightly more skin atrophy.\(^1\) The comparison with no mometasone was not assessed with GRADE, but the analysis demonstrated high rates of disease control with mometasone during 36 weeks, with only a few reports of mild atrophy.

Topical corticosteroids are effective, but potent corticosteroids have been shown to inhibit repair of the stratum corneum, in part due to filaggrin degradation.\(^1\) They may cause skin atrophy and interfere with recovery in the long term,\(^1\) although mometasone appears to be moderately potent and with fewer side-effects.\(^1\) Once daily treatment is sufficient and may even be superior to twice daily application.\(^1\) In AD, once daily treatment is reportedly as effective as twice daily,\(^1\) but it is at the clinician’s discretion to start use once or twice daily. The efficacy of systemic treatment with altiretinoin was found to be enhanced with the addition of topical corticosteroids.\(^1\)

Allergic contact dermatitis caused by a topical corticosteroid, or its vehicle, is not uncommon and should be considered when HE does not respond to topical treatment.\(^1\) Intermittent dosing may reduce the risk of skin atrophy, but little evidence supports this.\(^1\) Clinical experience suggests that alternating or combining a topical corticosteroid with a topical calcineurin inhibitor may be considered in order to reduce adverse effects,\(^1\) although the long-term safety of this approach is unknown.

Furthermore, it is important to recognize and address topical corticosteroid phobia, which has been mostly studied in AD, since it may interfere with compliance in HE.\(^1\) Pharmacists represent the group with the strongest topical corticosteroid phobia,\(^1\) making it important to guide patients during the consultation.

8.2.3 | Topical calcineurin inhibitors

- We suggest tacrolimus ointment for short-term treatment in the management of HE. Quality of evidence: moderate. Grade of recommendation: B.
- We suggest using tacrolimus ointment for HE patients either refractory to topical corticosteroid or when fear of side effects of topical corticosteroid exist, or in the chronic stage. Consensus-based recommendation (first round 92% [11/12], second round 91% [21/23]). Doctors and patients need to be aware that this is an off-label treatment, except for patients with atopic HE.

The topical calcineurin inhibitors tacrolimus and pimecrolimus are registered for the treatment of AD, not for HE of other aetiologies. The 2019 Cochrane review on HE included four small studies on tacrolimus (107 participants in total) and five larger studies on pimecrolimus (1059 participants), all of rather short duration (<8 weeks).\(^1\) Tacrolimus 0.1% ointment probably improves investigator-rated symptom control measured after 3 weeks compared to vehicle (14/14 tacrolimus vs 0/14 vehicle).\(^1\) Participant-rated symptoms were not measured. Burning or itching was reported in four out of 19 in the tacrolimus group vs none of the 14 in the vehicle group. The evidence was assessed as moderate certainty, based on GRADE. A within-participant study in 16 patients compared 0.1% tacrolimus to 0.1% mometasone furoate, but investigator- or participant-rated symptoms were not reported.\(^1\) Both treatments were well tolerated. The certainty of the evidence was rated as moderate.

Data for pimecrolimus 1% are conflicting and were not assessed with GRADE in the Cochrane review of 2019. Overall, no significant difference in efficacy was found between pimecrolimus and placebo. The skin barrier on the palms is fundamentally different from the dorsal aspects of the hands. Thus, the large calcineurin inhibitor molecules may more easily penetrate the dorsal aspects, in part resulting in better chance of efficacy.

8.3 | Physical therapies

8.3.1 | Phototherapy

- We suggest phototherapy of the hands in adult patients with CHE refractory to topical corticosteroids. Quality of evidence: moderate. Grade of recommendation: B. Consensus-based recommendation (first round 100% [10/10], second round 91% [21/23]).
- Long-term use of phototherapy may increase the risk of skin malignancy. Consensus-based statement (only one round: 100% [22/22]).

Ten studies on UV-therapy were included in the Cochrane systematic review.\(^1\) There was too much heterogeneity regarding interventions, comparators, and outcomes to perform a meta-analysis. Of these 10, one comparative study was assessed with GRADE:
narrow-band-UVB vs psoralen-UVA (PUVA).\textsuperscript{163} This study showed that there is probably little to no difference in efficacy, but that PUVA may result in more adverse events (9/30 vs 0/30) (both moderate certainty evidence). Oral as well as bath, paint, or cream PUVA are used in some countries\textsuperscript{164,165} and seem to be similarly effective. UVA1 may also be effective,\textsuperscript{166,167} but availability is often limited.

