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Chronic Hand Eczema Guidelines From an Expert Panel of the International Eczema Council

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Background: **Assessment of chronic hand eczema (CHE) is complex and warrants standardization.**

Objective: **We sought to guide clinicians on the assessment of CHE.**

Methods: **An electronic questionnaire regarding the diagnosis and assessment of CHE was completed by councilors (n=45) of the International Eczema Council, an international group of clinicians and researchers with expertise in CHE. The survey consisted of 52 statements for consensus.**

Results: **Overall, nine statements (17.3%) had strong, twenty-three (44.2%) moderate, 12 (23.1%) low, and 8 (15.4%) very low levels of agreement. Five statements had considerable disagreement, including the value of conducting a skin biopsy (62.2% disagreement), investigating for possible type 1 reactions (60.0%), conducting a fungal culture (44.4%), finding no history of relevant allergens and/or irritants (31.1%) in most or all cases, and performing patch testing irrespective of lesion location and morphology (28.9%). Agreement was generally highest among respondents from Europe (28.6–77.8% agreement), followed by Asia (7.1%–35.7% agreement), North America (0%–35.5% agreement), and other (0%–13.3% agreement).**

Conclusions: **There were substantial differences of agreement, suggesting there are many knowledge and/or practice gaps with respect to CHE. Future research is needed to inform evidence-based and/or consensus guidelines for CHE.**

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Chronic hand eczema (CHE) is a chronic inflammatory disease involving eczema of the hands and wrists that persists for 3 or more months or recurs 2 or more times within a 12-month time frame.[1] The condition is heterogeneous and shows variable morphology, typically with more erythema, edema, vesicles, and oozing in the acute phase, as well as erythema, xerosis, scales, lichenification, hyperkeratosis, and fissures in the chronic phase. Chronic hand eczema lesions may be located on the wrists, palms, dorsal hands, and fingers and lead to nail dystrophy. Chronic hand eczema patients may report that certain triggers including skin irritants, proteins, and contact allergens elicit or worsen their disease. They typically experience itch, pain, and burning sensation, which can impede the performance of activities of routine daily living, work, and recreation. Although most CHE patients have a mild to moderate disease,[2] the clinical course is often characterized by recurrent or persistent eczema that may last for many years.[3] Prevalence of CHE is higher in women than in men[4,5] and in persons with a history of atopic dermatitis (AD).[6] Chronic hand eczema can be caused or aggravated by exposures from a variety of different occupations, including industrial and health care workers.[7–9]

The diagnosis and assessment of CHE can be very complex and require a stringent exposure analysis, adequate allergy testing, and detailed patient education.[10] Treatments include emollients, topical corticosteroids, phototherapy, and use of systemic immunosuppressants and retinoids.[10] Various classification systems exist for CHE[11–16] and typically attempt to take into account etiology, morphology, anatomical location, and temporal development. For example, the Danish Contact Dermatitis Group classified hand eczema (HE) into 6 groups: chronic fissured HE, recurrent vesicular HE, hyperkeratotic palmar eczema, pulpitis, interdigital eczema, and nummular HE.[17] However, the clinical relevance of such classifications may be limited, because there was no relationship found between the type and underlying etiology of CHE.[13] In addition, there is no general consensus among dermatologists regarding CHE classification.

As drug development for CHE is increasingly planned and implemented on a global level, it is important to strive for global consensus with respect to classifying and assessing CHE. This article describes the results of a survey among eczema experts who are members of the International Eczema Council (IEC).

METHODS

The International Eczema Council

The IEC (http://www.eczemacouncil.org), founded in 2014, is a global nonprofit organization whose membership consists of 91 eczema experts from 22 countries on 6 continents. All councilors and associates complete an application process in which they are vetted for expertise in the field of eczema, including research track record, and most members also regularly care for CHE patients and do research in this area. All members have broad expertise in AD and CHE. Although the survey was not anonymous, the published results are anonymous as per the a priori research and publication plan.

Survey Development and Administration

An electronic questionnaire was developed by members of the IEC hand eczema task force (JIS, RB, AW, EG-Y). Survey items were extracted using thematic analysis of the CHE guidelines previously developed by the European Society of Contact Dermatitis (ESCD).[1] Each theme was edited for grammar and formatted as a proper sentence. The final survey consisted of 52 statements regarding CHE accompanied by scales ranging from "agree" to "neither agree nor disagree" to "disagree." The survey was sent to the IEC membership between January 24, 2019, and February 20, 2019; 2 reminder e-mails were sent to complete the survey. Study data were collected and managed using Microsoft Excel.

