Introduction
Hand eczema: interventions & contact allergies

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A few million years ago, our ancestors decided to start walking on two legs, which made it easier for them to collect food from high branches and to use tools. Moreover, humans standing upright appeared longer and more intimidating. Over the years, the proximal extremities developed for other functions, making it easier to conduct more precise tasks. Nowadays hands are an important part of the human body and play a prominent role in social interaction: they enable us to greet each other, shake hands, and hug or caress each other. Hands appear even in proverbs: “Many hands make light work”, “One hand washes the other” or “The hand that rocks the cradle rules the world”. Hands are indispensable to our daily lives. Therefore, diseases affecting the hands, such as hand eczema, can have a tremendous impact on daily activities and the quality of life.

Hand eczema, also called hand dermatitis, is an inflammatory skin reaction confined to the hands. It often manifests as a chronic and relapsing condition, involving pruritus and painful fissures. Although many patients suspect that allergies play a dominant role in their hand eczema, other factors like exposure to irritants such as water, detergents or oils are just as important.

This thesis discusses the treatment options for patients with hand eczema; it features a Cochrane review regarding interventions for hand eczema and a practical therapeutic plan. We also discuss the relationship between hand eczema and allergic contact dermatitis. Finally, it highlights two relatively unknown contact allergens which can play a role in hand eczema: ascaridole and isobornyl acrylate.

**Epidemiology**

Hand eczema is a common condition. The 1-year prevalence in the general Swedish population was estimated at 4%, though when mild cases were also included the 1-year prevalence was as high as 10%.\(^1\) The incidence was around 5.5 per 1,000 persons. Approximately one third of patients with hand eczema developed symptoms before the age of 20.\(^1\) A Swedish population-based study gave a self-reported 1-year prevalence of hand eczema of 8% (females 10%, males 6%).\(^2\) The highest prevalence was reported among females aged between 19 and 40 years; this seemed to be related to an increased frequency of hand washing, nickel contact allergy and childhood atopic dermatitis.\(^1\) In a cross-sectional study among 1,501 Danish school children (aged 12-16 years), the self-reported life time prevalence for hand eczema was 9.2% and the 1-year prevalence was 7.3%, with a preponderance in girls.\(^3\) Eczema was defined as itching, erythema, vesicles and/or papules and scaling localized to the fingers or finger webs, backs of hands or palms, and with a duration of at least two days. The clinically evaluated point-prevalence in these school children was 3.2%, with a borderline significant sex difference.\(^1\)

The majority of epidemiology studies of hand eczema have been conducted in Scandinavian countries and most are questionnaire based. Due to underestimation of mild cases or
recall bias, questionnaires might underestimate the true prevalence. However, investigating
large cohorts of “healthy” people for the diagnosis of hand eczema is expensive and very
time- and labor consuming. Moreover, a recent study of Danish hairdressers’ apprentices
concluded that self-reporting of hand eczema is a valid method for estimating its prevalence
with good sensitivity and very high specificity. Meding et al. validated the self-reported
1-year prevalence of hand eczema in car mechanics, dentists and office workers, based on
questionnaires, interviews and clinical examinations. Meding also found a high specificity
(96–99%), but a lower sensitivity (53–59%) for the use of a self-reporting questionnaire.
Occupational hand eczema is one of the most frequently recognized occupational skin
diseases. The incidence of notified hand eczema in occupational related cases (and thus
probably more severe cases) is above 0.5-1.9 per 1,000 workers a year. In a large database
of 1,504 Danish cases of occupational contact dermatitis, irritant contact dermatitis
accounted for 70% of all cases; 68% of these were caused by wet work. Occupations that
involve exposure to water, irritants or trauma are especially at risk for developing hand
dermatitis. Cleaners, bakers, hairdressers and caterers are exposed to a lot of wet-work and
are therefore prone to develop hand eczema, but one of the most investigated occupational
risk groups are health care workers. In the Netherlands the self-reported 1-year prevalence
of hand eczema among 1,232 health care workers was 12% (95% confidence interval 11–14)
with a point-prevalence of 4.9% (95% confidence interval 3.8–6.3). Almost half of all
questioned health professionals reported at least one symptom of hand eczema over the
last three months. In this study population 1.7% of workers with hand eczema reported sick
because of hand eczema in the past three months. These results were reproduced in 525
Taiwanese nurses: 75.6% of them reported symptoms of hand eczema, and 31.0% suffered
from self-reported hand eczema. Young age, history of atopic dermatitis, frequent hand
washing (>20 times/day) and wearing gloves longer than 5 minutes a day were risk factors
for hand eczema, while frequent use of hand moisturizer (>3-4 times/day) had a protective
effect. Other employees at risk for developing hand eczema are those at risk of occupational
sensitization because they work with well known allergens. Examples of these are
hairdressers with contact allergies for p-phenylenediamine (PPD), p-toluenediamine (PTD),
and ammonium persulfate; dental workers for (meth)acrylates or line assembly workers for
different allergens in glues or coatings.

