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Guidelines for diagnosis, prevention and treatment of hand eczema

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cod.14035

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Keywords: Guideline; hand eczema;allergic contact dermatitis; irritant contact dermatitis; treatment; prevention

INTRODUCTION AND METHODOLOGY

Scope and Purpose

Overall objective(s) of the guidelines

Eczema located on the hands, hand eczema (HE), is a disabling skin condition, which 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 Guideline aims 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 Guideline specifically targets 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 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 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.

Stakeholder Involvement

The Guideline Development Group (GDG) was established on behalf of the European Society of Contact Dermatitis (ESCD), aiming to include representatives of the target population. The GDG includes representatives from Dermatology, from Occupational and Environmental Medicine and from a Patient Association.

Systematic Review and Grading of the Evidence

The Guidelines are founded on the Cochrane systematic reviews on interventions for HE[1] and on interventions for 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 with 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 with Grading of Recommendations, Assessment, Development and Evaluations (GRADE) (see Table 1).[4] The literature searches were up to April 2018 and January 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 this guideline the searches were updated up to April 2020, and it is clearly stated per intervention how and on which data the evidence was assessed. Further details on the methodology and data synthesis, such as the risks of bias, the GRADE Summary of Findings tables and forest plots, can be found in the Cochrane reviews.[1,2]

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.

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:

- 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

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 7 comments were received. All comments and response from the steering committee is available in the supplementary material.

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, and therefore with no costs for meetings. All participants in the working group filled in a structured form to declare financial or nonfinancial interests. Disclosures are given in supplementary material. Guidelines have been approved by the executive committee of the ESCD October 2021.

Update

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

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 as well as the dermis and exhibits a specific pattern of histological and clinical findings, which vary depending on the stage of the disease .[6] 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 stage of the disease, and include intercellular oedema and spongiosis, acanthosis and parakeratosis in the epidermis, whereas perivascular infiltrate of lymphocytes are observed in the upper dermis, that in turn may migrate into the epidermis.

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

Chronic HE (CHE) refers to an eczematous process that lasts for more than three 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, e.g. palms, interdigital spaces, fingertips. Involvement of a large area at onset of the disease indicates a bad prognosis.[7] According to a consensus based recommendation, HE in this guideline is divided into the aetiological and clinical subtypes given in Table 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.[8] 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 between 19 and 29 years, and decreases with age, while in men the incidence rate increases gradually with age.[8,9] A population-based study from Norway found that the self-reported prevalence of work-related HE was 4.8%.[10] The higher prevalence in women is explained by a difference in distribution of exposure, domestically and occupationally.[8,11–13] 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.[14,15]

Risk factors

Table 4 summarizes the reported risk factors of HE. Environmental factors explain up to 59% of the aetiology of HE.[16] Risk factors often associated with HE include atopic dermatitis (AD) in childhood[17], persistent/severe AD [18,19], 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 humidity [23], as well as being active in certain occupations.[24,25] Risk of developing HE is significantly related to intensity of wet work, among females in particular, and in a dose-dependent manner.[22] Moreover, lifestyle factors, including tobacco smoking, have been reported to influence the prognosis of OHE.[26–32] 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.[32]

It remains unclear whether HE is associated with asthma, rhino-conjunctivitis, elevated specific IgE, a parental history of atopy, body weight, alcohol consumption, educational level, and mental stress.[9,17,18,28,32–35] Loss-of-function mutations in the filaggrin 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.[17,36,37] Recently, filaggrin gene mutations were reported to be associated to incident HE among metal workers apprentices.[38]

Occupational HE

HE has a substantial health economic and socio-medical impact due to considerable occupational, domestic, social and psychological consequences.[39] HE is the most common occupational skin disease with a prevalence up to 40% in high risk occupations [40] 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, workers in metal surface processing.(10, 42) The adoption of common prevention standards recently developed in a European consensus process [40] including aspects relevant for case definition, reporting and surveillance may contribute to better estimates for the occurrence of occupational HE (OHE).

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 multi-centre European study, 28% of HE patients were unfit for work, and disability persisted for longer than 12 weeks in 12% of cases.[45] In population-based studies, approximately 50% of all patients with HE receive treatment for their disease [46], although this was 69% in a Swedish study.[47] Amongst subjects who reported HE within the past 12 months, 67% had consulted a general practitioner and 44% a dermatologist in Denmark.[48] 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 (29 weeks) compared to those with irritant dermatitis (13 weeks) and atopic HE (12 weeks) in Sweden.[47] In a Danish prospective study, 57% of 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 Life (HR-QoL).[49] Furthermore, severe Occupational Hand Eczema (OHE), age 40 years or greater and severe impairment of HR-QoL at baseline predicted long-term sick leave and unemployment.[49]

A cross-sectional multi-centre 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.[50]

A systematic review, comparing cost-of-illness of HE showed that the mean total yearly costs per patient varied between €1,311 and €9,792. Particularly more severe HE and OHE resulted in higher costs.[51] 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.[52]

HE has a negative impact on HR-QoL to the same degree as psoriasis or asthma [53,54]; this negative impact is greater for females than for males [55] with a higher occurrence of depression among women [56], as well as in metropolitan than in non-metropolitan patients.[57] A European multi-centre study found that patients with HE reported significantly higher levels of distress, suicidal ideation, depression and anxiety as compared to controls.[55]

PREVENTION

- **We recommend offering health education and training to individuals in high risk groups like 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 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 a 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 about endogenous and other individual risk factors should also be taken into account. Preventive measures differ between countries depending on the local economical and especially regulatory situation as well as the health care system. Prevention comprises primary, secondary, and tertiary prevention strategies.[58] 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 which (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).

Legal regulations

Legal regulations of exposure to irritants or allergens, e.g. 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 health[59], or on exposures to contact allergens such as chromium in cement and leather, or nickel in jewellery and other personal items[60–63], and methylisothiazolinone in personal hygiene products and cosmetics.[64]

Risk assessment and hierarchy of prevention measures

Carrying out a risk assessment is essential for detecting and subsequently minimizing harmful skin exposures, particularly in workplaces.[40] The STOP principle describes the suggested hierarchy of prevention measures (Table 5). Harmful activities or exposure to hazardous substances should be eliminated or replaced whenever possible. A good example is the replacement of products containing allergens relevant for the individual HE (e.g. protective gloves, emollients or specific products from the workplace, such as metalworking fluids or disinfectants), and 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.[65] 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 allergic contact dermatitis, or natural rubber latex causing contact urticaria and/or protein contact dermatitis.[66,67] Inadequate equipment or failure in usage of adequate equipment may lead to development or worsening of HE and 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 the efficacy [68,69] is limited, and they may only be effective against certain irritants and may sometimes even intensify the irritant skin response.[70–72] 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.[73] 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 no sufficient 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.[74]

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 the individual's motivation and ability to apply appropriate protection measures as well as to foster a feeling of empowerment in terms of taking responsibility for one's own health. This can be achieved by e.g. campaigns, leaflets, or training. In addition, thorough information on how to avoid relevant allergens is crucial in patients with allergic contact dermatitis. To reduce the incidence of HE in occupations at risk, education on adequate skin protection behaviour should be provided as early as possible, preferably during vocational training. Even though there is only scant evidence for the effectiveness of health education in primary prevention of OHE [74], this strategy is supported by a few controlled prospective studies in apprentices.[27,38,69,71–77] Individuals with previous or current AD are particular at risk for development of OHE, however primary information should be given to everyone. On the level of secondary prevention of work-related HE, some interventions based on health education and ready access to personal protective equipment failed to show a clear benefit.[78–82] However, from others we have learned that in particular face-to-face education is an effective secondary prevention strategy in patients with HE [83,84], especially in those working in occupations at risk, including healthcare workers, hairdressers, food handlers, or cleaners.[85–87]. Nevertheless, recent data indicate that health care workers may not benefit from standard information, and may need education on a different level.[82] 'Hands-on' skin protection seminars in adequate skin protection behaviour has in some places become an effective standard procedure in management of individuals with OHE showing good short-term and long-term results regarding decrease of disease severity and continuance of the profession.[88–90] These interventions 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.[84,89] For those in which 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).[91] The TIP is based on a 3-weeks inpatient phase in a specialized centre providing intensified diagnostics and treatment as well as health education and psychological counselling followed by a 3-weeks outpatient phase

allowing the skin barrier to recover before returning to work. The TIP is associated with sustained improvements in terms of disease severity, ability to work, quality of life, and prognosis.[92–94]

Medical history, examinations and diagnostic procedures

- **We recommend a careful history taking with search for personal and occupational exposures along with clinical examination of the hands and the entire skin integument. Consensus-based recommendation (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 irresponsive 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), second round 100% (22/22)).**

The diagnosis of HE is based on medical history, clinical examination, 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 can be found in Fig. 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, duration and course of disease, exacerbations and remissions in relationship to work-related activities, personal and family history of AD, previous and concurrent skin or systemic diseases, regular use of medications and regular 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 care products, wet work as well as current and previous occupational, household and recreational exposure to known contact allergens and irritants.[95,96]

The clinical examination requires inspection of the hands, and when judged relevant, followed by 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.[97] The clinical manifestations of HE show similarities to a broad spectrum of dermatoses of different aetiology that should be excluded (Table 7).[96,98] Genital involvement may occur in allergic

contact dermatitis cases, and here it may be worth asking the patient specifically about such involvement.

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 irresponsive to adequate treatment 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 dermatitis and often with vesicular morphology supporting an aetiology.[25,99]

The indication for patch testing and the spectrum of substances to be tested must be carefully considered in view of patient's history, occupational and private including recreational exposures.[100,101] The ESCD guidelines on epicutaneous patch testing describes in detail how patch testing is practically planned and performed.[102]

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 centres.[102–104].