Response data for each question were categorized into level of consensus or agreement with 90% or more selecting "agree" considered as strong, 70% to 89% as moderate, 50% to 69% as low, and less than 50% as very low agreement. In addition, responses for each statement were stratified by continent of respondents (North America, Europe, Asia, others).

RESULTS

Respondent Characteristics

Forty-five (49%) of 91 IEC councilors and associates responded to the survey, with all respondents completing the survey. Respondents were from institutions in Australia (n = 2), Austria (n = 1), Brazil (n = 1), Canada (n = 4), China (n = 1), Denmark (n = 5), France (n = 3), Germany (n = 6), India (n = 1), Israel (n = 2), Italy (n = 2), Japan (n = 1), Korea (n = 2), the Netherlands (n = 1), Singapore (n = 1), United Kingdom (n = 3), and United States (n = 9). The distribution of responses is presented in Table 1. Response rates for councilors and associates were 100% for Australia, China, Denmark, India, Italy, and Singapore; 50% to 99% for Austria, Brazil, Canada, France, Germany, Israel, Korea, and United Kingdom; and less than 50% for Germany, Ireland, Japan, the Netherlands, Poland, Spain, Switzerland, Taiwan, and Tanzania.

Level of Agreement and Disagreement

Nine statements (17.3%) had a strong level of agreement, including the following: allergic HE can have spreading lesions to adjacent and even distant areas from allergen exposure (100%); irritant HE can be secondary to prolonged or repeated exposure to primary irritants and depends on the duration and intensity of exposure to the potentially responsible agent(s) (97.8%); interaction of the epidermis with the outside environment contributes to CHE (97.8%); HE is a polymorphic eruption (95.6%); epidermal barrier defect in AD predisposes to the development of irritant contact dermatitis (ICD, 95.6%); diagnosis of allergic HE is confirmed with a positive patch test reaction (93.3%); atopic HE is defined as HE in a patient with

TABLE 1. Responses and Levels of Agreement for Different Items Related to CHE

			Overall						Agree			
Levels of Agreement	Total Responses	Question Content	Agree		Neither Agree nor Disagree		Disagree		North America	Europe	Asia	Others
Strong (>90% agree)	45	In cases of allergic HE, early lesions appear at the sites of allergen contact, but spreading to adjacent and even distant areas may occur.	45	100.0%	0	0.0%	0	0.0%	28.9%	46.7%	17.8%	6.7%
	45	The interaction of the epidermis with the outside environment includes factors that are chemical or physical, organic or inorganic, allergens, or irritants.	44	97.8%	1	2.2%	0	0.0%	26.7%	46.7%	17.8%	6.7%
	45	Irritant HE develops because of prolonged or repeated exposure to primary irritants and depends on the duration and intensity of exposure to the potentially responsible agent(s).	44	97.8%	0	0.0%	1	2.2%	28.9%	44.4%	17.8%	6.7%
	45	Hand eczema/dermatitis is a polymorphic eruption, which could include macules, papules, vesicles, oozing, crusting, scaling, lichenification, hyperkeratosis, and fissuring.	43	95.6%	1	2.2%	1	2.2%	28.9%	44.4%	15.6%	6.7%
	45	There is an epidermal barrier defect in atopic dermatitis that predisposes to the development of ICD, as evident by the enhanced transepidermal water loss, reduced irritancy threshold, increased percutaneous absorption, and dry appearance of lesional skin.	43	95.6%	2	4.4%	0	0.0%	26.7%	44.4%	17.8%	6.7%
	45	The diagnosis of allergic HE is confirmed when there is a positive patch test reaction to a topical allergen or a cross-reacting allergen, and a relevant–either documented or suspected–current exposure to this allergen.	42	93.3%	2	4.4%	1	2.2%	24.4%	44.4%	17.8%	6.7%
	45	Atopic hand eczema is defined as HE in a patient with a medical history of atopic eczema, previous or current. Irritant exposure and/or relevant contact allergen may coexist with and aggravate atopic eczema.	42	93.3%	2	4.4%	1	2.2%	26.7%	42.2%	17.8%	6.7%
	45	The diagnosis of protein contact dermatitis is based on exposure to proteins (food, latex, and other biological material) and is supported by a positive prick test, or proven specific IgE, to suspected items.	41	91.1%	4	8.9%	0	0.0%	24.4%	42.2%	17.8%	6.7%
	44	Hand eczema can be defined as eczema, localized to the hands and/or wrists.	40	90.9%	2	4.6%	2	4.6%	25.0%	45.5%	13.6%	6.8%
Moderate (70%–89% agree)	45	Hand eczema and hand dermatitis are used as synonyms.	40	88.9%	3	6.7%	2	4.4%	28.9%	40.0%	15.6%	4.4%
	45	Hand eczema is histologically characterized by both epidermal and dermal involvement with histological changes in the epidermis of intercellular edema and spongiosis, acanthosis, and parakeratosis and in the upper dermis of a perivascular infiltrate of lymphocytes that migrate into the epidermis.	40	88.9%	4	8.9%	1	2.2%	24.4%	40.0%	17.8%	6.7%
	45	Allergic HE is caused by a delayed-type reaction (type IV reaction) as an immunological response to contact with an allergen in a sensitized individual.	40	88.9%	3	6.7%	2	4.4%	28.9%	37.8%	15.6%	6.7%
	45	The most frequent triggers of protein contact dermatitis are latex and food allergens.	40	88.9%	5	11.1%	0	0.0%	22.2%	44.4%	15.6%	6.7%
	45	Atopic HE occurs in individuals with previous or current atopic dermatitis.	40	88.9%	4	8.9%	1	2.2%	26.7%	40.0%	15.6%	6.7%