Clinical presentation of hand eczema and diagnostic strategy
Hand eczema or hand dermatitis is primarily an inflammatory skin reaction of the hands,
although the feet and other body parts may also be affected. Clinically, the condition is
characterized by erythema, vesicles, papules, edema, scaling, fissures, erosions and/or
hyperkeratosis, signs which may appear at different times. Acute hand eczema often
presents with erythema and vesicles, while in the chronic variants scaling, fissures and
hyperkeratosis are more apparent. Chronic hand eczema is defined as eczema of the hands which lasts for more than three months, or relapses at least twice within 12 months despite adequate treatment. Itch is a common feature and can be very severe, resulting in loss of sleep. Fissures and vesicles can be painful and cause bleeding of the skin. Eczema can also become superimposed with a bacterial infection, resulting in oozing and crusting and, although less likely, with viral infections such as herpes.

A thorough history of the patient’s hand eczema is crucial. The history should focus on exposure to potential irritants and allergens at home, during hobbies and in occupational settings. Frequent exposure to water, detergents, frequent hand washing and the use of occlusive gloves are well known risk factors. The course of the disease should be discussed, including the age of onset and aggravating factors. Improvement of the eczema during holidays or sick leave might point to an occupational dermatitis. A history of atopic dermatitis predisposes for hand eczema. One should discuss a personal and family history of atopic dermatitis, rhino conjunctivitis or asthma. Furthermore, the family history should take into account alternative diagnoses such as psoriasis or hereditary palmoplantar keratodermas.

Dermatological examination of the hands is the main pillar in the diagnostic procedures. One should investigate the different morphological features, the extent of the hand eczema and the localization on the hand. In addition, one should inspect other body sites like the feet to confirm or exclude other diagnoses such as psoriasis or dermatomycosis.

After history taking and dermatological examination, further diagnostics can be issued. Patch tests can be performed to rule out the possibility of an allergic contact dermatitis. This will be discussed in a separate section. Prick-testing and a serum radioallergosorbent (RAST) test to determine an IgE-mediated type I allergy is not routinely recommended, except in the case of protein contact dermatitis and recurrent contact urticaria. Neither is the determination of allergen-specific IgE levels in the routine work-up of a patient with hand eczema, though it can help to establish the atopy status. Laboratory evaluations are required only when systemic therapy is considered.

Histopathological examination of hand eczema lesions is rarely necessary in daily practice, since the diagnosis is based on clinical findings. However, when the hand eczema is refractory to therapy or when other diagnoses need to be excluded one can consider a biopsy. Different stages and morphologies of hand eczema result in different histopathological features. In general, histological biopsies of hand eczema demonstrate dermatitis with spongiosis and varying degrees of acanthosis. Superficial perivascular infiltrate of lymphocytes and histiocytes can be seen. Acute vesicular hand eczema is characterized by intra-epidermal spongiotic vesicles or bullae that do not involve the intra-epidermal portion of the eccrine sweat duct (acrosyringium). Other changes include a sparse, superficial perivascular infiltrate of lymphocytes with some exocytosis.
tomycosis one can perform a periodic acid–Schiff (PAS) staining, particularly if neutrophils are present within the vesicles or stratum corneum. Hyperkeratotic hand eczema consists of chronic spongiotic dermatitis with marked hyperkeratosis, compact orthokeratosis and possible small foci of parakeratosis. Psoriasiform hyperplasia of the epidermis can be present, although the elongation of the rete ridges is usually less regular than in psoriasis. In addition, the amount of spongiosis and the absence of psoriasis spongiform pustules or microabscesses and neutrophils in the epidermis help to distinguish hyperkeratotic hand eczema from psoriasis.22,24