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 [105] with or without occupational relevance.[105–110] 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 due to its generally good safety profile, sensitivity, specificity, rapidity of performance and low costs. 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.[111] Prick-to prick testing is the method of choice when considering a test with fresh foods of plant or animal origin, given the 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 case 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, approximately 20-minute direct exposure to fish or meat on the finger where protein contact dermatitis occur may lead to wheals and even vesicles and support the diagnosis. If the patient however has had generalised symptoms in the past, the risk of anaphylaxis should always be considered and the test be only performed if emergency medication available. The evaluation of the results of a prick-to-prick test with fresh materials must be done carefully due to 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.

Microbiology tests

The clinical examination may give rise to suspicion of a secondary infection, primarily driven by *Staphylococcus aureus* (*S aureus*), as 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 antibiotic treatment prescription.[112] The possibility of a dermatophyte infection (tinea) should be considered. In particular in unilateral cases of HE, skin scrapings for microscopy and culture or PCR 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.[113]

Skin biopsy examination

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

EXPOSURE ASSESSMENT

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 hand eczema and plays a substantial role in implementation of specific preventive measures. Consensus based statement (first round 100% (12/12), second round 100% (22/22)).**

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 allergic contact dermatitis, protein contact dermatitis and/or irritant contact dermatitis, for determining work-relation and for effective prevention.[102]

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.[114] 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.[114] Often the manufacturer must be contacted to retrieve additional information. 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.[114] These principles are illustrated in Fig. 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; this includes minimum requirements for workplace exposure assessment.[40]

Methods for identification of specific exposures

Contact Allergens

Allergic contact dermatitis can play a significant role in HE, both as a single aetiologic 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 chances of resolution.

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 [115], although spot tests for cobalt and chromium release have also been developed.[116,117] 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.[118] A special advantage of the dimethylglyoxime test is that it can be used to demonstrate deposition of nickel directly on the hands e.g. by employing it before and after work in cases suspected of occupational allergic contact dermatitis to nickel.[119] More advanced methods for measuring skin deposition of nickel, chromium and cobalt have been developed [120,121], but has until now mostly been used in experimental and research settings.

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 allergen. 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.[122,123]

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 [108] and HE. Exposure assessment to proteins is relevant to those in occupations handling food [124], as well as in those in occupations handling insects or animals such as zookeepers [125], experimental animal assistants 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.

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 irritant contact dermatitis and the disease is usually multifactorial.[126] Irritant reactions are nonspecific, meaning that most people exposed to an irritant would react similarly, albeit with varying inflammatory reaction, depending on intensity and duration of exposure, as well as individual skin resistance level. The effects of different irritants can compound; skin damage and 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.[65,127] It is important to quantify exposures to irritants by taking a careful history, including of 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, 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.[128]

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

CLASSIFICATION

- **We recommend the following classification of hand eczema. Consensus based recommendation (first round 100% (12/12), second round 100% (22/22)).**
  - **Aetiological subtypes:** Irritant Contact Dermatitis; Allergic Contact Dermatitis; Protein Contact Dermatitis/Contact Urticaria; Atopic Hand Eczema
  - **Clinical subtypes:** Hyperkeratotic palmar HE; Acute recurrent vesicular HE; Nummular HE; Pulpitis (fingertip eczema)
  - **Mixed forms:** More than one aetiological and clinical subtype may be present

HE is a multifactorial disease with a polymorphic clinical picture.[129–131] 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.[132] Often more than one aetiological factor is found to play a role in the development of the disease, e.g. irritant contact dermatitis is often found together with allergic contact dermatitis and atopic HE.[131] 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 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 additional feature when aetiological factors remain unclear. Some examples of recent classification approaches can be found in previous publications.[25,129,133–135]

Irritant contact dermatitis is an exclusion diagnosis, and it is a prerequisite that other aetiologies, especially allergic contact dermatitis, have been ruled out, and that the patient has been exposed to skin irritants. Combination with other aetiological HE subtypes is frequent.
With respect to allergic contact dermatitis identifying contact allergy does not automatically

explain the cause or the complete cause of HE. A diagnosis of allergic contact dermatitis 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 dorsal location of eczema and sparse palmar involvement.[136,137] HE due to protein contact dermatitis is uncommon, but is diagnosed based on 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.[135] 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 which seems to be stronger than for the other subtypes.[138,139] Acute recurrent vesicular HE (previously called dyshidrotic endogenous eczema or pompholyx) has been described as a separate entity in most proposed classifications [25,129,135], and poses challenges with regards 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 emerge.[140] 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 allergic contact dermatitis. A recent publication has confirmed the role of formaldehyde and formaldehyde releasers in nummular eczema and with its results support patch testing in this patient group.[141] Fingertip eczema is hand eczema localized to the tips of the fingers. Most common underlying aetiology is chronic skin irritation but it can also be seen in the context of atopic dermatitis or allergic contact dermatitis. The term pulpitis sicca is used to describe a subtype of atopic dermatitis with painful fissures on the fingers (and toes) as predominant clinical feature.

Concomitant eczema on the feet may be present in all subtypes of HE, however more often in hyperkeratotic HE and in allergic contact dermatitis; however even in HE categorized as ICD, concomitant eczema on the feet is found in 20% of all cases.[97]

An open question remains why some cases of HE heal after counselling and topical treatment whereas other cases progress into CHE, which may last for many years. Some patients may

even develop hardening phenomenon following irritant exposure.[142] 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.

TREATMENT

A wide range of approaches is available for the management of acute HE and CHE. In the Cochrane review on which this chapter is based) [1], 60 RCTs were identified, with a total of 5469 included 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 four 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 chapter on prevention.

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, acuteness, 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 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.

Topical treatments

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 individualized 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 3 studies on the protective effects of moisturizers in primary prevention of occupational irritant hand dermatitis (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 studies [143,144] and three that were additionally identified [145–147], showed that emollients may reduce severity and itch, and may reduce time to next flare. There is no evidence that supports use of any specific moisturizers in HE.[1,148,149]

However, the guideline working group recommends that emollients be used in HE to maintain and/or improve skin barrier function. The preference of the patient and existing (contact) allergies are important factors for the choice of emollient(s). To optimise 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.

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 maintenance 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 or less) and mostly compared two corticosteroids, or compared the same corticosteroid yet in different vehicles, or with different dosages or application frequency. All showed a reduction in disease severity, although the certainty of the evidence was not assessed with GRADE. Two studies compared a topical corticosteroid versus vehicle or no treatment, and were assessed with GRADE. In a 15 day study, clobetasol foam yielded favourable participant-rated disease control versus vehicle after 15 days, but not in investigator-rated control (both moderate certainty evidence).[150] The only study with a longer duration (36 weeks) assessed, after having reached remission, disease control with mometasone two times per week versus three times per week versus no mometasone.[151] Three times a week mometasone may work slightly better than two times per week (low certainty evidence), but led to slightly more skin atrophy.[151] 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.[152,153] They may cause skin atrophy and interfere with recovery in the long-term[154], although mometasone appears to be moderately potent and with fewer side-effects.[155] Once daily treatment is sufficient and may even be superior to twice daily application.[156] In AD, once daily is reportedly also as effective as twice daily[157–159], but it is at the clinician's discretion to start once or twice daily. The efficacy of systemic treatment with alitretinoin was found to be enhanced with the addition of topical corticosteroids.[160]

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.[161] Intermittent dosing may reduce the risk of skin atrophy, but little evidence supports this.[151] Clinical experience suggests that alternating or combining a topical corticosteroid with a topical calcineurin inhibitor may be considered in order to reduce adverse effects [162], although the long-term safety of this approach is unknown.

Furthermore, it's important to recognize and address topical corticosteroid phobia, which has been mostly studied in AD, since it may interfere with compliance in HE.[163] Pharmacists represent the group with the strongest topical corticosteroid phobia [164] in turn making it important to guide patients during the consultation

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 TCS or when fear of side effects of TCS 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 ones on pimecrolimus (1059 participants), all of rather short duration (≤ 8 weeks).[1] Tacrolimus 0.1% ointment probably improves investigator-rated symptom control measured after three weeks compared to vehicle (14/14 tacrolimus versus 0/14 vehicle).[165] Participant-rated symptoms were not measured. Burning or itching was reported in 4/19 in the tacrolimus group versus 0/14 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.[162] 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 differences in efficacy were 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 easier penetrate on the dorsal aspects, in part resulting in better chance of efficacy.

Physical therapies

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% (12/12), second round 100% (22/22)).**
- **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 ten, one comparative study was assessed with GRADE: narrow-band-UVB versus PUVA.[166] This study showed that there is probably little to no difference in efficacy, but that PUVA may result in more adverse events (9/30 versus 0/30) (both moderate certainty evidence). Oral as well as bath, paint or cream PUVA are used in some countries [167,168] and seem to be similarly effective. UVA1 may also be effective[169,170], 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.[171]

Grenz ray treatment was used in the past, but is considered obsolete due to a possible increased risk of skin cancer.[172–177]

Systemic Treatment

- **We recommend alitretinoin as 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, e.g. when starting systemic treatment with 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 for 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 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)).**
- **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)).**

With the exception of alitretinoin no other systemic treatments are licensed for the treatment of CHE.

Oral corticosteroids

No RCTs on oral corticosteroids in treating HE were found and included in the Cochrane review.[1] In 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), e.g. as part of a treatment plan when starting other, slow-acting systemic treatments.

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 versus placebo were included in the Cochrane review.[1] These studies entailed dosages of 10mg and 30mg versus 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 30mg versus 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 (IGA/PaGA 0 or 1; scale 0-4). Investigators reported achieving good/excellent control of 44.4% on alitretinoin 30mg and 15.7% on placebo. The participants reported 39.6% achieving good/excellent control on alitretinoin 30mg versus 14.3% on placebo. Two RCTs on 10 mg alitretinoin versus 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 versus 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 e.g. hyperkeratotic and vesicular HE. Post-hoc it was shown that alitretinoin was probably more effective in hyperkeratotic types.[178] This is reflected in the SmPC (Summary of product characteristics) of alitretinoin which states that HE with predominantly hyperkeratotic features is more likely to respond than HE presenting as pompholyx.[179] Treatment should be stopped if after 3-4 months no adequate effect has been observed.[178] 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.[180,181]

The most common adverse effect was headache[180], 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.[134] Its safety profile is consistent with other molecules from the retinoid class. Being a retinoid, alitretinoin is teratogenic and therefore pregnancy prevention measures are indicated during treatment, for which local guidelines should be followed.