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TABLE 1. *(Continued)*

Levels of Agreement	Total Responses	Question Content	Overall						Agree			
			Agree		Neither Agree nor Disagree		Disagree		North America	Europe	Asia	Others
	45	Mutations of filaggrin, responsible for the formation of the epidermal barrier, are found in increased rates in patients with atopic HE. A possible association between the variant alleles and chronic HE has been studied, but no clear conclusions have been reached except for the already well-established association between atopic dermatitis and HE.	40	88.9%	4	8.9%	1	2.2%	26.7%	40.0%	15.6%	6.7%
	45	An example of a well-defined irritant exposure likely to cause contact dermatitis is wet work: wet hands or wearing of gloves for 2 h, or more than 20 hand washes daily.	39	86.7%	5	11.1%	1	2.2%	24.4%	40.0%	15.6%	6.7%
	45	Clinically pompholyx is by definition characterized by isolated vesicles on the palms of the hands, frequently also affecting the sides of the fingers, and accompanied by erythema of variable intensity and severe pruritus.	39	86.7%	4	8.9%	2	4.4%	22.2%	42.2%	15.6%	6.7%
	45	Histology cannot reliably distinguish between different etiologies of eczema or psoriasis on the hands.	38	84.4%	7	15.6%	0	0.0%	24.4%	37.8%	15.6%	6.7%
	45	ICD may set the scene for the development of ACD.	38	84.4%	6	13.3%	1	2.2%	24.4%	42.2%	11.1%	6.7%
	45	Pompholyx is a type of chronic vesicular HE.	38	84.4%	5	11.1%	2	4.4%	26.7%	35.6%	15.6%	6.7%
	45	A subjective sensation of itching is present in most cases of hand eczema.	37	82.2%	8	17.8%	0	0.0%	22.2%	40.0%	15.6%	4.4%
	45	CHE can be defined as eczema, localized to the hands, that lasts for more than 3 mo.	37	82.2%	6	13.3%	2	4.4%	22.2%	40.0%	13.3%	6.7%
	45	Scaling and fissures are found in most cases of chronic HE.	37	82.2%	6	13.3%	2	4.4%	20.0%	42.2%	13.3%	6.7%
	45	ICD is commonly associated with previous or current atopic dermatitis, which is an important endogenous cofactor that is associated with lower irritant threshold.	37	82.2%	8	17.8%	0	0.0%	26.7%	35.6%	13.3%	6.7%
	45	Protein contact dermatitis is a rare, distinct form of allergic or irritant HE in which IgE-mediated mechanisms or nonimmunological mechanisms give rise to clinical manifestations characterized by an initial urticarial phase, followed by eczema.	37	82.2%	7	15.6%	1	2.2%	26.7%	37.8%	13.3%	4.4%
	45	Exogenous HE is caused by the interaction of the epidermis with the outside environment.	36	80.0%	7	15.6%	2	4.4%	20.0%	37.8%	15.6%	6.7%
	45	Positive patch tests, often related to topical treatments and other components, are commonly found in atopics, and patch testing should be performed in other patients with HE.	36	80.0%	7	15.6%	2	4.4%	17.8%	46.7%	11.1%	4.4%
	44	Combinations of irritant and allergic contact dermatitis cases are common.	35	79.6%	6	13.6%	3	6.8%	25.0%	38.6%	9.1%	6.8%
	45	Relevance of the irritant exposure in irritant HE may be defined as either suspected or proven.	35	77.8%	8	17.8%	2	4.4%	20.0%	35.6%	17.8%	4.4%