Differential diagnosis
The clinician should consider alternative diagnoses before diagnosing hand eczema. Hand eczema is most frequently confused with psoriasis, dermatomycosis, scabies and lichen planus.
Classic psoriasis consists of erythematous plaques, which are sharply demarcated and especially affect the extensor sites of elbows, knees and scalp, though the palms and knuckles of the hands may be affected as well. Vesicles are absent in psoriasis. A positive family history of psoriasis and the presence of arthritis may help in making the diagnosis. Moreover, the presence of nail pits, without involvement of the nail fold and without itching, are suggestive for psoriasis. However, the distinction between hyperkeratotic palmar eczema and psoriasis can be difficult, and definite cases of hand eczema may over time be labeled as psoriasis and vice versa.
Dermatomycosis (fungal infection, tinea) is a scaling skin condition which mimics hand eczema. Fungal infections should be ruled out, especially when one hand is more prominently affected than the other or when the lesion is more active in the borders. Moreover, the feet, especially the interdigital spaces, or the groin can be affected. Diagnosis in these cases is confirmed by fungal examination of skin surface scrapings.
Scabies is a skin condition caused by mites; it usually presents with small erythematous papules, associated with variable numbers of excoriations; vesicles, indurated nodules, eczematous dermatitis and secondary bacterial infection may also be present. The pathognomonic sign is a burrow, representing the 1-10 mm long tunnel that a female mite excavates to lay eggs. Usually the hands are affected, and often the web-spaces and volar wrist sites, as well as the trunk and limbs. Multiple family members might be affected and (nocturnal) itch can be a prominent future.
Lichen planus is an idiopathic, inflammatory disease which affects the skin and mucosa. Classical lichen planus is characterized by pruritic, sharply demarcated violaceous papules, which mainly affect the extremities. These polygonal papules may be flat and slightly shiny or transparent, with a network of white lines (Wickham’s striae). The papules can develop into plaques and hyperkeratotic lichen rubber planus can resemble hyperkeratotic hand
eczema; well demarcated margins and typical lichen planus lesions may also be present. Examples of other conditions which might resemble hand eczema are granuloma annulare, keratolysis exfoliativa (dyshidrosis lamellosa sicca), adverse drug reactions, keratoderma palmare et plantare or porphyria cutanea tarda, though this list is by far not extensive.26,27

Etiology of hand eczema

The etiology of hand eczema is often unclear. Multiple risk factors may play a role. The most important is probably onset early in life, even if only a single episode. In one third of the patients the disease starts before the age of 20.1 It affects more women than men and its highest incidence is among young women. Another important risk factor is atopic dermatitis, especially a history of childhood atopic dermatitis. In a population-based study, childhood atopic dermatitis was found to be more important than female gender or occupational exposure.28 Between one third and half of hand eczema patients are atopic, which is defined by the World Allergy Organization as: “a personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins.”29 Subjects can develop typical symptoms of asthma, rhino conjunctivitis, or atopic dermatitis. Atopic dermatitis is associated with a worse prognosis for hand eczema; patients with atopic dermatitis, hand eczema and filaggrin null mutations had an earlier onset of the disease and a more persistent form in adulthood.30 Filaggrins are a key component of the epidermal differentiation complex of the stratum corneum. Loss-of-function mutations in the filaggrin gene cause an impaired skin barrier function, which can result in ichthyosis vulgaris and an increased risk of atopic dermatitis. Thyssen et al. demonstrated that filaggrin loss-of-function mutations not only increase the risk of atopic dermatitis and dry skin, but also the risk of fissured hand eczema in subjects without atopic dermatitis.31 Other studies concluded that atopic dermatitis was a major confounder in cases of more severe hand eczema accompanied by mutations within the filaggrin gene,32 but the debate on the role of filaggrin mutations in hand eczema is ongoing. Allergic contact dermatitis seemed to be associated with filaggrin null mutations in the presence of atopic dermatitis.33 Despite the important role of genetic factors in hand eczema, external factors such as exposure to wet work are often involved as well. Lerbaek et al. conducted an epidemiological twin study on hand eczema and concluded that, after correcting for atopic dermatitis, 59% of hand eczema could be attributed to external factors.34 The most common external cause of hand eczema is probably exposure to irritants or toxic agents, such as water and soap, which result in irritant contact dermatitis. Repeated and prolonged exposure to irritants impairs the skin barrier function and results in inflammation. Patients often present with a history of exposure to wet work, contact with soaps, solvents, or prolonged use of occlusive gloves. Patch tests are negative or demonstrate irritant reac-
tions, but a simple diagnostic procedure to establish irritant contact dermatitis in daily clinic does not exist.