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.[1,182] This single-blind RCT was conducted in 29 patients with

hyperkeratotic HE, of which 14 were treated with acitretin 30mg/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 four weeks there was a 51% reduction of the physician-rated severity score in the acitretin-group versus 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.

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 versus topical betamethasone dipropionate in 34 participants with HE was included in the Cochrane review.[1,183] After six 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). Due to 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 differences in risk of adverse events; dizziness was similar between groups (moderate certainty evidence). In an open-label study, cyclosporine (3mg/kg/day) achieved a one-year success rate of 74% in CHE of unspecified severity.[184] A recent retrospective study comparing both cyclosporine (3-5 mg/kg/day) and alitretinoin (30mg/day) during 24 weeks, showed responder rates of 40.9% for cyclosporine and 68.2% for alitretinoin.[185]

Usage of cyclosporine requires careful monitoring, since 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.

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 versus clobetasol plus azathioprine 50 mg/day.[186] Although 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.

Methotrexate

Methotrexate (MTX) is not registered for use in HE nor in AD. No RCTs on the efficacy of MTX for HE have 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 generalisation is very limited due to the methodologies and outcomes used.[187,188] In the study that included 12 CHE patients treated with MTX, 40% reached clearance or almost clearance after 12 months.[187] 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.[188] In general, the proportion of patients reaching remission or 'good response' according to physicians is limited, as is the overall drug survival (median 5.2 months).

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 RCTs on the efficacy of dupilumab for HE have been published yet. 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.[189–192] In the prospective, observational study, which included 47 patients with AD and concomitant HE, a minimal reduction of 75% on the Hand Eczema Severity Index (HECSI-75) was achieved by 60%, with a mean HECSI score reduction of 49.2 points after 16 weeks [189], which exceeds the 41 points regarded as the minimally measurable true change in HECSI.[193]

Recently, topical treatment with delgocitinib, a novel pan-Janus kinase (JAK) inhibitor, was reported in a randomized, double-blind, phase IIa study (2019).[194] 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 individualised 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 optimise 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 a dupilumab and tralokinumab, whereas pan JAK-inhibitors may benefit all types. Yet this requires that research focuses more on HE, with research that is robustly carried out, 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.

Conclusion

Hand eczema is a very common condition in the general population. Many risk factors have been identified. A subgroup develops CHE which 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 finally initiate adequate anti-inflammatory treatment.

FIGURES AND TABLES

Fig. 1. A diagnostic work-up for HE

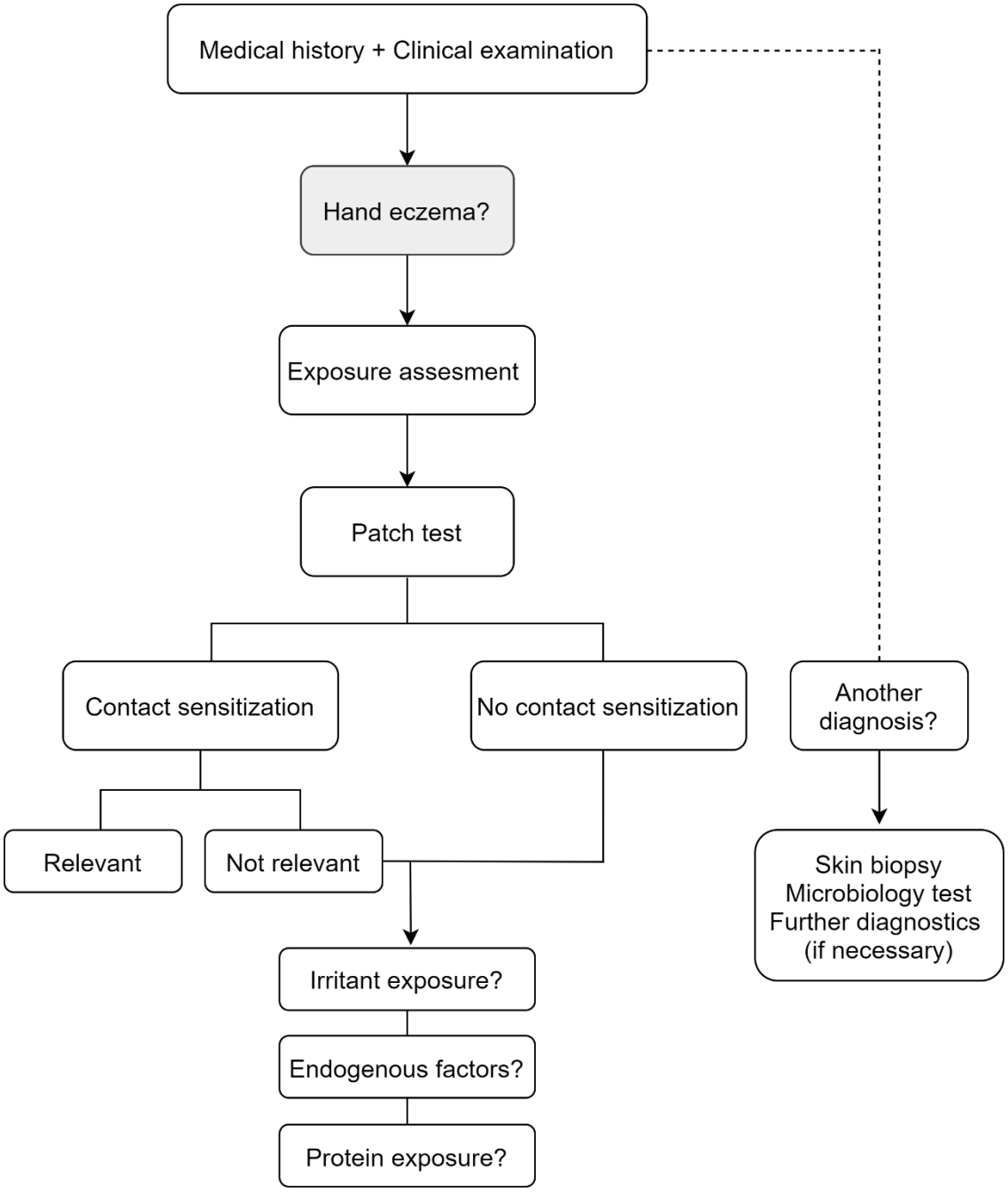

Fig. 2. Main components of exposure assessment

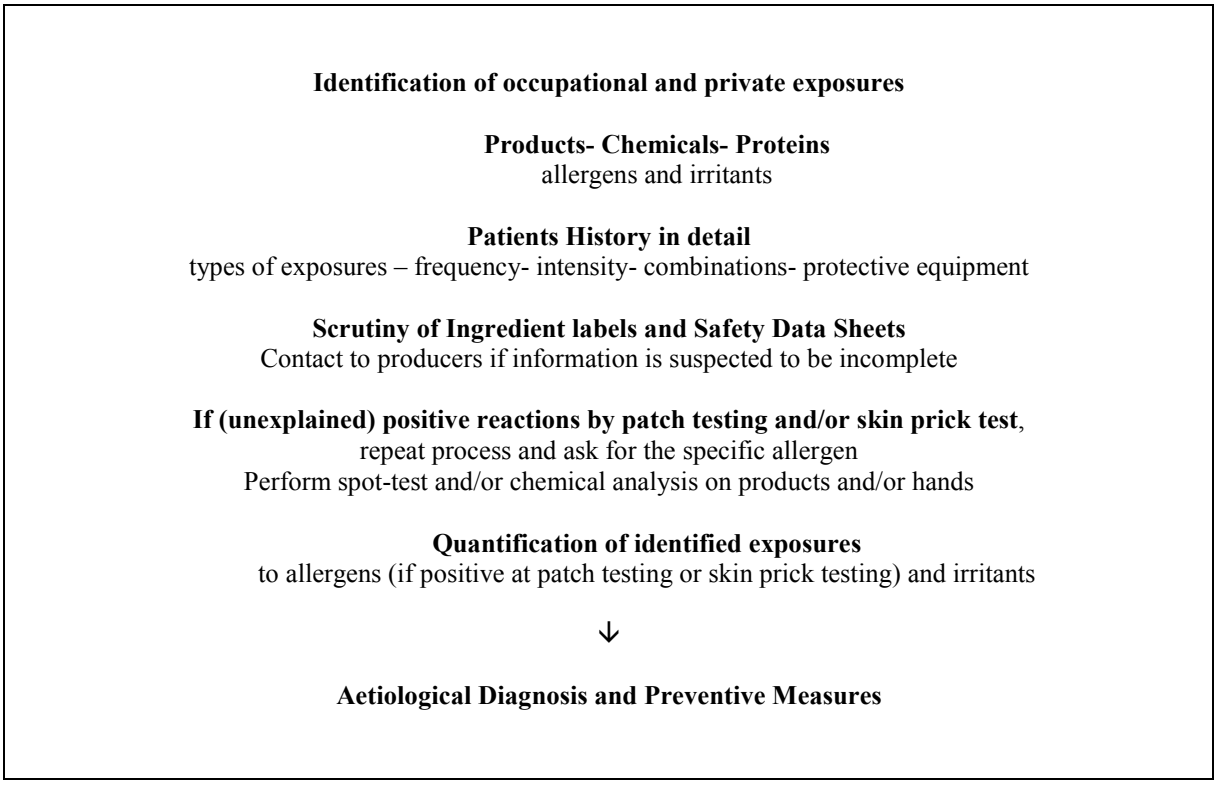

Table 1: Assessment of the strength of evidence

Syntax	Quality/Certainty of evidence
We are very confident that the true effect lies close to that of the estimate of the effect	High
We are moderately confident in the effect estimate	Moderate
Our confidence in the effect is limited/ we have very little confidence in the effect estimate	Low and very low

Table 2: Grades of Recommendation

Syntax	Grade of Recommendation	Symbol
"we recommend", "we do not recommend"	Strong	A
"we suggest", we do not suggest"	Weak	B
"may be considered"	Open	0

Table 3. Classification of HE, including characteristics of subtypes. Not infrequently two or more HE sub-diagnoses are required for HE characterisation, and the sub-diagnoses may change with time (modified from references[25,95,129,133,134]).