	45	Clinical manifestations of irritant and allergic HE may be highly variable, making it impossible to differentiate, clinically or histologically, between the 2, although ACD tends to take a more acute course.	35	77.8%	9	20.0%	1	2.2%	24.4%	37.8%	11.1%	4.4%
	45	In irritant HE, the eczema in most cases remains limited to the sites of exposure and will rarely spread to unexposed skin areas.	34	75.6%	6	13.3%	5	11.1%	17.8%	40.0%	11.1%	6.7%
	45	No sweat gland involvement has been found in pompholyx using histological and electron microscopy studies. Thus, the term *dyshidrotic* is confusing and should be avoided.	34	75.6%	10	22.2%	1	2.2%	15.6%	40.0%	15.6%	4.4%
Low (50%–69% agree)	45	The diagnosis of irritant HE is based on a documented exposure (1) to an irritant that is quantitatively likely to cause contact dermatitis and (2) on the absence of relevant contact allergy (no current exposure to allergens to which the patient has reacted positive in patch test, if any).	31	68.9%	11	24.4%	3	6.7%	17.8%	31.1%	15.6%	4.4%
	45	Contact urticaria/protein contact dermatitis is defined as HE in patients exposed to proteins (food, latex, and other biological material) with a positive prick test, or proven specific IgE, to suspected items. A considerable proportion of patients with contact urticaria will also have atopic symptoms.	31	68.9%	13	28.9%	1	2.2%	20.0%	33.3%	8.9%	6.7%
	45	Pompholyx is defined as recurrent HE with vesicular eruptions. No relevant contact allergy. No documented irritant exposure likely to cause dermatitis.	31	68.9%	8	17.8%	6	13.3%	24.4%	24.4%	15.6%	4.4%
	45	It is difficult to differentiate HE and hand psoriasis.	31	68.9%	10	22.2%	4	8.9%	22.2%	28.9%	11.1%	6.7%
	45	A considerable proportion of patients with contact urticaria have atopic symptoms too.	30	66.7%	15	33.3%	0	0.0%	17.8%	33.3%	8.9%	6.7%
	45	Each episode of pompholyx often lasts a few weeks, resolves with desquamation, and clears completely.	30	66.7%	9	20.0%	6	13.3%	15.6%	33.3%	11.1%	6.7%
	45	CHE is histologically characterized by hyperkeratosis.	29	64.4%	12	26.7%	4	8.9%	15.6%	33.3%	8.9%	6.7%
	45	In cases of endogenous HE, there often is a genetic component.	29	64.4%	15	33.3%	1	2.2%	17.8%	33.3%	8.9%	4.4%
	45	Endogenous HE arises from a constitutional predisposition of the patient, as an exaggerated response to external stimuli, autoantigens, as a result of a defective epidermal barrier, and possibly influenced by emotional factors.	28	62.2%	14	31.1%	3	6.7%	13.3%	26.7%	15.6%	6.7%
	45	Recurrences of pompholyx may be triggered by stress, systemic contact dermatitis, dust mites, or fungus infections elsewhere.	27	60.0%	13	28.9%	5	11.1%	8.9%	33.3%	13.3%	4.4%
	45	A subjective sensation of burning and pain is present in most cases of hand eczema.	25	55.6%	15	33.3%	5	11.1%	8.9%	28.9%	11.1%	6.7%
	45	There is no reliable connection between morphology and etiology of hand eczema.	23	51.1%	16	35.6%	6	13.3%	13.3%	28.9%	6.7%	2.2%
Very low (<50% agree)	45	Patch testing should be performed irrespective of the location or morphology of lesions.	22	48.9%	10	22.2%	13	28.9%	6.7%	35.6%	6.7%	0.0%
	45	Although the term *vesicular HE* can be used for vesicular eruptions of chronic allergic or irritant contact, as well as endogenous vesicular dermatitis, the term *pompholyx* is used only for the endogenous form.	21	46.7%	16	35.6%	8	17.8%	11.1%	22.2%	8.9%	4.4%
	45	Nonimmunological forms of protein contact dermatitis also exist.	20	44.4%	23	51.1%	2	4.4%	13.3%	17.8%	8.9%	4.4%