Adverse events of phototherapy, especially local PUVA, are erythema and burning of the skin, and long-term use increases the risk of (non-melanoma) skin cancer.\textsuperscript{168}

Grenz ray treatment was used in the past but is considered obsolete because of a possible increased risk of skin cancer.\textsuperscript{169–174}

8.4 | Systemic treatment

- We recommend alitretinoin as a second-line treatment (relative to topical treatment) for patients with severe CHE. Quality of evidence: high. Grade of recommendation: A. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).
- We suggest short-term oral corticosteroids to be used only in acute and severe inflammation as part of a treatment plan, for example, when starting systemic treatment with a slower onset of effect. Consensus-based recommendation (first round 100%, [12/12], second round 100% [22/22]).
- We suggest cyclosporine for CHE patients refractory or contra-indicated to first- and second-line therapy. Consensus-based recommendation. Doctors and patients need to be aware that this is an off-label treatment, except for patients with atopic HE. Consensus-based recommendation (first round 100% [12/12], second round 100% [22/22]).
- Azathioprine may be considered for CHE patients refractory or contra-indicated to first- and second-line therapy, although evidence for its efficacy is limited. Consensus-based recommendation. Doctors and patients need to be aware that this is an off-label treatment. Consensus-based recommendation (first round 100% [12/12], second round 100% [23/23]).
- Methotrexate may be considered for CHE patients refractory or contra-indicated for first- and second-line therapy, although evidence for its efficacy is limited. Consensus-based recommendation. Doctors and patients need to be aware that this is an off-label treatment. Consensus-based recommendation (first round 100% [12/12], second round 100% [23/23]).
- Acitretin may be considered for hyperkeratotic CHE, if other therapeutic options are unavailable or contra-indicated, although evidence for its efficacy is limited Consensus-based recommendation. Doctors and patients need to be aware that this is an off-label treatment. Consensus-based recommendation (first round 100% [12/12], second round 100% [23/23]).

Except for alitretinoin, no other systemic treatments are licensed for the treatment of CHE.

8.4.1 | Oral corticosteroids

No RCTs on oral corticosteroids in treating HE were found and included in the Cochrane review.\textsuperscript{1} From experience, they can be very effective, but long-term or repeated use should be avoided as they are associated with long-term adverse events. Oral corticosteroids can be used briefly to treat acute severe HE (generally for a maximum of 3 weeks, beginning at 0.5 mg/kg/d [dosage for prednisone], with a tapering-down schedule), for example, as part of a treatment plan when starting other, slow-acting systemic treatments.

8.4.2 | Alitretinoin

The oral vitamin-A derivative (retinoid) alitretinoin is registered for use of treating severe CHE that inadequately responds to treatment with (very) potent topical corticosteroids. Four studies with alitretinoin vs placebo were included in the Cochrane review.\textsuperscript{1} These studies entailed dosages of 10 mg and 30 mg vs placebo and were as such assessed with GRADE. Two RCTs (n = 1210) in people with severe CHE that was refractory to standard treatment, assessed the efficacy of alitretinoin 30 mg vs placebo (both arms could use emollients). The main outcomes were the proportion of participants who achieved good/excellent control of symptoms, defined as reaching clear or almost clear, both assessed by investigators and participants (investigator global assessment/patient global assessment 0 or 1; scale 0-4). Investigators reported achieving good/excellent control of 44.4% on alitretinoin 30 mg and 15.7% on placebo. The participants reported 39.6% achieving good/excellent control on alitretinoin 30 mg vs 14.3% on placebo. Two RCTs on 10 mg alitretinoin vs placebo (n = 781) used the same primary outcomes. Here, investigators reported achieving good/excellent control of 29.3% on alitretinoin 10 mg and 19.4% on placebo. Participants reported 24.8% achieving good/excellent control on alitretinoin 10 mg vs 14.4% on placebo. The reported adverse events (including headache) did not differ between alitretinoin 10 mg and placebo, but the risk of headache increased with alitretinoin 30 mg. A limitation of these four studies might be that the characterization of the type of HE was not stratified, and thus could not show difference in efficacy between, for example, hyperkeratotic and vesicular HE. Post hoc it was shown that alitretinoin was probably more effective in hyperkeratotic types.\textsuperscript{175} This is reflected in the Summary of Product Characteristics (SmPC) of alitretinoin, which states that HE with predominantly hyperkeratotic features is more likely to respond than HE presenting as pompholyx.\textsuperscript{176} Treatment should be stopped if after 3-4 months no adequate effect has been observed.\textsuperscript{175} A regular treatment cycle lasts up to 24 weeks. Re-treatment could be effective in those who had responded well to a first treatment but experienced a relapse afterwards and extending treatment >24 weeks could be beneficial in those who experience improvement without complete healing within the first 24 weeks.\textsuperscript{177,178}

The most common adverse effect was headache.\textsuperscript{177} and alitretinoin is associated with an increase in plasma cholesterol and triglyceride levels, and a decrease in thyroid function parameters; these should be monitored during therapy.\textsuperscript{131} Its safety profile is consistent with other
molecules from the retinoid class. Being a retinoid, allitretinoin is teratogenic and, therefore, pregnancy prevention measures are indicated during treatment, for which local guidelines should be followed.