Although allergic contact dermatitis is probably less common than irritant contact dermatitis patients often assume that contact allergy is the cause of their hand eczema. Allergic contact dermatitis (ACD) is a delayed-type hypersensitive immune response, also known as Gell and Coombs type IV hypersensitivity. The adaptive T-cell-mediated immune response is one of the key players in allergic contact dermatitis, though the innate immunity also plays a roll. The immune response can be divided into two distinct phases: the sensitization (induction) phase and the elicitation (effector) phase.

The sensitization phase is initiated by contact allergens. Contact allergens (also known as haptens) such as nickel, are natural or synthetic low-molecular-weight chemicals, which are usually lipophilic. Because of these qualities, haptens can easily penetrate the stratum corneum and diffuse into the skin. In the epidermis, haptens react with various intra- or extracellular endogenous proteins such as major histocompatibility complex proteins (MHC), resulting in a hapten-carrier complex. This complex activates Langerhans cells and other dendritic cells in the epidermis. The activated Langerhans cells then migrate in less than 24 hours from the epidermis through the afferent lymphatic vessels to the regional lymph nodes. In the paracortical areas of the draining lymph node the Langerhans cell presents the hapten to naive T-cells. Subsequently, the naive T-cells with matching T-cell receptors are activated by the presence of a specific hapten and start to proliferate. These activated T-cells start to produce IL-2 and other interleukins. After this, specific memory T-cells are formed, which target only the specific hapten. The activated T-cells migrate through the blood and start their surveillance. This sensitization phase requires from three days to several weeks; during this phase patients are usually asymptomatic. The elicitation phase (effector) follows, wherein the allergic contact dermatitis is now established and on each subsequent contact with the hapten, however small, the patient can develop a rash. After hapten penetration of the skin, a hapten-carrier complex comes in contact with memory T-cells in the epidermis, whereupon the T-cell produces pro-inflammatory cytokines. Because of the release of cytokines, more T-cells start to migrate to the contact site and further stimulate the inflammatory response; the result is an eczematous reaction. The skin rash continues to develop and reaches its maximum after 18-48 hours. After elimination of the hapten the rash gradually disappears within a few days. However, since hand eczema is rarely caused by a single hapten, elimination of one hapten does not necessarily cure the hand eczema.

Allergic contact dermatitis is diagnosed by means of an epicutanous patch test. A fixed amount of contact allergen is placed in a patch test chamber and applied to the subject’s upper back for 48 hours. This activates the elicitation phase; if a subject is sensitized to the specific hapten, a skin reaction can be expected. The results of the patch test are read 72
hours after application. An additional reading on day 7 can preempt late reactions. A combination of erythema and infiltration covering the whole patch test area is considered as a positive patch test reaction. The strength of the patch test reaction is scored according to the guidelines of the International Contact Dermatitis Research Group (ICDRG). The reactions are quantified as negative (−), doubtful (±+), weak positive (+), strong positive (++), extremely positive (+++) or irritant (IR).