	Demographics	Med. history	Most freq. clinical signs & symptoms	Most frequent locations
Aetiological subtypes				
(a) *Irritant contact dermatitis (ICD)	Most frequent form of HE; women > men	Relevant irritant exposure, domestic and/or occupational	Itch and scaling Pain if fissures	Extensor and lateral surfaces of fingers, back of hands
(b) *Allergic contact dermatitis (ACD)	Men > women	Relevant exposure to allergens, positive patch test to culprit allergen(s)	Erythema, often vesicles. Itch. Pain if fissures	Areas of allergen exposure, e.g. finger tips or palms
(c) Atopic hand eczema	Onset at young age	Atopic dermatitis	Often absence of vesicles	Dorsal aspect of hands, palms, often adjacent areas of ventral wrist, interdigital spaces
(d) Protein contact dermatitis/contact urticaria		Relevant exposure to proteins. History of immediate skin reactions	Immediate urticarial rash, then lasting erythema, scaling, infiltration	Initially areas of exposure, may significantly spread beyond afterwards
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

		Relevant exposure to allergens, positive patch test to culprit allergen(s)		
Pulpitis		Relevant irritant exposure Relevant exposure to allergens, positive patch test to culprit allergen(s) Fissures Atopic dermatitis	Little itch. Often atrophic skin. Often pain.	Fingertips

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

Table 4. Risk factors associated with hand eczema based on available evidence and expert consensus

Risk factors	**References**
Atopic dermatitis	15,16*
Low age of onset of hand eczema	20
Filaggrin gene mutations	38
Contact allergy	17,20
Wet work	21,22
Cold/dry weather conditions and decreased indoor humidity	23
Occupation	24,25
Tobacco use	26–32,38
Lower educational level	34
Stress	30

**persistent and severe atopic dermatitis*

Table 5. Hierarchy of preventive measures according to the STOP principle to reduce hazardous exposures

		Measure	**Examples**
1.	S	Substitution/elimination	Elimination of the hazardous exposure by prohibition, omission, or substitution with a safer alternative
2.	T	Technological measures	Automation Encapsulated machines Dust absorbing or ventilation system Splash guard
3.	O	Organizational measures	Equal distribution of hazardous work Regular change between hazardous and non-hazardous tasks Exemption of diseased individuals from hazardous tasks
4.	P	Personal protective equipment	Use of personal protective equipment (e.g. protective gloves)

Table 6. Practical recommendations for use of personal protective equipment and protective behaviour to prevent hand eczema

Protective gloves	**References**
Use protective gloves for wet work and work with hand contact to hazardous substances, both at home and at work.	38,40,77,195–198
When choosing protective gloves, permeation rates and degradation of glove materials must be respected.	199,200
Protective gloves should be intact, clean and dry inside.	38,40,198,201
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.	38,40,77,195,198,201–205
When protective gloves are used for more than 10 minutes, cotton gloves should be worn underneath and regularly changed to reduce occlusive effects.	38,40,198,201
Single use gloves should be worn only once.	40,77,197
Use insulating gloves in the winter or when working in the cold.	38,77,198,206
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.	65,204,207
Wash hands in lukewarm, not hot water.	38,59,198,208
Use of crude brushes and abrasives or even organic solvents to clean the skin should be abandoned.	203
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.	203,205,209
Emollients/barrier creams	
Apply emollients on your hands during the working day but especially after work and before bedtime.	38,69,74,195,198,210,211
It may be reasonable to use a lighter emollients lotion during the day and a greasier, preferably fragrance-free, lipid rich moisturizer before bedtime.	38,77,198
If barrier creams are used, apply them before work and again after hand washing before continuing work.	69,195
Emollients and barrier creams should be applied all over the hands, including the webs, fingertips and dorsal aspects.	38,40,198
General	
Do not wear finger rings or any other jewellery on the hands when performing wet work.	38,77,198

Table 7. Differential diagnoses of HE[94,96,98]

- 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

Table 8. Treatment recommendations for hand eczema

	Standard therapy	**Almost clear HE**	**Moderate HE**	**Severe or very severe HE**
Recommend	• Educational programs and instructions • Emollients • Protective gloves • Avoidance of clinically relevant allergens	• Moderate topical corticosteroids	• Moderate and potent topical corticosteroids	• Moderate and potent topical corticosteroids • Alitretinoin
Suggest		• Tacrolimus ointment	• Photo-therapy • Tacrolimus ointment	• Cyclosporine A[a]
May be considered				• Methotrexate[b] • Azathioprine[b] • Acitretin[b], in hyperkeratotic hand eczema

Severity is based on the photographic guide.[212]

[a]Off-label systemic treatment, except for atopic hand eczema in some countries.

[b]Off-label systemic treatment for hand eczema.

REFERENCES

1. Christoffers WA, Coenraads P-J, Svensson Å, et al. Interventions for hand eczema. *Cochrane Database Syst Rev*. 2019;4:CD004055.
2. Bauer A, Schmitt J, Bennett C, et al. Interventions for preventing occupational irritant hand dermatitis. *Cochrane Database Syst Rev*. 2010;6:CD004414.
3. Higgins JP, Altman DG, Gøtzsche PC, et al. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* Updated March 2011. The Cochrane Collaboration; 2011. Available from www.handbook.cochrane.org.
4. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. *GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations.* Updated October 2013. The GRADE Working Group, 2013. Available from www.guidelinedevelopment.org/handbook.
5. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from www.gradepro.org.
6. Silverberg JI, Thyssen JP, Paller AS, et al. What's in a name? Atopic dermatitis or atopic eczema, but not eczema alone. *Allergy*. 2017;72(12):2026-2030.
7. Meding B, Wrangsjö K, Järvholm B. Hand eczema extent and morphology--association and influence on long-term prognosis. *J Invest Dermatol*. 2007;127(9):2147-2151.
8. Thyssen JP, Johansen JD, Linneberg A, Menné T. The epidemiology of hand eczema in the general population--prevalence and main findings. *Contact Dermatitis*. 2010;62:75-87.
9. Meding B, Järvholm B. Incidence of hand eczema—a population-based retrospective study. *J Invest Dermatol*. 2004;(122):873-877.
10. Vindenes HK, Svanes C, Lygre SH, Hollund B-E, Langhammer A, Bertelsen RJ.

Prevalence of, and work-related risk factors for, hand eczema in a Norwegian general population (The HUNT Study). *Contact Dermatitis*. 2017;77(4):214-223.

11. Mollerup A, Veien NK, Johansen JD. An analysis of gender differences in patients with hand eczema - everyday exposures, severity, and consequences. *Contact Dermatitis*. 2014;71(1):21-30.
12. Anveden Berglind I, Alderling M, Järvholm B, Lidén C, Meding B. Occupational skin exposure to water: a population-based study. *Br J Dermatol*. 2009;160(3):616-621.
13. Meding B, Lindahl G, Alderling M, Wrangsjö K, Anveden Berglind I. Is skin exposure to water mainly occupational or nonoccupational? A population-based study. *Br J Dermatol*. 2013;168(6):1281-1286.
14. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. *Br J Dermatol*. 2001;144(3):523-532.
15. Yngveson M, Svensson A, Johannisson A, Isacsson A. Hand dermatosis in upper secondary school pupils: 2-year comparison and follow-up. *Br J Dermatol*. 2000;142(3):485-489.
16. Lerbaek A, Kyvik KO, Mortensen J, Bryld LE, Menné T, Agner T. Heritability of hand eczema is not explained by comorbidity with atopic dermatitis. *J Invest Dermatol*. 2007;127(7):1632-1640.
17. Heede NG, Thyssen JP, Thuesen BH, Linneberg A, Johansen JD. Predictive factors of self-reported hand eczema in adult Danes: a population-based cohort study with 5-year follow-up. *Br J Dermatol*. 2016;175(2):287-295.
18. Grönhagen C, Lidén C, Wahlgren C-F, et al. Hand eczema and atopic dermatitis in adolescents: a prospective cohort study from the BAMSE project. *Br J Dermatol*.

2015;173(5):1175-1182.

19. Ruff SM, Engebretsen KA, Zachariae C, et al. The association between atopic dermatitis and hand eczema: a systematic review and meta-analysis. *Br J Dermatol*. 2018;178(4):879-888.
20. Meding B, Wrangsjö K, Järvholm B. Fifteen-year follow-up of hand eczema: predictive factors. *J Invest Dermatol*. 2005;124(5):893-897.
21. Carøe TK, Ebbehøj N, Agner T. A survey of exposures related to recognized occupational contact dermatitis in Denmark in 2010. *Contact Dermatitis*. 2014;70(1):56-62.
22. Lund T, Petersen SB, Flachs EM, Ebbehøj NE, Bonde JP, Agner T. Risk of work-related hand eczema in relation to wet work exposure. *Scand J Work Environ Health*. 2020;46(4):437-445.
23. Rycroft RJ, Smith WD. Low humidity occupational dermatoses. *Contact Dermatitis*. 1980;6(7):488-492.
24. Diepgen TL. Occupational skin-disease data in Europe. *Int Arch Occup Environ Health*. 2003;76(5):331-338.
25. Diepgen TL, Andersen KE, Brandao FM, et al. Hand eczema classification: a cross-sectional, multicentre study of the aetiology and morphology of hand eczema. *Br J Dermatol*. 2009;160(2):353-358.
26. Cazzaniga S, Ballmer-Weber BK, Gräni N, et al. Chronic hand eczema: a prospective analysis of the Swiss CARPE registry focusing on factors associated with clinical and quality of life improvement. *Contact Dermatitis*. 2018;79(3):136-148.
27. Lukács J, Schliemann S, Elsner P. Association between smoking and hand dermatitis--a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol*. 2015;29(7):1280-1284.