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TABLE 1. *(Continued)*

Levels of Agreement	Total Responses	Question Content	Overall					Agree			
			Agree	Neither Agree nor Disagree		Disagree		North America	Europe	Asia	Others
	45	Severe and/or widespread lesions at onset of the disease indicate a bad prognosis.	15	33.3%	23	51.1%	7 15.6%	8.9%	11.1%	8.9%	4.4%
	45	No relevant contact allergy and no documented irritant exposure likely to cause dermatitis are present in most cases of HE.	14	31.1%	17	37.8%	14 31.1%	8.9%	8.9%	11.1%	2.2%
	45	There is value in conducting a fungal culture in most patients with HE.	14	31.1%	11	24.4%	20 44.4%	8.9%	17.8%	2.2%	2.2%
	45	All cases of HE should be fully investigated for possible type 1 reactions.	9	20.0%	9	20.0%	27 60.0%	0.0%	15.6%	4.4%	0.0%
	45	There is value in conducting a skin biopsy in most patients with HE.	6	13.3%	11	24.4%	28 62.2%	4.4%	6.7%	2.2%	0.0%

ACD, allergic contact dermatitis; CHE, chronic hand eczema; HE, hand eczema; ICD, irritant contact dermatitis; IgE, immunoglobulin E.

a history of previous or current AD (93.3%); diagnosis of protein contact dermatitis is based on exposure to proteins and is supported by a positive prick test or specific immunoglobulin E to suspected items (91.1%); and hand eczema is localized to the hands and/or wrists (90.9%).

Twenty-three statements (44.2%) had a moderate level of agreement, 12 (23.1%) had a low level of agreement, and 8 (15.4%) had a very low level of agreement. Five statements had a considerable level of disagreement: value of conducting a skin biopsy in most CHE patients (62.2% disagreement), investigation for possible type 1 reactions in all cases of CHE (60.0% disagreement), value in conducting a fungal culture in most CHE patients (44.4%), lack of relevant allergens and/or irritants in most cases of CHE (31.1%), and whether patch testing should be performed irrespective of the location and morphology of lesions (28.9%).

Regional Differences of Agreement

In general, level of agreement across all statements was highest among respondents from Europe (28.6%–77.8% agreement), followed by Asia (7.1%–35.7% agreement), North America (0%–35.5% agreement), and others (0%–13.3% agreement).

DISCUSSION

Among a large international group of clinicians and researchers with expertise in eczema, consensus was achieved for only a small subset of items addressed in the ESCD guidelines for CHE.[1] This finding should be viewed in light of the overall lack of consensus regarding CHE classification and management at a global level.[11–16] Level of agreement was low even among respondents from Europe, but numerically even lower among those from North America and Asia. Some of the disagreement may be due to lack of familiarity with the ESCD guidelines outside of Europe. However, the disagreement likely reflects regional differences in how clinicians perceive CHE and/or how CHE presents clinically. There was a particularly low level of agreement on many key aspects of the diagnosis and investigation of CHE, including the role of skin biopsy, patch testing, testing for type 1 reactions, and fungal cultures. The lack of consensus likely stems from important knowledge and practice gaps in CHE and perhaps from cultural differences and limited experience or education in CHE management, as well as access to diagnostic workup. Furthermore, each of these diagnostic tests may be indicated in individual patients to sort out the heterogeneous etiologies of CHE and its mimics, including irritancy, type 1– and type 4–mediated allergies, and idiopathic inflammation. However, routine performance of all of these diagnostic tests in most CHE patients may be inappropriate and a waste of health care resources. Chronic hand eczema is one of the most common disorders in dermatologic and occupational settings. There are woefully inadequate numbers of patch testers available to patch test most CHE patients. Aside from inadequate access to patch testing, some mild CHE patients may improve with conservative treatment, including gentle skin care,

use of emollients, and minimal topical anti-inflammatory therapy. In such cases, patch testing and other diagnostic testing may be unnecessary. Together, the results underscore the need for further research to fill these gaps.