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Morphology</th>
<th>ICDRG score</th>
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<tbody>
<tr>
<td>−</td>
<td>No reaction</td>
<td>Negative</td>
</tr>
<tr>
<td>±+</td>
<td>Erythema only, no infiltration, or erythema and infiltration not covering the whole area</td>
<td>Doubtful reaction</td>
</tr>
<tr>
<td>+</td>
<td>Erythema, infiltration, possibly discrete papules</td>
<td>Weak positive reaction</td>
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<tr>
<td>++</td>
<td>Erythema, infiltration, papules, vesicles</td>
<td>Strong positive reaction</td>
</tr>
<tr>
<td>+++</td>
<td>Erythema, infiltration, confluent vesicles</td>
<td>Extremely positive reaction</td>
</tr>
<tr>
<td>IR</td>
<td>Different types of reactions (silky skin/ cigarette paper skin, blisters, erosions, pustules, necrosis)</td>
<td>Irritant reaction</td>
</tr>
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Table 1: Scoring of patch test reactions according to ICDRG recommendations

Although patch testing is the gold standard for diagnosing sensitization, its sensitivity and specificity are not optimal. Moreover, its interobserver variation is considerable, even among experts. For these reasons a patch test calibration protocol was developed. This protocol contains a scoring list with standardized criteria. Calibration of the patch test grading system improved the quality of patch testing and thus its diagnostic accuracy. However, since a positive patch test reaction is in itself not necessarily relevant for the current complaints of the patient a repeated open application test (ROAT) with a suspected product can further establish the clinical relevance of the patch test reaction. During a ROAT the product is repeatedly applied to the volar side of the forearm. If a rash develops within two weeks, the ROAT is positive.

Protein contact dermatitis is a rare subtype of allergic contact dermatitis, which can affect workers in the food industry. The initial reaction to proteins is urticarial (contact urticaria), but over time eczema may develop. In this specific subtype of hand eczema determination of IgE levels of specific proteins is of additional value. Therefore prick tests or serum levels should be evaluated.

Classification of hand eczema
The classification of hand eczema is complex. Some physicians even wonder if the term hand eczema is not used for different entities. An accurate diagnosis of hand eczema is,
however, crucial for proper registration of the disease and its clinical course. A uniform
disease classification is also essential for conducting clinical trials. Although the debate on
the classification of hand eczema is ongoing, it can be classified according to its etiology or
morphology or a combination of both. Etiological classifications include:

- Irritant contact dermatitis
- Allergic contact dermatitis
- Atopic hand eczema
- Hybrid hand eczema
- Protein contact dermatitis

Recently, the Danish Contact Dermatitis Group developed another classification for hand
eczema. They applied to every patient one clinical diagnosis and one or more etiological
diagnoses. The following clinical subtypes were distinguished, which included morphologi-

cal features:

- **Chronic fissured hand eczema**: dry eczema, usually with scaling and possibly with
  hyperkeratotic areas and fissures, with a limited number of vesicles on the sides and
  palmar aspects of the fingers or on the palmar aspects of the hands. This morphology is
typically seen in hand eczema that lasts from months to years (Fig. 1a).

- **Recurrent vesicular hand eczema**: recurrent eruptions of vesicles on the palms and/
or on the sides of the fingers, and possibly also on the palmar aspects of the fingers
and around the fingernails. Eruptions may occur at intervals of weeks or months or be
ongoing, mimicking a chronic eczema. The plantar aspects of the feet may be involved.
The history of the patient provides information about the eruptive nature of this type
of hand eczema (Fig. 1b). The recurrent vesicular hand eczema subtype is also called
’dyshidrotic’ hand eczema (although not related to sweat glands) and ‘pompholyx’.

- **Hyperkeratotic palmar eczema**: well demarcated hyperkeratosis on the palms,
  possibly extending to the palmar aspects of the fingers. There may be fissures. This type
of eczema is distinguished from psoriasis by not being inflammatory and by having no
psoriasiform scaling. It does not evolve into psoriasis. There are no accompanying nail
changes. There are no vesicles at any time. This eczema can also be seen on the plantar
aspects of the feet. This type of eczema is most common among middle-aged men (Fig.
1c). It is also called hyperkeratotic-rhagdiform hand eczema.

- **Pulpitis**: hyperkeratotic eczema on the fingertips, possibly with fissures extending under
  the nails, especially on the thumbs and middle fingers, but it may affect all fingers;
  vesicles are occasionally seen (Fig. 1d). This subgroup is also called chronic finger tip
dermatitis.