28. Sørensen JA, Fisker MH, Agner T, Clemmensen KK, Ebbehøj NE. Associations between lifestyle factors and hand eczema severity: are tobacco smoking, obesity and stress significantly linked to eczema severity? *Contact Dermatitis*. 2017;76(3):138-145.

29. Brans R, Skudlik C, Weisshaar E, et al. Association between tobacco smoking and prognosis of occupational hand eczema: a prospective cohort study. *Br J Dermatol*. 2014;171(5):1108-1115.

30. Sørensen JA, Clemmensen KK, Nixon RL, Diepgen TL, Agner T. Tobacco smoking and hand eczema - is there an association? *Contact Dermatitis*. 2015;73(6):326-335.

31. Zimmer KA, Armbrecht ES, Burkemper NM. The association of smoking with contact dermatitis and hand eczema - a review. *Int J Dermatol*. 2018;57(4):375-387.

32. Olesen CM, Agner T, Ebbehøj NE, Carøe TK. Factors influencing prognosis for occupational hand eczema: new trends. *Br J Dermatol*. 2019;181(6):1280-1286.

33. Thyssen JP, Linneberg A, Menné T, Nielsen NH, Johansen JD. The effect of tobacco smoking and alcohol consumption on the prevalence of self-reported hand eczema: a cross-sectional population-based study. *Br J Dermatol*. 2010;162(3):619-626.

34. Anveden Berglind I, Alderling M, Meding B. Life-style factors and hand eczema. *Br J Dermatol*. 2011;165(3):568-575.

35. Hafsia M, Kacem I, El Maalel O, et al. Relationship between hand eczema severity and occupational stress: a cross-sectional study. *Dermatol Res Pract*. 2019;2019:8301896.

36. Heede NG, Thyssen JP, Thuesen BH, Linneberg A, Johansen JD. Anatomical patterns of dermatitis in adult filaggrin mutation carriers. *J Am Acad Dermatol*. 2015;72(3):440-448.

37. Lagrelius M, Wahlgren C-F, Bradley M, et al. Filaggrin gene mutations in relation to contact allergy and hand eczema in adolescence. *Contact Dermatitis*. 2020;82(3):147-152.

38. Reich A, Wilke A, Gediga G, et al. Health education decreases incidence of hand eczema in metal work apprentices: results of a controlled intervention study. *Contact Dermatitis*. 2020;82(6):350-360.

39. Cazzaniga S, Ballmer-Weber BK, Gräni N, et al. Medical, psychological and socio-economic implications of chronic hand eczema: a cross-sectional study. *J Eur Acad Dermatol Venereol*. 2016;30(4):628-637.

40. Alfonso JH, Bauer A, Bensefa-Colas L, et al. Minimum standards on prevention, diagnosis and treatment of occupational and work-related skin diseases in Europe - position paper of the COST Action StanDerm (TD 1206). *J Eur Acad Dermatol Venereol*. 2017;31 Suppl 4:31-43.

41. Dalgard F, Svensson A, Holm JØ, Sundby J. Self-reported skin morbidity in Oslo. Associations with sociodemographic factors among adults in a cross-sectional study. *Br J Dermatol*. 2004;151(2):452-457.

42. Diepgen TL, Maibach H. Occupational skin-care management. *Int Arch Occup Environ Health*. 2003;76(5):323-324.

43. Turner S, Carder M, van Tongeren M, et al. The incidence of occupational skin disease as reported to The Health and Occupation Reporting (THOR) network between 2002 and 2005. *Br J Dermatol*. 2007;157(4):713-722.

44. Dickel H, Kuss O, Blesius CR, Schmidt A, Diepgen TL. Occupational skin diseases in Northern Bavaria between 1990 and 1999: a population-based study. *Br J Dermatol*. 2001;145(3):453-462.

45. Diepgen TL, Elsner P, Fartasch M, et al. Guideline on the management of hand eczema ICD-10 Code: L20. L23. L24. L25. L30. *J Dtsch Dermatol Ges.* 2009;7(Suppl. 3):S1-S16.

46. Lerbaek A, Kyvik KO, Ravn H, Menné T, Agner T. Incidence of hand eczema in a

population-based twin cohort: genetic and environmental risk factors. *Br J Dermatol*. 2007;157(3):552-557.

47. Meding B, Swanbeck G. Predictive factors for hand eczema. *Contact Dermatitis*. 1990;23(3):154-161.
48. Hald M, Berg ND, Elberling J, Johansen JD. Medical consultations in relation to severity of hand eczema in the general population. *Br J Dermatol*. 2008;158(4):773-777.
49. Cvetkovski RS, Zachariae R, Jensen H, Olsen J, Johansen JD, Agner T. Prognosis of occupational hand eczema: a follow-up study. *Arch Dermatol*. 2006;142(3):305-311.
50. Scalone L, Cortesi PA, Mantovani LG, et al. Clinical epidemiology of hand eczema in patients accessing dermatological reference centres: results from Italy. *Br J Dermatol*. 2015;172(1):187-195.
51. Politiek K, Oosterhaven JA, Vermeulen KM, Schuttelaar ML. Systematic review of cost-of-illness studies in hand eczema. *Contact Dermatitis*. 2016;75(2):67-76.
52. Oosterhaven JA, Flach PA, Bültmann U, Schuttelaar ML. Presenteeism in a Dutch hand eczema population—a cross-sectional survey. *Contact Dermatitis*. 2018;79(1):10-19.
53. Cvetkovski RS, Zachariae R, Jensen H, Olsen J, Johansen JD, Agner T. Quality of life and depression in a population of occupational hand eczema patients. *Contact Dermatitis*. 2006;54(2):106-111.
54. Moberg C, Alderling M, Meding B. Hand eczema and quality of life: a population-based study. *Br J Dermatol*. 2009;161(2):397-403.
55. Agner T, Andersen KE, Brandao FM, et al. Hand eczema severity and quality of life: a cross-sectional, multicentre study of hand eczema patients. *Contact Dermatitis*. 2008;59(1):43-47.

56. Marron SE, Tomas-Aragones L, Navarro-Lopez J, et al. The psychosocial burden of hand eczema: data from a European dermatological multicentre study. *Contact Dermatitis*. 2018;78(6):406-412.

57. Nørreslet LB, Agner T, Sørensen JA, Ebbehøj NE, Bonde JP, Fisker MH. Impact of hand eczema on quality of life: metropolitan versus non-metropolitan areas. *Contact Dermatitis*. 2018;78(5):348-354.

58. Diepgen TL. Occupational skin diseases. *J Dtsch Dermatol Ges.* 2012;10(5):295-297.

59. Mahler V, Aalto-Korte K, Alfonso JH, et al. Occupational skin diseases: actual state analysis of patient management pathways in 28 European countries. *J Eur Acad Dermatol Venereol*. 2017;31 Suppl 4:12-30.

60. Ahlström MG, Thyssen JP, Menné T, Johansen JD. Prevalence of nickel allergy in Europe following the EU Nickel Directive - a review. *Contact Dermatitis*. 2017;77(4):193-200.

61. Schnuch A, Schwitulla J. Decrease in nickel allergy in women after the second EU nickel directive. *Contact Dermatitis*. 2013;69(4):253-256.

62. Stocks SJ, McNamee R, Turner S, Carder M, Agius RM. Has European Union legislation to reduce exposure to chromate in cement been effective in reducing the incidence of allergic contact dermatitis attributed to chromate in the UK? *Occup Environ Med*. 2012;69(2):150-152.

63. Alinaghi F, Zachariae C, Thyssen JP, Johansen JD. Temporal changes in chromium allergy in Denmark between 2002 and 2017. *Contact Dermatitis*. 2019;80(3):156-161.

64. Uter W, Aalto-Korte K, Agner T, et al. The epidemic of methylisothiazolinone contact allergy in Europe: follow-up on changing exposures. *J Eur Acad Dermatol Venereol*. 2020;34(2):333-339.

65. Carøe TK, Ebbehøj NE, Bonde JP, Flachs EM, Agner T. Hand eczema and wet work:

dose-response relationship and effect of leaving the profession. *Contact Dermatitis*. 2018;78(5):341-347.

66. Geier J, Lessmann H, Mahler V, Pohrt U, Uter W, Schnuch A. Occupational contact allergy caused by rubber gloves--nothing has changed. *Contact Dermatitis*. 2012;67(3):149-156.

67. Allmers H, Schmengler J, John SM. Decreasing incidence of occupational contact urticaria caused by natural rubber latex allergy in German health care workers. *J Allergy Clin Immunol*. 2004;114(2):347-351.

68. Mostosi C, Simonart T. Effectiveness of Barrier Creams against Irritant Contact Dermatitis. *Dermatology*. 2016;232(3):353-362.

69. Fartasch M, Diepgen TL, Drexler H, Elsner P, John SM, Schliemann S. S1 guideline on occupational skin products: protective creams, skin cleansers, skin care products (ICD 10: L23, L24)--short version. *J Dtsch Dermatol Ges*. 2015;13(6):594-606.

70. Schliemann S, Kleesz P, Elsner P. Protective creams fail to prevent solvent-induced cumulative skin irritation - results of a randomized double-blind study. *Contact Dermatitis*. 2013;69(6):363-371.

71. Frosch PJ, Kurte A. Efficacy of skin barrier creams (IV). The repetitive irritation test (RIT) with a set of 4 standard irritants. *Contact Dermatitis*. 1994;31(3):161-168.