8.4.3 | Acitretin

Acitretin is registered for psoriasis and not for the treatment of HE and data on its efficacy in HE is limited. One 8-week study was included in the Cochrane systematic review, but not assessed with GRADE.1,179 This single-blind RCT was conducted in 29 patients with hyperkeratotic HE, of which 14 were treated with acitretin 30 mg/d and 15 with placebo. The physician-rated total severity score was composed of the absence/severity of hyperkeratosis, fissuring, scaling, itch, redness, and vesicle count. After 4 weeks there was a 51% reduction of the physician-rated severity score in the acitretin-group vs 9% in placebo. No further effect was observed between 4 and 8 weeks. These results might also be biased since patients with concomitant psoriasis were included. Being a retinoid, acitretin is teratogenic and, therefore, pregnancy prevention measures are indicated during and after treatment, for which local guidelines should be followed.

8.4.4 | Cyclosporine

Cyclosporine is registered in some countries for the use in AD, but not specifically for HE and, thus, off-label in HE of other aetiologies. One small study assessing the efficacy of cyclosporin vs topical betamethasone dipropionate in 34 participants with HE was included in the Cochrane review.1,180 After 6 weeks of treatment, oral cyclosporin 3 mg/kg/d slightly improved investigator-rated control of symptoms and participant-rated control compared to topical betamethasone dipropionate 0.05% (moderate certainty evidence). Because of the design of the study, adverse events were assessed over a period of 36 weeks (maximum 12 weeks of active treatment) and yielded probably no difference in risk of adverse events; dizziness was similar between groups (moderate certainty evidence). In an open-label study, cyclosporine (3 mg/kg/day) achieved a 1-year success rate of 74% in CHE of unspecified severity.181 A recent retrospective study comparing both cyclosporine (3-5 mg/kg/day) and allitretinoin (30 mg/day) for 24 weeks, showed responder rates of 40.9% for cyclosporine and 68.2% for allitretinoin.182

Usage of cyclosporine requires careful monitoring as treatment can be associated with potentially serious adverse events including risk of malignancy, nephrotoxicity, hypertension, and increased risk of infection. If no effect has been observed within 8 weeks, cyclosporine should be discontinued.

8.4.5 | Azathioprine

Azathioprine is not registered for HE but is frequently prescribed off-label for HE. One single-blind RCT including 108 participants, compared treatment with topical clobetasol vs clobetasol plus azathioprine 50 mg/day.183 Although the HECSI was used as an outcome, baseline HECSI scores were not reported. The mean duration of HE was 4.78 years (range 6 months–30 years). This study was included in the Cochrane review but not assessed with GRADE.1 The outcomes reported were the proportion of participants with good/excellent control of symptoms, defined as 75% reduction in signs and symptoms, and change in investigator-rated severity as assessed with HECSI. After 24 weeks, the group with additional azathioprine reported better outcomes. Patient-rated control was achieved in 39.1% in the clobetasol group and 91.1% with added azathioprine. Investigator-rated severity assessed with the HECSI showed a reduction of 11.5 points (64.7%) in the clobetasol group and 22.2 points (91.3%) in the group with added azathioprine. The mean difference was 10.79 points in favour of the group with added azathioprine.

8.4.6 | Methotrexate

Methotrexate (MTX) is not registered for use in HE nor in AD. No RCT on the efficacy of MTX for HE has been conducted, therefore this intervention is not included in the Cochrane review.1 Two retrospective studies on CHE of unreported severity have been published (one in 12 HE patients, one in 42), but their generalization is very limited because of the methodologies and outcomes used.184,185 In the study that included 12 CHE patients treated with MTX, 40% reached clearance or almost clearance after 12 months.184 In the retrospective study, including a drug-survival analysis, 36.8% (47.6% in hyperkeratotic HE, 25.0% in non-hyperkeratotic HE) achieved physician rated ‘good response’ after 3 months respectively.185 In general, the proportion of patients reaching remission or ‘good response’, according to physicians, is limited as is overall drug survival (median 5.2 months).