- **Interdigital eczema**: eczema in the proximal part of the interdigital spaces with
  erythema and scaling. Vesicles are rarely seen (Fig. 1e).
• **Nummular hand eczema**: located on the dorsal aspects of the hands or fingers. The well-circumscribed lesions are characterized by erythema, keratosis, vesicles, and possibly oozing. Nummular eczema can secondarily become infected with *Staphylococcus Aureus* (Fig. 1f).

• **Non-classifiable**: contains the remaining groups of hand eczema, such as apron hand eczema, acute red hand eczema or other unclassifiable groups.

Fig. 1. (a) Chronic fissured hand eczema, (b) Recurrent vesicular hand eczema, (c) Hyperkeratotic palmar eczema, (d) Pulpitis, (e) Interdigital eczema, (f) Nummular hand eczema

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Johansen *et al.* studied this classification in a prospective cohort of 710 Danish hand eczema patients, although they eliminated the ‘interdigital eczema’ and divided the ‘vesicular hand eczema’ into two subgroups: ‘repeated eruptions’ and ‘few eruptions’. Johansen did not identify a simple relationship between the etiology and morphology of hand eczema, but
they did establish some clinical patterns. Irritant contact dermatitis was, for example, most frequently the diagnosis in cases of chronic, dry fissured hand eczema (44.3%), pulpitis (41.7%), and nummular hand eczema (40.9%), whereas allergic contact dermatitis dominated as etiological diagnosis for vesicular types of hand eczema. Hyperkeratotic palmar hand eczema was most frequently diagnosed in older men and showed a trend towards non-specific dermatitis.

Diepgen et al. studied the etiology and morphology of hand eczema and came up with a mixture of etiological and morphological diagnoses: allergic contact dermatitis, irritant contact dermatitis, atopic hand eczema, discoid hand eczema, vesicular hand eczema and hyperkeratotic hand eczema. The majority of patients were diagnosed with either irritant (21.5%) or allergic (15.2%) contact dermatitis or a combination of both (15.2%), while diagnoses of vesicular hand eczema (9.3%) and hyperkeratotic hand eczema (5.3%) were less frequent. The diagnosis of atopic hand eczema was applied especially to younger age groups and in combination with irritant contact dermatitis. However, with this mixed classification system a single hand eczema patient can be diagnosed in different groups; for example an atopic nurse with vesicular hand eczema due to allergic contact dermatitis caused by nickel can be classified as irritant, allergic, atopic and/or vesicular hand eczema. Molin et al. formulated an algorithm for the diagnosis of hand eczema. Based on features such as irritant skin damage, contact allergies, atopy and the involvement of the feet, they defined eight different subtypes of chronic hand eczema. When these were combined with the morphologic type (hyperkeratotic-rhagdiform or dyshidrotic or mixed), certain types of hand eczema seemed to fit a certain morphology. With the use of this algorithm chronic hand eczemas are easy to diagnose, although multiple diagnoses of the same patient remain possible.

Since the Danish guideline clearly distinguishes an etiological and a clinical subtype and the other classification systems face difficulties with overlapping diagnoses, we will use the Danish classification system in this thesis.

**Outcome measurements**

In daily practice, grading the severity of hand eczema helps to assess disease severity and the impact of therapeutic interventions. In clinical studies a severity score is necessary to demonstrate the effectiveness of an intervention and to compare different interventions. Either the patient or the physician can grade the severity of the hand eczema, using various scoring systems. In 2010 Weistenhöfer et al. reviewed the skin scores used for the quantification of hand eczema. A total of 45 different scoring methods were used in 69 studies; for only three of these methods the inter- and/or intra-observer variability were studied. The most extensively studied scoring systems are the Hand Eczema Severity Index (HECSI) and the Osnabrück hand eczema severity index (OHSI).
The Hand Eczema Severity Index (HECSI) assesses the clinical severity of hand eczema; it scores the intensity of six clinical signs (erythema, induration/papules, vesicles, fissures, scaling and oedema) on a scale from 0 to 3 in five different locations on both hands (fingertips, fingers [except the tips], palms, back of hands and wrists), combined with the extent of the affected area. The score ranges from 0 to 360. This objective severity assessment based on clinical symptoms has an excellent inter- and intra-observer reliability and has been used in various studies.\(^{30-52}\)