72. Schliemann S, Petri M, Elsner P. Preventing irritant contact dermatitis with protective creams: influence of the application dose. *Contact Dermatitis*. 2014;70(1):19-26.

73. Kütting B, Baumeister T, Weistenhöfer W, Pfahlberg A, Uter W, Drexler H. Effectiveness of skin protection measures in prevention of occupational hand eczema: results of a prospective randomized controlled trial over a follow-up period of 1 year. *Br J Dermatol*. 2010;162(2):362-370.

74. Bauer A, Rönsch H, Elsner P, et al. Interventions for preventing occupational irritant

hand dermatitis. *Cochrane database Syst Rev*. 2018;4:CD004414.

75. Bauer A, Kelterer D, Bartsch R, et al. Skin protection in bakers' apprentices. *Contact Dermatitis*. 2002;46(2):81-85.

76. Bregnhøj A, Menné T, Johansen JD, Søsted H. Prevention of hand eczema among Danish hairdressing apprentices: an intervention study. *Occup Environ Med*. 2012;69(5):310-316.

77. Held E, Wolff C, Gyntelberg F, Agner T. Prevention of work-related skin problems in student auxiliary nurses: an intervention study. *Contact Dermatitis*. 2001;44(5):297-303.

78. van der Meer EW, Boot CR, van der Gulden JW, et al. Hands4U: the effects of a multifaceted implementation strategy on hand eczema prevalence in a healthcare setting. Results of a randomized controlled trial. *Contact Dermatitis*. 2015;72(5):312-324.

79. Soltanipoor M, Kezic S, Sluiter JK, et al. Effectiveness of a skin care programme for the prevention of contact dermatitis in healthcare workers (the Healthy Hands Project): a single-centre, cluster randomized controlled trial. *Contact Dermatitis*. 2019;80(6):365-373.

80. Madan I, Parsons V, Ntani G, et al. A behaviour change package to prevent hand dermatitis in nurses working in health care: the SCIN cluster RCT. *Health Technol Assess*. 2019;23(58):1-92.

81. Fisker MH, Agner T, Sørensen JA, et al. Simple, low-cost group-counselling programme vs treatment as usual for patients with newly notified occupational hand eczema-Exploratory analyses of effects on knowledge, behaviour and personal resources of the randomized PREVEX clinical trial. *Contact Dermatitis*. 2018;79(3):127-135.

82. Fisker MH, Ebbehøj NE, Vejlstrup SG, et al. Prevention of hand eczema: effect of an educational program versus treatment as usual - results of the randomized clinical PREVEX trial. *Scand J Work Environ Health*. 2018;44(2):212-218.

83. Tauber M, Lourari S, Bérard E, et al. Positive change in hand care habits using therapeutic patient education in chronic hand eczema. *Contact Dermatitis*. 2020;82(1):10-17.

84. Mollerup A, Veien NK, Johansen JD. Effectiveness of the Healthy Skin Clinic--a randomized clinical trial of nurse-led patient counselling in hand eczema. *Contact Dermatitis*. 2014;71(4):202-214.

85. Ibler KS, Jemec GB, Diepgen TL, et al. Skin care education and individual counselling versus treatment as usual in healthcare workers with hand eczema: randomised clinical trial. *BMJ*. 2012;345:e7822.

86. Wulfhorst B, Bock M, Gediga G, Skudlik C, Allmers H, John SM. Sustainability of an interdisciplinary secondary prevention program for hairdressers. *Int Arch Occup Environ Health*. 2010;83(2):165-171.

87. Weisshaar E, Radulescu M, Soder S, et al. Secondary individual prevention of occupational skin diseases in health care workers, cleaners and kitchen employees: aims, experiences and descriptive results. *Int Arch Occup Environ Health*. 2007;80(6):477-484.

88. Apfelbacher CJ, Soder S, Diepgen TL, Weisshaar E. The impact of measures for secondary individual prevention of work-related skin diseases in health care workers: 1-year follow-up study. *Contact Dermatitis*. 2009;60(3):144-149.

89. Wilke A, Gediga G, Schlesinger T, John SM, Wulfhorst B. Sustainability of interdisciplinary secondary prevention in patients with occupational hand eczema: a 5-year follow-up survey. *Contact Dermatitis*. 2012;67(4):208-216.

90. Wilke A, Gediga G, Goergens A, et al. Interdisciplinary and multiprofessional outpatient secondary individual prevention of work-related skin diseases in the metalworking industry: 1-year follow-up of a patient cohort. *BMC Dermatol*. 2018;18(1):12.

91. Skudlik C, Weisshaar E, Scheidt R, et al. Multicenter study "medical-occupational rehabilitation procedure skin--optimizing and quality assurance of inpatient-management (ROQ)". *J Dtsch Dermatol Ges.* 2009;7(2):122-126.

92. Brans R, Skudlik C, Weisshaar E, et al. Multicentre cohort study "rehabilitation of occupational skin diseases - optimization and quality assurance of inpatient management (ROQ)": results from a 3-year follow-up. *Contact Dermatitis*. 2016;75(4):205-212.

93. Skudlik C, Weisshaar E, Scheidt R, et al. First results from the multicentre study rehabilitation of occupational skin diseases--optimization and quality assurance of inpatient management (ROQ). *Contact Dermatitis*. 2012;66(3):140-147.

94. Weisshaar E, Skudlik C, Scheidt R, et al. Multicentre study 'rehabilitation of occupational skin diseases -optimization and quality assurance of inpatient management (ROQ)'-results from 12-month follow-up. *Contact Dermatitis*. 2013;68(3):169-174.

95. Agner T, Elsner P. Hand eczema: epidemiology, prognosis and prevention. *J Eur Acad Dermatology Venereol*. 2020;34(S1):4-12.

96. Mahler V. Hand dermatitis – differential diagnoses, diagnostics, and treatment options. *J Dtsch Dermatol Ges.* 2016;14(1):7-22.

97. Agner T, Aalto-Korte K, Andersen KE, et al. Factors associated with combined hand and foot eczema. *J Eur Acad Dermatol Venereol*. 2017;31(5):828-832.

98. Antonov D, Schliemann S, Elsner P. Hand dermatitis: a review of clinical features,

prevention and treatment. *Am J Clin Dermatol*. 2015;16(4):257-270.

99. Cronin E. Clinical patterns of hand eczema in women. *Contact Dermatitis*. 1985;13(3):153-161.

100. Mahler V, Nast A, Bauer A, et al. S3 guidelines: epicutaneous patch testing with contact allergens and drugs - short version, part 1. *J Dtsch Dermatol Ges.* 2019;17(10):1076-1093.

101. Mahler V, Nast A, Bauer A, et al. S3 Guidelines: epicutaneous patch testing with contact allergens and drugs - short version, part 2. *J Dtsch Dermatol Ges.* 2019;17(11):1187-1207.

102. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. *Contact Dermatitis*. 2015. 2015;73(4):195-221.

103. Johansen JD, Bruze M, Andersen KE, et al. The repeated open application test: suggestions for a scale of evaluation. *Contact Dermatitis*. 1998;39(2):95-96.

104. Johansen JD, Frosch PJ, Svedman C, et al. Hydroxyisohexyl 3-cyclohexene carboxaldehyde- known as Lyral: quantitative aspects and risk assessment of an important fragrance allergen. *Contact Dermatitis*. 2003;48(6):310-316.

105. Hjorth N, Roed-Petersen J. Occupational protein contact dermatitis in food handlers. *Contact Dermatitis*. 1976;2(1):28-42.

106. Pesonen M, Koskela K, Aalto-Korte K. Contact urticaria and protein contact dermatitis in the Finnish register of occupational diseases in a period of 12 years. *Contact Dermatitis*. 2020;83(1):1-7.

107. Barbaud A. Mechanism and diagnosis of protein contact dermatitis. *Curr Opin Allergy Clin Immunol*. 2020;20(2):117-121.

108. Barbaud A, Poreaux C, Penven E, Waton J. Occupational protein contact dermatitis.

Eur J Dermatol. 2015;25(6):527-534.

109. Bauer A, Schubert S, Geier J, Mahler V. [Type IV contact allergies in the food processing industry: an update]. *Hautarzt*. 2018;69(6):443-448.

110. Lukács J, Schliemann S, Elsner P. Occupational contact urticaria caused by food - a systematic clinical review. *Contact Dermatitis*. 2016;75(4):195-204.

111. Ansotegui IJ, Melioli G, Canonica GW, et al. IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. *World Allergy Organ J*. 2020;13(2):100080.

112. Haslund P, Bangsgaard N, Jarløv JO, Skov L, Skov R, Agner T. Staphylococcus aureus and hand eczema severity. *Br J Dermatol*. 2009;161(4):772-777.

113. Fatahzadeh M, Schwartz RA. Human herpes simplex virus infections: epidemiology, pathogenesis, symptomatology, diagnosis, and management. *J Am Acad Dermatol*. 2007;57(5):736-737.

114. Friis UF, Menné T, Flyvholm M-A, Bonde JP, Johansen JD. Occupational allergic contact dermatitis diagnosed by a systematic stepwise exposure assessment of allergens in the work environment. *Contact Dermatitis*. 2013;69(3):153-163.

115. Thyssen JP, Skare L, Lundgren L, et al. Sensitivity and specificity of the nickel spot (dimethylglyoxime) test. *Contact Dermatitis*. 2010;62(5):279-288.

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

117. Thyssen JP, Menné T, Johansen JD, et al. A spot test for detection of cobalt release - early experience and findings. *Contact Dermatitis*. 2010;63(2):63-69.

118. Hamann D, Hamann CR, Thyssen JP. The impact of common metal allergens in daily devices. *Curr Opin Allergy Clin Immunol*. 2013;13(5):525-530.

119. Julander A, Skare L, Vahter M, Lidén C. Nickel deposited on the skin-visualization by DMG test. *Contact Dermatitis*. 2011;64(3):151-157.