Some respondents selected "neither agree nor disagree" for various questions. These responses suggest that there is partial agreement. As such, these items might be able to achieve better consensus in future guidelines with minor modifications, whereas items with high levels of disagreement may reflect more fundamental differences of opinion.

Despite having good agreement on the typical histological findings of hand eczema, most disagreed on the value of skin biopsy in CHE. This discrepancy is likely related to the good agreement that histology cannot differentiate between different etiologies of CHE.[18] These results are consistent with a previous report, which pointed out that differentiation between allergic contact dermatitis (ACD), ICD, and AD remains difficult if based solely on histology.[19] Nevertheless, skin biopsy may be helpful in selected cases to rule out other conditions such as tinea, cutaneous T-cell lymphoma, or autoimmune blistering disease.

There was low agreement regarding the lack of relevant allergens and/or irritants in most cases of CHE. The lack of agreement may also stem from the lack of appreciation of the overlap between different forms of CHE, that CHE may be caused or maintained by an unrecognized allergen, and that CHE may chronically persist even after removal of the initial offending irritants/allergens.[20] Clinicians should thoroughly attempt to identify and eliminate exposures to causative allergens, irritants, and proteins in CHE, as this can lead to remission. It is possible that early investigation and prompt elimination of allergen exposure may reduce the persistence of CHE caused by ACD. However, even in patients initially diagnosed with ICD or ACD from specific irritant or allergen exposures, the CHE can persist even after complete avoidance of such exposures. Moreover, a positive patch test to 1 or more allergens by itself does not mean that the CHE is caused by ACD. First, it is imperative to establish clinical relevance of allergens identified by positive patch tests.[21] Moreover, patients with CHE may become sensitized to allergens after the initial development of CHE. Indeed, there was moderate agreement about there commonly being combinations of ICD and ACD and that ICD may set the scene for developing ACD. This has ramifications on both patient education and treatment. The presumptive diagnosis of ICD alone may delay appropriate allergy testing. Moreover, an incorrect diagnosis of ACD or ICD may delay prescription of treatments that are needed to improve the disease and lead to false hope that the CHE can be managed by avoidance of exposures alone. This may delay appropriate treatment with medications that can reduce signs and symptoms.

Pompholyx is a noteworthy type of CHE.[22] There was a moderate to high level of agreement about pompholyx being a chronic vesicular dermatitis and the distribution of lesions on the sides of the fingers. However, there was a low to very low level of agreement about the clinical course, relevant triggers, role of irritant, and/or allergen exposures in pompholyx. It seems that pompholyx is a particular subset of CHE that requires further research and clarification. The use of "pompholyx" has been previously discouraged.[23] In general, the terminology used for chronic vesicular HE varies by clinician and region. Terms, such as *pompholyx* and *dyshidrosis*, are inappropriately used as synonyms for all chronic vesicular hand eczema. However, these terms connote specific etiologies, risk factors, and disease course, which are not relevant to most patients with chronic vesicular HE. It is important that clinicians use the more precise terminology for chronic vesicular HE and consider the full spectrum of etiologies when assessing patients with chronic vesicular HE.

There were mixed levels of agreement about some of the commonly used nomenclature and/or classifications of CHE. Although there was a high level of agreement about using hand eczema and dermatitis synonymously, there was moderate agreement that the term *dyshidrosis* is confusing and should be avoided, similar to a previous report.[23] Furthermore, there was a low level of agreement about when to use the term *pompholyx*. The inconsistent and confusing terminology used in CHE is concerning and may impair patient education and/or lead to the incorrect use of *International Classification of Diseases* (*ICD*) codes. Ironically, there is only one *ICD, 10th Edition*, code for dyshidrosis (pompholyx), but not for any other CHE subtypes. The incorrect use of diagnosis codes may limit epidemiology and health services research of CHE. So far, the *ICD, 11th Edition*, classification does not add further nuances. Most experts agreed that the term *hand eczema* should encompass lesions affecting the hands and/or wrists; only a few did not agree with this definition. Some experts did not agree with the classification of exogenous HE being caused by the interaction of the epidermis with the outside environment. This lack of agreement may stem from the consideration that all CHE is impacted by the outside environment, regardless of the underlying etiology.