In the Osnabrück hand eczema severity index (OHSI) the clinical characteristics of six morphological criteria (erythema, infiltration, papules, vesicles, fissures and scaling) are scored in eight different areas (two palmar areas, the backs of both hands, and the dorsal and palmar aspects of the fingers of each hand).\(^{49}\) The extent is assessed by the area of the skin of the hands affected by one or more of the morphological characteristics, which are added up and finally divided by 8. This results in a score between 0 and 18; a score above 7 represents severe hand eczema. The interobserver variability is good, but the intra-observer reliability has not been investigated. The OHSI's validity and responsiveness to changes make it suitable for monitoring the severity of hand eczema and the effects of treatment in a clinical trial.\(^{53}\) The intensity of lesions is, however, not included in the OHSI, contrary to the HECSI. In addition, the HECSI score seems more sensitive to minimal changes. Both scores can be performed on an average of less than three minutes.\(^{54}\) Each of the mentioned scoring systems has its (dis)advantages. Most of them take several minutes, which is too long in everyday clinical practice. In daily practice physicians use less complicated scoring systems such as the Physician Global Assessments (PGA) to determine the overall severity of hand eczema on a scale from 0 to 4 or 5. The current development of easy-to-use tools will also contribute to the ongoing debate as to a feasible scoring system for hand eczema.\(^{55}\)

**Primary prevention**

Adequate education and the use of personal protective equipment like emollients, barrier creams and gloves are widely recommended for people in professions involving skin hazards. A Cochrane review concluded that the protective effects of barrier creams, moisturizers, after work creams, and complex educational interventions had been demonstrated with regard to occupational related irritant hand eczema, but without statistical significance.\(^{56}\) For the protective effect of gloves no randomized controlled trials were identified. Bauer et al. concluded that much larger randomized controlled trials over extended time periods (up to one year) are needed to determine the effectiveness of interventions to prevent occupational irritant hand eczema.\(^{56}\) Education of apprentices in occupations at risk, such as nurses\(^{57}\) and hairdressers\(^{58}\), has been found to be worthwhile, for though adherence to prevention measures diminishes over time, those educated about prevention were less likely to develop hand eczema.
Management
Various treatment regimes and different guidelines have been developed to treat hand eczema.\textsuperscript{15,19,20,59} All guidelines agree on the importance of prevention and education. All guidelines encourage education and the use of emollients. Topical corticosteroids are a next important step; if topical corticosteroids are insufficient one can consider other options like phototherapy or systemic treatment. These treatment options and the evidence supporting their effectiveness are discussed in this thesis.

Implications for daily life
Hands are important organs in communication and expression. Therefore hand eczema has a tremendous impact on a person’s health related quality of life. Hand eczema can cause itching, pain, discomfort, embarrassment and social stigmatization.\textsuperscript{60} The burden of this disease is comparable to that of eczema on the whole body\textsuperscript{61}, psoriasis and asthma.\textsuperscript{62} One explanation for this level of distress is that hand eczema afflicts visible parts of the body; Picardi \textit{et al.} demonstrated that especially female outpatients with lesions in the face or hands were more likely to suffer from psychiatric co-morbidity.\textsuperscript{63} Another explanation is the level of itching and pain suffered, often resulting in sleep deprivation or even in loss of function. The latter can lead to absence from work or even change or loss of occupation. Cvetkovski reported that among 612 cases of severe occupational hand eczema, 22% disclosed that they had in the past year lost their jobs at least once due to their hand eczema.\textsuperscript{64} Especially patients in food-related occupations reported job loss.

In 120 German patients with chronic occupational related hand eczema and threatened with job loss, three-quarters expressed moderate to very severe impairments in their health related quality of life (HRQoL), both their physical and mental health were impaired.\textsuperscript{65} A multicenter study by Agner \textit{et al.} also found that frequent eruptions of eczema and long sick leave contributed negatively to the quality of life.\textsuperscript{66} Although females were often less severely affected with hand eczema, they experienced an impairment in their quality of life comparable to that of severely affected men. One in four women experienced impairment in doing (wet) work in private and occupational settings.\textsuperscript{62} Another factor, which may especially be important for women, was the cosmetic appearance.