120. Lidén C, Skare L, Nise G, Vahter M. Deposition of nickel, chromium, and cobalt on the skin in some occupations - assessment by acid wipe sampling. *Contact Dermatitis*. 2008;58(6):347-354.

121. Gawkrodger DJ, McLeod CW, Dobson K. Nickel skin levels in different occupations and an estimate of the threshold for reacting to a single open application of nickel in nickel-allergic subjects. *Br J Dermatol*. 2012;166(1):82-87.

122. Fasth IM, Ulrich NH, Johansen JD. Ten-year trends in contact allergy to formaldehyde and formaldehyde-releasers. *Contact Dermatitis*. 2018;79(5):263-269.

123. Hauksson I, Pontén A, Gruvberger B, Isaksson M, Engfeldt M, Bruze M. Skincare products containing low concentrations of formaldehyde detected by the chromotropic acid method cannot be safely used in formaldehyde-allergic patients. *Br J Dermatol*. 2016;174(2):371-379.

124. Vester L, Thyssen JP, Menné T, Johansen JD. Occupational food-related hand dermatoses seen over a 10-year period. *Contact Dermatitis*. 2012;66(5):264-270.

125. Bregnbak D, Friis UF, Zachariae C, Menné T, Johansen JD. Protein contact dermatitis caused by worms and insects used to feed exotic birds. *Contact Dermatitis*. 2014;70(1):64-66.

126. Slodownik D, Lee A, Nixon R. Irritant contact dermatitis: a review. *Australas J Dermatol*. 2008;49(1):1.

127. Behroozy A, Keegel TG. Wet-work exposure: a main risk factor for occupational hand dermatitis. *Saf Health Work*. 2014;5(4):175-80.

128. Friis UF, Menné T, Schwensen JF, Flyvholm M-A, Bonde JP, Johansen JD. Occupational irritant contact dermatitis diagnosed by analysis of contact irritants and

allergens in the work environment. *Contact Dermatitis*. 2014;71(6):364-370.

129. Agner T, Aalto-Korte K, Andersen KE, et al. Classification of hand eczema. *J Eur Acad Dermatology Venereol*. 2015;29(12):2417-2422.
130. Coenraads PJ. Hand eczema. *N Engl J Med*. 2012;367(19):1829-1837.
131. Molin S. Pathogenese des Handekzems. *Der Hautarzt*. 2019;70(10):755-759.
132. Diepgen TL, Andersen KE, Chosidow O, et al. Guidelines for diagnosis, prevention and treatment of hand eczema. *J Dtsch Dermatol Ges.* 2015;13(1):e1-e22.
133. Molin S, Diepgen TL, Ruzicka T, Prinz JC. Diagnosing chronic hand eczema by an algorithm: a tool for classification in clinical practice. *Clin Exp Dermatol*. 2011;36(6):595-601.
134. Menné T, Johansen JD, Sommerlund M, Veien NK. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis*. 2011;65(1):3-12.
135. Johansen JD, Hald M, Andersen BL, et al. Classification of hand eczema: clinical and aetiological types. Based on the guideline of the Danish Contact Dermatitis Group. *Contact Dermatitis*. 2011;65(1):13-21.
136. Fartasch M, Diepgen TL, Hornstein OP. Are hyperlinear palms and dry skin signs of a concomitant autosomal ichthyosis vulgaris in atopic dermatitis? *Acta Derm Venereol Suppl (Stockh)*. 1989;144:143-145.
137. Simpson EL, Thompson MM, Hanifin JM. Prevalence and morphology of hand eczema in patients with atopic dermatitis. *Dermat Contact, Atopic, Occup Drug*. 2006;17(3):123–127.
138. 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.

139. Politiek K, Loman L, Pas HH, et al. Hyperkeratotic hand eczema: eczema or not? *Contact Dermatitis*. 2020;83(3):196-205.

140. Tauber M, Bérard E, Lourari S, et al. Latent class analysis categorizes chronic hand eczema patients according to skin barrier impairment. *J Eur Acad Dermatol Venereol*. 2020;34(7):1529-1535.

141. Silverberg JI, Hou A, DeKoven JG, et al. Prevalence and trend of allergen sensitization in patients referred for patch testing with a final diagnosis of psoriasis: North American Contact Dermatitis Group data, 2001-2016. *Contact Dermatitis*. Epub 2021 May 19.

142. Watkins SA, Maibach HI. The hardening phenomenon in irritant contact dermatitis: an interpretative update. *Contact Dermatitis*. 2009;60(3):123-130.

143. Kucharekova M, Van De Kerkhof PC, Van Der Valk PG. A randomized comparison of an emollient containing skin-related lipids with a petrolatum-based emollient as adjunct in the treatment of chronic hand dermatitis. *Contact Dermatitis*. 2003;48(6):293-299.

144. ClinicalTrials.gov. Identifier NCT00556855, A 4-week randomized, double-blind, placebocontrolled, right-left comparison study with E-DO® in chronic hand dermatitis [Comparison study with E-DO in chronic hand dermatitis]. Available from https://clinicaltrials.gov/ct2/show/NCT00556855. Accessed September 18, 2020.

145. Berndt U, Wigger-Alberti W, Gabard B, Elsner P. Efficacy of a barrier cream and its vehicle as protective measures against occupational irritant contact dermatitis. *Contact Dermatitis*. 2000;42(2):77-80.

146. McCormick RD, Buchman TL, Maki DG. Double-blind, randomized trial of scheduled use of a novel barrier cream and an oil-containing lotion for protecting the hands of health care workers. *Am J Infect Control*. 2000;28(4):302-310.

147. Lodén M, Wirén K, Smerud K, et al. Treatment with a barrier-strengthening moisturizer prevents relapse of hand-eczema. An open, randomized, prospective,

parallel group study. *Acta Derm Venereol*. 2010;90(6):602-606.

148. Lindh JD, Bradley M. Clinical effectiveness of moisturizers in atopic dermatitis and related disorders: a systematic review. *Am J Clin Dermatol*. 2015;16(5):341-359.

149. Van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen A, Arents BW. Emollients and moisturisers for eczema. *Cochrane database Syst Rev*. 2017;2(2):CD012119.

150. Kircik LH, Eastman WJ, Gwazdauskas J. A randomized, double-blind phase 4 study of the efficacy and safety of ethanol-free clobetasol propionate foam, 0.05%, vs vehicle foam in the treatment of chronic hand dermatitis. *J Drugs Dermatol*. 2013;12(3):328-334.

151. Veien NK, Olholm Larsen P, Thestrup-Pedersen K, Schou G. Long-term, intermittent treatment of chronic hand eczema with mometasone furoate. *Br J Dermatol*. 1999;140(5):882-886.

152. Kao JS, Fluhr JW, Man M-Q, et al. Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: inhibition of epidermal lipid synthesis accounts for functional abnormalities. *J Invest Dermatol*. 2003;120(3):456-464.

153. Del Rosso JQ, Cash K. Topical corticosteroid application and the structural and functional integrity of the epidermal barrier. *J Clin Aesthet Dermatol*. 2013;6(11):20-27.

154. Schoepe S, Schäcke H, May E, Asadullah K. Glucocorticoid therapy-induced skin atrophy. *Exp Dermatol*. 2006;15(6):406-420.

155. Spada F, Barnes TM, Greive KA. Comparative safety and efficacy of topical mometasone furoate with other topical corticosteroids. *Australas J Dermatol*. 2018;59(3):e168-e174.

156. Lodén M, Wirén K, Smerud KT, et al. The effect of a corticosteroid cream and a

barrier-strengthening moisturizer in hand eczema. A double-blind, randomized, prospective, parallel group clinical trial. *J Eur Acad Dermatol Venereol*. 2012;26(5):597-601.

157. Green C, Colquitt JL, Kirby J, Davidson P. Topical corticosteroids for atopic eczema: clinical and cost effectiveness of once-daily vs. more frequent use. *Br J Dermatol*. 2005;152(1):130-141.
158. Lagos BR, Maibach HI. Frequency of application of topical corticosteroids: an overview. *Br J Dermatol*. 1998;139(5):763-766.
159. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess*. 2000;4(37):1-191.
160. Cheon DU, Kim JE, Ko JY, Ro YS. Efficacy of alitretinoin depending on the concomitant use of topical corticosteroids in chronic hand eczema patients. *J Dermatol*. 2019;46(11):998-1005.
161. Baeck M, Goossens A. Immediate and delayed allergic hypersensitivity to corticosteroids: practical guidelines. *Contact Dermatitis*. 2012;66(1):38-45.
162. Schnopp C, Remling R, Möhrenschlager M, Weigl L, Ring J, Abeck D. Topical tacrolimus (FK506) and mometasone furoate in treatment of dyshidrotic palmar eczema: a randomized, observer-blinded trial. *J Am Acad Dermatol*. 2002;46(1):73-77.
163. Li AW, Yin ES, Antaya RJ. Topical corticosteroid phobia in atopic dermatitis: a systematic review. *JAMA dermatology*. 2017;153(10):1036-1042.
164. Lambrechts L, Gilissen L, Morren M-A. Topical corticosteroid phobia among healthcare professionals using the TOPICOP score. *Acta Derm Venereol*. 2019;99(11):1004-1008.
165. Pacor ML, Di Lorenzo G, Martinelli N, et al. Tacrolimus ointment in nickel sulphate-induced steroid-resistant allergic contact dermatitis. *Allergy asthma Proc*.

2006;27(6):527-531.

166. Brass D, Fouweather T, Stocken DD, et al. An observer-blinded randomized controlled pilot trial comparing localized immersion psoralen–ultraviolet A with localized narrowband ultraviolet B for the treatment of palmar hand eczema. *Br J Dermatol*. 2018;179(1):63-71.

