Hand dermatitis in adults referred for patch testing: Analysis of North American Contact Dermatitis Group Data, 2000 to 2016

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Background: Hand eczema (HE) is a heterogeneous and burdensome disorder.

Objective: To characterize the clinical characteristics, etiologies and allergen relevance in adults with HE referred for patch testing.

Methods: Retrospective analysis (2000-2016) of North American Contact Dermatitis Group data (n = 37,113).

Results: Overall, 10,034 patients had HE, with differences of overlap between allergic contact, irritant contact, and atopic dermatitis. Allergic contact HE fluctuated, whereas atopic HE steadily increased, and irritant HE decreased over time. HE was associated with higher proportions of positive patch tests (67.5% vs 63.8%; χ^2, $P < .0001$). The five most common clinically relevant allergens were methylisothiazolinone, nickel, formaldehyde, quaternium-15, and fragrance mix I. HE was associated with significantly higher odds of positive patch test reactions and clinical relevance in 13 and 16 of the 25 most common allergens, respectively, including preservatives, metals, topical medications, and rubber accelerators.

Limitations: No data on HE phenotype.

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Funding sources: None.

IRB approval status: Approved by the institutional review board of Northwestern University.

This study was supported by resources and use of facilities at the Minneapolis Veterans Affairs Medical Center. The contents do not represent the views of the U.S. Department of Veterans Affairs or the U.S. Government.

Accepted for publication November 19, 2020.

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Published online November 28, 2020.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.11.054

Conclusion: HE in adults was associated with higher proportions of positive patch tests, with a heterogeneous profile of allergens. Patch testing remains an important tool in the evaluation of patients with HE. (J Am Acad Dermatol 2021;84:989-99.)

Key words: allergic contact dermatitis; arm; atopic dermatitis; contact allergy; eczema; foot; hand; irritant contact dermatitis.

INTRODUCTION

Hand eczema (HE) is a complex and burdensome disorder with heterogeneous morphology and triggers.[1,2] HE is found to be associated with a history of atopic dermatitis (AD)[3,4] and filaggrin gene (*FLG*) mutations.[5,6] In addition, HE is commonly caused by allergic contact dermatitis (ACD) and/or irritant contact dermatitis (ICD). The European Society of Contact Dermatitis guidelines for HE recommend that patch testing be performed regardless of the location and morphology of lesions.[7]

CAPSULE SUMMARY

- Hand eczema in adults was associated with distinct clinical characteristics and higher proportions of positive allergic and clinically relevant patch test reactions, with a heterogeneous profile of allergens.
- Patch testing is an important tool in the evaluation of patients with HE.

Previous studies examined the profile of the most common and relevant allergens for HE in North America and Europe.[8-10] However, the use of potential allergens in personal care product and workplace exposures has evolved considerably over the last decade.[11-13] Yet, little is known about recent trends in North America with respect to the clinical presentation and role of patch testing in HE. This study sought to determine the clinical characteristics and etiologies of HE in a large North American cohort of adults referred for patch testing and determine the frequency of positive patch test allergens, and allergen relevance.

METHODS

North American Contact Dermatitis Group database and data elements

This retrospective study examined de-identified data from adults (age ≥18 years) who were patch tested by the North American Contact Dermatitis Group (NACDG) screening series from 2000 to 2016. Patch testing was conducted per NACDG standards.[12,14-16] Data were entered at a centralized location (Access 2010 and Excel 2019; Microsoft).

Collected data included patient demographics (age, sex, race/ethnicity, occupation), history of atopy (asthma, AD, hay fever), body site(s) of dermatitis (up to 3 coded), and final diagnoses based on clinical history and physical examination (up to 3 coded, 12 diagnoses including ACD, ICD, AD, pompholyx, and/or other). Tested allergens varied by 2-year cycles; not all allergens were tested during every cycle. At the 48-hour and final readings (72-168 hours after application), patch tests were graded as +/- (weak/doubtful/macular erythema), + (mild), ++ (strong), or +++ (very strong) based on degrees of induration, papules, vesicles and/or spreading. A final determination of presumed allergic or not allergic was determined by each investigator based on the temporal pattern (crescendo/decrescendo), patch test appearance, and known characteristics of that allergen. For example, a weak/doubtful (macular erythema) reaction to a formaldehyde-releasing agent could be determined to be an allergic/positive reaction in the setting of multiple or stronger reactions to related formaldehyde-releasing allergens.

Current clinical allergen relevance comprised reactions coded as definite, (a positive patch and/or use test with a skin contactant verified to contain the allergen and suspected to be the source of the allergen), probable (the allergen was verified as present in a known skin contactant of the patient), or possible (the patient was exposed to circumstances in which skin contact with materials likely to contain the allergen were possible).[17] Other relevance categories included past or unknown. Past relevance is considered if the allergen exposure was in the past but not the present.

This study included previously published data on HE from the 2000 to 2004 NACDG cycle (n = 10,061).[8] The study was approved by the institutional review board at Northwestern University.