8.4.7 | Further treatments and research

Dupilumab, a human monoclonal antibody inhibiting interleukin (IL) 4 and IL-13 signalling, is used for the treatment of AD but is not licensed for HE. No RCT on the efficacy of dupilumab for HE has yet been published. Small observational studies and case reports show a favourable response of HE to dupilumab in patients with atopic HE, and possibly in patients with vesicular and hyperkeratotic HE.186–189 In the prospective observational study, which included 47 patients with AD and concomitant HE, a minimal reduction of 75% on the HECSI was achieved by 60%, with a mean HECSI score reduction of 49.2 points after 16 weeks,186 which exceeds the 41 points regarded as the minimally measurable true change in the HECSI.190

Recently, topical treatment with delgocitinib, a novel pan-Janus kinase (JAK) inhibitor, was reported in a randomized, double-blind, phase IIa study (2019).191 In this RCT patients were treated for 8 weeks and indicated delgocitinib to be an efficacious and well-tolerated topical treatment for (unclassified) CHE. As no plateau phase
of efficacy was observed, longer treatment could probably lead to even more improvement.

An individualized approach to treatment of CHE is another focus for future research, as is currently the case for AD. The aetiology, morphology and endotypical features of HE may vary extensively between patients, and, therefore, more knowledge about the response within different subgroups of HE to different types of drugs could optimize treatment. A hypothesis, based on experience and research, could be that hyperkeratotic subtypes may benefit more from retinoids, Th2-subtypes more from Th2-targeted therapies, such as dupilumab and tralokinumab, whereas pan JAK-inhibitors may benefit all types. Yet this requires that research focuses more on robust HE research that takes sub-/endotypes into account, whilst reporting consistently validated and comparable outcomes. Considering the burden of disease of HE in general, and the consequences for patients in daily life particularly, this is justified, warranted, and highly needed.

9 | CONCLUSION

Hand eczema is a very common condition in the general population. Many risk factors have been identified. A subgroup develops CHE that negatively affects HR-QoL and occupational performance. It is important that health care providers rapidly remove possible environmental triggers, educate patients about skin protection and prevention, and initiate adequate anti-inflammatory treatment.

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AUTHOR CONTRIBUTIONS

Jacob Pontoppidan Thyssen: Conceptualization (equal); project administration (equal); supervision (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). Marie Louise Anna Schuttelaar: Methodology (equal); writing – original draft (equal); writing – review and editing (equal). Jose Herman Alfonso: Supervision (equal); writing – original draft (equal). Klaus Ejner Andersen: Project administration (equal); supervision (equal); writing – review and editing (equal). Irena Angelova-Fischer: Writing – original draft (equal); writing – review and editing (equal). Jose H. Alfonso: Conceptualization (equal); project administration (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). Ana M. Giménez-Arnau: Methodology (equal); writing – original draft (equal); writing – review and editing (equal). Margarida Gonçalo: Writing – review and editing (equal). Margarida Gonçalo: Writing – original draft (equal); writing – review and editing (equal). Carsten R. Hamann: Writing – review and editing (equal). Wietske Andrea Chrispeels: Writing – review and editing (equal). Jacob Pontoppidan Thyssen: Writing – review and editing (equal). Marie-Noëlle Crépy: Writing – review and editing (equal). Tove Agner: Conceptualization (equal); project administration (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). Swen Malte John: Writing – review and editing (equal). A.C.M Kunkeler: Writing – review and editing (equal). Suzana Ljubojević Hadžavdić: Writing – review and editing (equal). Sonja Molin: Methodology (equal); writing – original draft (equal); writing – review and editing (equal). rosemary nixon: Writing – review and editing (equal). Jart Ate Franke Oosterhaven: Writing – review and editing (equal). Thomas Rustemeyer: Writing – review and editing (equal). Esther Serra-Baldrich: Writing – review and editing (equal). mili shah: Writing – review and editing (equal). Dagmar Simon: Writing – original draft (equal); writing – review and editing (equal). Christoph Skudlik: Writing – review and editing (equal). Radoslav Spiewak: Writing – review and editing (equal). Skaidra Valiukeviciene: Writing – review and editing (equal). Angelique Nadine Voorberg: Methodology (equal); project administration (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). Elke Weisshaar: Writing – review and editing (equal). Tove Agner: Conceptualization (equal); project administration (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

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REFERENCES


113. Bregnbak D, Johansen JD, Jellesen MS, Zachariae C, Thysen JP. Chromium(VI) release from leather and metals can be detected with a diphenylcarbazide spot test. Contact Dermatitis. 2015;73(5):281-288.


135. van der Heiden J, Agner T, Rustemeyer T, Clemmensen KK. Hyperkeratotic hand eczema compared to other subgroups of hand eczema - a retrospective study with a follow-up questionnaire. Contact Dermatitis. 2018;78(3):216-222.


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