167. Van Coevorden AM, Kamphof WG, Van Sonderen E, Bruynzeel DP, Coenraads PJ. Comparison of oral psoralen-UV-A with a portable tanning unit at home vs hospital-administered bath psoralen-UV-A in patients with chronic hand eczema: An open-label randomized controlled trial of efficacy. *Arch Dermatol*. 2004;140(12):1463-1466.

168. Tzaneva S, Kittler H, Thallinger C, Hönigsmann H, Tanew A. Oral vs. bath PUVA using 8-methoxypsoralen for chronic palmoplantar eczema. *Photodermatol Photoimmunol Photomed*. 2009;25(2):101-105.

169. Said N, Lim K, Chong W, CTS T. A comparative study of UVA-1 phototherapy versus betamethasone valerate 0.1% cream for chronic vesicular hand eczema. *J Am Acad Dermatol*. 2011;64(2):AB139.

170. Adams S, Bayerl C. Mittel-Dosis-UVA-1- und lokale PUVA-Therapie beim dyshidrosiformen Handekzem - eine prospektive randomisierte Studie. *Aktuelle Derm*. 2007;33:142-145.

171. Nijsten TE, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen+ultraviolet A: a cohort study. *J Invest Dermatol*. 2003;121(2):252-258.

172. Cartwright PH, Rowell NR. Comparison of Grenz rays versus placebo in the treatment of chronic hand eczema. *Br J Dermatol*. 1987;117(1):73-76.

173. Fairris GM, Mack DP, Rowell NR. Superficial X-ray therapy in the treatment of constitutional eczema of the hands. *Br J Dermatol*. 1984;111(4):445-449.

174. Fairris GM, Jones DH, Mack DP, Rowell NR. Conventional superficial X-ray versus Grenz ray therapy in the treatment of constitutional eczema of the hands. *Br J Dermatol*. 1985;112(3):339-341.

175. King CM, Chalmers RJ. A double-blind study of superficial radiotherapy in chronic palmar eczema. *Br J Dermatol*. 1984;111(4):451-454.

176. Lindelöf B, Wrangsjö K, Lidén S. A double-blind study of Grenz ray therapy in chronic eczema of the hands. *Br J Dermatol*. 1987;117(1):77-80.

177. Sheehan-Dare RA, Goodfield MJ, Rowell NR. Topical psoralen photochemotherapy (PUVA) and superficial radiotherapy in the treatment of chronic hand eczema. *Br J Dermatol*. 1989;121(1):65-69.

178. Ruzicka T, Lynde CW, Jemec GB, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol*. 2008;158(4):808-817.

179. SmPC text alitretinoin. https://www.medicines.org.uk/emc/product/10466/smpc. Published 2019. Accessed September 24, 2020.

180. Bissonnette R, Worm M, Gerlach B, et al. Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. *Br J Dermatol*. 2010;162(2):420-426.

181. Lynde C, Cambazard F, Ruzicka T, Sebastian M, Brown TC, Maares J. Extended treatment with oral alitretinoin for patients with chronic hand eczema not fully responding to initial treatment. *Clin Exp Dermatol*. 2012;37(7):712-717.

182. Thestrup-Pedersen K, Andersen KE, Menné T, Veien NK. Treatment of hyperkeratotic dermatitis of the palms (eczema keratoticum) with oral acitretin. A single-blind placebo-controlled study. *Acta Derm Venereol*. 2001;81(5):353-355.

183. Granlund H, Erkko P, Eriksson E, Reitamo S. Comparison of cyclosporine and topical

betamethasone-17,21-dipropionate in the treatment of severe chronic hand eczema. *Acta Derm Venereol*. 1996;76(5):371-376.

184. Granlund H, Erkko P, Reitamo S. Long-term follow-up of eczema patients treated with cyclosporine. *Acta Derm Venereol*. 1998;78(1):40-43.

185. Jang YJ, Yoon JH, Park EJ, Kim KJ, Kim KH. Efficacy and safety of treatment with oral alitretinoin and oral cyclosporine for chronic hand eczema: a retrospective review of 118 cases. *Acta Derm Venereol*. 2020;100(1):adv00043.

186. Agarwal US, Besarwal RK. Topical clobetasol propionate 0.05% cream alone and in combination with azathioprine in patients with chronic hand eczema: an observer blinded randomized comparative trial. *Indian J Dermatol Venereol Leprol*. 2013;79(1):101-103.

187. O'Shea PM, Lugo-Somolinos A. Methotrexate versus acitretin in the treatment of chronic hand dermatitis. *J Drugs Dermatol*. 2015;14(12):1389-1391.

188. Politiek K, van der Schaft J, Christoffers WA, et al. Drug survival of methotrexate treatment in hand eczema patients: results from a retrospective daily practice study. *J Eur Acad Dermatol Venereol*. 2016;30(8):1405-1407.

189. Oosterhaven JA, Voorberg AN, Romeijn GL, de Bruin-Weller MS, Schuttelaar ML. Effect of dupilumab on hand eczema in patients with atopic dermatitis: an observational study. *J Dermatol*. 2019;46(8):680-685.

190. Waldman RA, DeWane ME, Sloan B, Grant-Kels JM, Lu J. Dupilumab for the treatment of dyshidrotic eczema in 15 consecutive patients. *J Am Acad Dermatol*. 2020;82(5):1251-1252.

191. Halling A-S, Zachariae C, Thyssen JP. Severe treatment-resistant acute and recurrent vesicular chronic hand eczema successfully treated with dupilumab. *Contact Dermatitis*. 2020;83(1):37-38.

192. Loman L, Diercks GF, Schuttelaar ML. Three cases of non-atopic hyperkeratotic hand eczema treated with dupilumab. *Contact Dermatitis*. 2021;84(2):124-127.

193. Oosterhaven JA, Schuttelaar ML. Responsiveness and interpretability of the Hand Eczema Severity Index. *Br J Dermatol*. 2020;182(4):932-939.

194. Worm M, Bauer A, Elsner P, Mahler V, Molin S, Nielsen TS. Efficacy and safety of topical delgocitinib in patients with chronic hand eczema: data from a randomized, double-blind, vehicle-controlled phase IIa study. *Br J Dermatol*. 2020;182(5):1103-1110.

195. Uter W, Pfahlberg A, Gefeller O, Schwanitz HJ. Hand dermatitis in a prospectively-followed cohort of hairdressing apprentices: final results of the POSH study. Prevention of occupational skin disease in hairdressers. *Contact Dermatitis*. 1999;41(5):280-286.

196. Geens T, Aerts E, Borguet M, Haufroid V, Godderis L. Exposure of hairdressers to aromatic diamines: an interventional study confirming the protective effect of adequate glove use. *Occup Environ Med*. 2016;73(4):221-228.

197. Agner T, Held E. Skin protection programmes. *Contact Dermatitis*. 2002;47(5):253-256.

198. Kwon S, Campbell LS, Zirwas MJ. Role of protective gloves in the causation and treatment of occupational irritant contact dermatitis. *J Am Acad Dermatol*. 2006;55(5):891-896.

199. Havmose M, Thyssen JP, Zachariae C, Johansen JD. Use of protective gloves by hairdressers: a review of efficacy and potential adverse effects. *Contact Dermatitis*. 2020;83(2):75-82.

200. Ramsing DW, Agner T. Effect of glove occlusion on human skin. (I). short-term experimental exposure. *Contact Dermatitis*. 1996;34(1):1-5.

201. Tiedemann D, Clausen ML, John SM, Angelova-Fischer I, Kezic S, Agner T. Effect of glove occlusion on the skin barrier. *Contact Dermatitis*. 2016;74(1):2-10.

202. Kampf G, Löffler H. Prevention of irritant contact dermatitis among health care workers by using evidence-based hand hygiene practices: a review. *Ind Health*. 2007;45(5):645-652.

203. Ramsing DW, Agner T. Effect of glove occlusion on human skin (II). Long-term experimental exposure. *Contact Dermatitis*. 1996;34(4):258-262.

204. Hamnerius N, Svedman C, Bergendorff O, Björk J, Bruze M, Pontén A. Wet work exposure and hand eczema among healthcare workers: a cross-sectional study. *Br J Dermatol*. 2018;178(2):452-461.

205. Agner T, Serup J. Seasonal variation of skin resistance to irritants. *Br J Dermatol*. 1989;121(3):323-328.

206. Visser MJ, Verberk MM, van Dijk FJ, Bakker JG, Bos JD, Kezic S. Wet work and hand eczema in apprentice nurses; part I of a prospective cohort study. *Contact Dermatitis*. 2014;70(1):44-55.

207. Berardesca E, Vignoli GP, Distante F, Brizzi P, Rabbiosi G. Effects of water temperature on surfactant-induced skin irritation. *Contact Dermatitis*. 1995;32(2):83-87.

208. Löffler H, Kampf G, Schmermund D, Maibach HI. How irritant is alcohol? *Br J Dermatol*. 2007;157(1):74-81.

209. Yokota M, Maibach HI. Moisturizer effect on irritant dermatitis: an overview. *Contact Dermatitis*. 2006;55(2):65-72.

210. Williams C, Wilkinson SM, McShane P, et al. A double-blind, randomized study to assess the effectiveness of different moisturizers in preventing dermatitis induced by hand washing to simulate healthcare use. *Br J Dermatol*. 2010;162(5):1088-1092.

211. Wigger-Alberti W, Maraffio B, Wernli M, Elsner P. Self-application of a protective cream. Pitfalls of occupational skin protection. *Arch Dermatol*. 1997;133(7):861-864.

212. Coenraads PJ, Van Der Walle H, Thestrup-Pedersen K, et al. Construction and validation of a photographic guide for assessing severity of chronic hand dermatitis. *Br J Dermatol*. 2005;152(2):296-301.

Graphical abstract

The Hand Eczema Guideline on diagnosis, prevention and treatment of hand eczema is an update of a previous ESCD guideline, The Guideline Development Group (GDG) was established on behalf of the European Society of Contact Dermatitis (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 one month.