Hand eczema and HE subsets

The 2 study groups, HE and no HE, were defined based on the presence or absence of hands as 1 of the 3 coded body site(s) of dermatitis, respectively.

Abbreviations used:

ACHE:	allergic contact hand eczema
ACD:	allergic contact dermatitis
AD:	atopic dermatitis
AHE:	atopic hand eczema
HE:	hand eczema
ICD:	irritant contact dermatitis
ICHE:	irritant contact hand eczema
NACDG:	North American Contact Dermatitis Group
SPIN:	significance-prevalence index number

Sensitivity analyses were also performed in the patient subset with hands as the primary site of dermatitis, which excluded patients that had HE as a second or third site of dermatitis. The overlap of HE with dermatitis affecting the arms and/or feet was also examined. The following HE subsets were also examined: allergic contact HE (ACHE: hand eczema and a primary diagnosis of ACD), irritant contact HE (ICHE: hand eczema and a primary diagnosis of ICD), atopic HE (AHE: hand eczema and a primary diagnosis of AD) and pompholyx.

Data analysis

The frequency and proportions of HE and dermatitis affecting hands, arms, and/or feet were estimated. Among HE patients, the frequency and proportion of patients with ACD, ICD, and/or AD were estimated. Venn diagrams were created to present the overlap of the 3 sites of dermatitis and 3 diagnoses in HE patients. Trends in HE and HE subsets over time were assessed by Cochran-Armitage Trend test.

Summary statistics were estimated for the age, race/ethnicity (white/black/Hispanic/Asian/other), sex (male/female), occupation (employed/unemployed), and history of eczema, asthma, or hay fever (yes/no) for the overall cohort and those with or without any HE, primary HE, ACHE, ICHE, and AHE. Multivariable logistic regression models were constructed to examine the associations of all these factors (independent variables) with HE or HE subsets (binary dependent variables). Adjusted odds ratio and 95% confidence intervals (CI) were estimated.

The proportion and number of positive allergic patch tests were compared between those with versus without HE using χ^2 and t tests, respectively. The frequency and proportion of positive allergic patch test and relevant allergic patch test reactions were estimated for those with any HE and primary HE compared with other patch-tested patients without documented HE, and sorted in descending order of most common positive reactions. Multivariable logistic regression models were constructed to determine whether allergic patch test (yes vs no) or relevant allergic patch test reactions (definite/probable/possible vs none; excluding past relevance) to the 25 most common allergens were associated with any or primary HE (yes/no), while adjusting for age, race/ethnicity, sex, and employment. Adjusted odds ratio and 95% CI were estimated.

Significance-prevalence index number (SPIN) is a weighted calculation that for each allergen incorporates a composite measure of clinical relevance combined with prevalence to determine "hot" allergens.[18] SPIN was calculated each year by: (proportion of population allergic) * (1*percentage with definite relevance + 0.66*percentage with probable relevance + 0.33*percentage with possible relevance) * 100. Mean SPIN was calculated for adults with HE.

All statistical analyses were performed in SAS v9.4.3 (SAS Institute, Cary, NC). Complete case analysis was performed. Post-hoc correction for multiple dependent tests was performed by minimizing the false discovery rate with the approach of Benjamini and Hochberg,[19] and corrected P values are presented. Two-sided corrected P values less than or equal to .05 were considered significant. Uncorrected 95% CI are presented.

RESULTS

Population characteristics

The cohort consisted of 37,113 adults, including 12,102 (32.6%) males and 31,945 (86.6%) whites. A total of 8,342 (22.6%) had AD, 5,503 (14.9%) had asthma, and 10,809 (29.2%) had hay fever. A total of 26,781 (72.6%) were age 40 years or more (Table I) with 24,443 (65.9%) allergic reactions. Overall, 8,632 (24.2%) and 10,034 (27.1%) had hands coded as the primary or any of up to 3 site(s) of dermatitis, respectively.

HE compared with no HE was associated with higher proportions of dermatitis affecting the feet (14.2% vs 4.2%) and arms (20.4% vs 13.7%) but lower proportions of all other sites (data not shown; $P < .0001$ for all).

The overlap of dermatitis affecting the hands, arms, and/or feet was examined. A higher proportion of patients had dermatitis only affecting the hands (18.1% of adults who were patch tested) than the arms (9.6%) or feet (2.5%), that is, no HE; 3.5% and 5.2% also had dermatitis of the feet or arms, respectively (Fig 1, *A*).