This study has several strengths, including use of a comprehensive survey regarding the assessment of CHE response in a global cohort of CHE experts. Limitations include lack of data collection regarding respondent demographics or focus of practice, or reasons for disagreement with guideline statements. We did not assess potential conflicts of interest of respondents, because there were no topics related to any branded diagnostic or therapeutic approaches. We do not believe that the results are biased by any conflicts of interest. Nevertheless, the study demonstrates the lack of consensus, as well as regional variability. Future studies are warranted to better understand how these factors impact perspectives on CHE.

In conclusion, there were numerical differences of agreement for multiple aspects of CHE by continent, suggesting that experience with and perception of CHE vary around the world. Future international studies are needed and planned to determine whether there are regional differences in how CHE presents. Finally, future consensus guidelines for CHE should include expert stakeholders from around the world.

REFERENCES

1. 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.

2. Thyssen JP, Johansen JD, Linneberg A, et al. The epidemiology of hand eczema in the general population—prevalence and main findings. *Contact Dermatitis* 2010;62(2):75–87.
3. Meding B, Wrangsjo K, Jarvholm B. Fifteen-year follow-up of hand eczema: predictive factors. *J Invest Dermatol* 2005;124(5):893–897.
4. Vindenes HK, Svanes C, Lygre SHL, et al. 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.
5. Johannisson A, Ponten A, Svensson A. Prevalence, incidence and predictive factors for hand eczema in young adults—a follow-up study. *BMC Dermatol* 2013;13:14.
6. Ruff SMD, 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.
7. Ibler KS, Jemec GB, Flyvholm MA, et al. Hand eczema: prevalence and risk factors of hand eczema in a population of 2274 healthcare workers. *Contact Dermatitis* 2012;67(4):200–207.
8. Jensen P, Thyssen JP, Johansen JD, et al. Occupational hand eczema caused by nickel and evaluated by quantitative exposure assessment. *Contact Dermatitis* 2011;64(1):32–36.
9. Uter W, Pfahlberg A, Gefeller O, et al. Hand eczema in a prospectively-followed cohort of office-workers. *Contact Dermatitis* 1998;38(2):83–89.
10. Diepgen TL, Andersen KE, Chosidow O, et al. Guidelines for diagnosis, prevention and treatment of hand eczema–short version. *J Dtsch Dermatol Ges* 2015;13(1):77–85.
11. Agner T, Aalto-Korte K, Andersen KE, et al. Classification of hand eczema. *J Eur Acad Dermatol Venereol* 2015;29(12):2417–2422.
12. Molin S, Diepgen TL, Ruzicka T, et al. Diagnosing chronic hand eczema by an algorithm: a tool for classification in clinical practice. *Clin Exp Dermatol* 2011;36(6):595–601.
13. 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.
14. 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.
15. Giwercman C, Lerbaek A, Bisgaard H, et al. Classification of atopic hand eczema and the filaggrin mutations. *Contact Dermatitis* 2008;59(5):257–260.
16. Duarte I, Terumi Nakano J, Lazzarini R. Hand eczema: evaluation of 250 patients. *Am J Contact Dermat* 1998;9(4):216–223.
17. Menne T, Johansen JD, Sommerlund M, et al. Danish Contact Dermatitis Group. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis* 2011;65(1):3–12.
18. Vestergaard L, Clemmensen OJ, Sorensen FB, et al. Histological distinction between early allergic and irritant patch test reactions: follicular spongiosis may be characteristic of early allergic contact dermatitis. *Contact Dermatitis* 1999;41(4):207–210.
19. Frings VG, Boer-Auer A, Breuer K. Histomorphology and immunophenotype of eczematous skin lesions revisited—skin biopsies are not reliable in differentiating allergic contact dermatitis, irritant contact dermatitis, and atopic dermatitis. *Am J Dermatopathol* 2018;40(1):7–16.
20. Thyssen JP, Silverberg JI, Guttman-Yassky E. Chronic hand eczema understanding has ramifications on clinical management. *J Eur Acad Dermatol Venereol* 2020;34(8):e429–e430.
21. 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;73(4):195–221.
22. Veien NK. Acute and recurrent vesicular hand dermatitis. *Dermatol Clin* 2009;27(3):337–353, vii.
23. Storrs FJ. Acute and recurrent vesicular hand dermatitis not pompholyx or dyshidrosis. *Arch Dermatol* 2007;143(12):1578–1580.