Psychiatric co-morbidity is a neglected issue in patients with skin disorders.\textsuperscript{67} Hand eczema can lead to or influence mental disorders; especially female patients with occupation related hand eczema were more likely to have higher anxiety scores, correlating with higher scores for VAS pruritus and sleeplessness.\textsuperscript{65} In addition, 13.5% of the hand eczema patients had a positive depression scale. However, this high depression score was not reproduced by Cvetkovski \textit{et al}, who found a moderate-to-severe depression rate in 9% of patients with newly-diagnosed hand eczema, as compared with the general Danish population.\textsuperscript{68} One
year after diagnosis this number increased only slightly, although 31% of the participants no longer had any signs of hand eczema.

One unexpected complication of hand eczema is the change of the fingerprint or even its complete disappearance (adermatoglyphia). Fingerprints are increasingly used for identification to access buildings, phones, computers or bank accounts and are nowadays registered in the biometric passport. A recent study of Lee et al. demonstrated that 27% of hand eczema patients failed to identify themselves by means of a thumb print, versus 2% of the healthy controls. The main explanations for this were dystrophy due to scaling and abnormal white lines due to fissures and wrinkling. Another hypothesis is that treatment with topical corticosteroids causes loss of fingerprints. Impaired fingerprint recognition leads to less secure forms of identification and might even result in economic loss. One case report described an employee unable to identify himself at work by using a fingerprint. As a result he was unable to clock-in properly, unfairly resulting in absence from work. Another patient with vesicular hand eczema was repeatedly put in detention by the immigration department when travelling to the USA because he was unable to identify himself by his fingerprints. The failure to provide proper fingerprint identification can in the future result in unforeseeable problems in the light of the increasing demand for biometric authentication techniques.

**Prognosis**

After 1 and 5 years following initial presentation at the dermatologist, respectively 41% and 70% of the patients reported improvement. During a 15 year period two-thirds of the patients reported periods of hand eczema and 44% reported hand eczema in the past year. And although after 15 years 74% of the patients reported that the hand eczema was less severe, the disease has a chronic and relapsing course and its prognosis is poor. The mean disease duration is more than 10 years. Unfortunately, patients wait an average of 3 months before consulting a physician. Longer delay is associated with a poorer prognosis, and the more chronic and severe the hand eczema becomes, the more difficult will be the treatment. It is therefore important to start treatment in an early phase.

**Aims of this thesis**

The aims of this thesis are:

- To describe and compare different pharmacological interventions for hand eczema.
- To study the drug survival of cyclosporine for patients with hand eczema in a daily use setting.
- To evaluate the diagnostic value of patch testing in patients with different clinical subtypes of hand eczema.
To investigate whether two relatively unknown chemicals (ascaridole in household and cosmetic products and isobornyl acrylate in an occupational setting) are sensitizers and whether they play a role in hand eczema.

This thesis contains a Cochrane review (chapter 2), which studies different pharmacological interventions for hand eczema. It also includes a review which aims to answer questions a clinician might encounter in daily practice when dealing with hand eczema patients (chapter 3). In addition, we studied the drug survival of cyclosporine which is prescribed off-label to treat hand eczema (chapter 4). Based on this we composed a practical tool to treat clinical subtypes of hand eczema (chapter 10).

The second part of this thesis focuses on allergic contact dermatitis, a well-known cause of hand eczema. We investigated the relationship between different clinical subtypes of hand eczema and sensitization to contact allergens (chapter 5). Finally, the thesis focuses on two relatively unknown contact allergens: isobornyl acrylate (chapter 7) and ascaridole (chapter 8 and 9). Isobornyl acrylate is, as its name implies, an acrylate and (meth)acrylates are a well-known cause of occupational-related hand eczema. Ascaridole is a degradation product of tea tree oil. Tea tree oil can be used as alternative treatment for hand eczema, but is also used in household or cosmetic products. The degradation products of tea tree oil can be sensitizers.
References

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