Most patients had ACD (59.4%), followed by ICD (29.1%), AD (15.4%), and pompholyx (2.5%). The overlap of the 3 most common diagnoses (ACD, ICD, and AD) was examined: 40.6%, 13.6%, and 5.6% had

Table I. Association of hand eczema with demographics and atopic history

		HE							
		Hand involvement coded as any of up to 3 anatomic sites (n = 10034)				Hand involvement coded as the primary anatomic site (n = 8632)			
	Overall (n = 37,113)	No	Yes			No	Yes		
Variable	Freq (%)	Freq (%)	Freq (%)	Adjusted OR (95% CI)	*P* value*	Freq (%)	Freq (%)	Adjusted OR (95% CI)	*P* value*
Age (y)									
18-30	4935 (13.3)	3163 (64.1)	1769 (35.9)	1.000 [ref]	—	3163 (67.2)	1541 (32.8)	1.000 [ref]	—
31-40	6110 (16.5)	4044 (66.2)	2064 (33.8)	0.823 (0.754-0.897)	<.0001	4044 (69.3)	1793 (30.7)	0.828 (0.760-0.902)	<.0001
41-50	8043 (21.7)	5638 (70.1)	2403 (29.9)	0.676 (0.622-0.735)	<.0001	5638 (73.0)	2082 (27.0)	0.678 (0.624-0.736)	<.0001
51-60	8546 (23.0)	6162 (72.2)	2379 (27.9)	0.625 (0.575-0.679)	<.0001	6162 (74.9)	2062 (25.1)	0.637 (0.587-0.692)	<.0001
61-70	5785 (15.6)	4718 (81.6)	1064 (18.4)	0.420 (0.379-0.465)	<.0001	4718 (84.3)	879 (15.7)	0.426 (0.385-0.471)	<.0001
≥70	3694 (10.0)	3335 (90.4)	355 (9.6)	0.215 (0.185-0.250)	<.0001	3335 (92.4)	275 (7.6)	0.221 (0.191-0.256)	<.0001
Sex									
Female	25007 (67.4)	19122 (76.5)	5871 (23.5)	0.525 (0.497-0.554)	<.0001	19122 (79.6)	4892 (20.4)	0.521 (0.494-0.549)	<.0001
Male	12102 (32.6)	7936 (65.6)	4161 (34.4)	1.000 [ref]	—	7936 (68.0)	3738 (32.0)	1.000 [ref]	—
Race/ethnicity									
White	31945 (86.6)	23197 (72.7)	8730 (27.3)	1.000 [ref]	—	23197 (75.5)	7528 (24.5)	1.000 [ref]	—
Black	1835 (5.0)	1384 (75.4)	451 (24.6)	0.799 (0.706-0.906)	.0007	1384 (78.4)	381 (21.6)	0.794 (0.702-0.899)	.0005
Hispanic	693 (1.9)	487 (70.3)	206 (25.4)	1.077 (0.898-1.292)	.5088	487 (73.1)	179 (26.9)	1.051 (0.877-1.261)	.6442
Asian	1802 (4.9)	1343 (74.5)	459 (25.5)	0.798 (0.707-0.901)	.0005	1343 (77.5)	390 (22.5)	0.800 (0.710-0.903)	.0005
Other	615 (1.7)	464 (75.6)	150 (24.4)	0.706 (0.570-0.874)	.0016	464 (69.6)	118 (20.3)	0.703 (0.569-0.869)	.0018
Occupation									
Unemployed	12839 (35.8)	10682 (83.3)	2148 (16.7)	1.000 [ref]	—	10682 (86.1)	1720 (13.9)	1.000 [ref]	—
Employed	23011 (64.2)	15404 (67.0)	7602 (33.0)	1.916 (1.793-2.046)	<.0001	15404 (69.8)	6672 (30.2)	1.916 (1.800-2.046)	<.0001
Atopic disease									
AD									
No	28621 (77.4)	21216 (74.2)	7389 (25.8)	1.000 [ref]	—	21216 (76.7)	6451 (23.3)	1.000 [ref]	—
Yes	8342 (22.6)	5725 (68.7)	2614 (31.4)	1.166 (1.092-1.244)	<.0001	5725 (72.7)	2154 (27.3)	1.182 (1.108-1.260)	<.0001
Asthma									
No	31506 (85.1)	23044 (73.2)	8447 (26.8)	1.000 [ref]	—	23044 (76.0)	7293 (24.0)	1.000 [ref]	—
Yes	5503 (14.9)	3939 (71.6)	1560 (28.4)	0.976 (0.903-1.054)	.6064	3939 (75.0)	1316 (25.0)	0.977 (0.905-1.055)	.6189
Hay fever									
No	26195 (70.8)	19245 (73.5)	6936 (26.5)	1.000 [ref]	—	19245 (76.1)	6034 (23.9)	1.000 [ref]	—
Yes	10809 (29.2)	7731 (71.6)	3073 (28.4)	0.966 (0.908-1.027)	.3371	7,731 (75.0)	2577 (25.0)	0.970 (0.913-1.032)	.4154

Missing values were encountered in 28 (0.07%) for age, 8 (0.02%) for sex, 240 (0.6%) for race/ethnicity, 1288 (3.3%) for occupation, 160 (0.4%) for history of AD, 111 (0.03%) for history of asthma and 115 (0.3%) for history of hay fever.

*Corrected *P* values are presented.

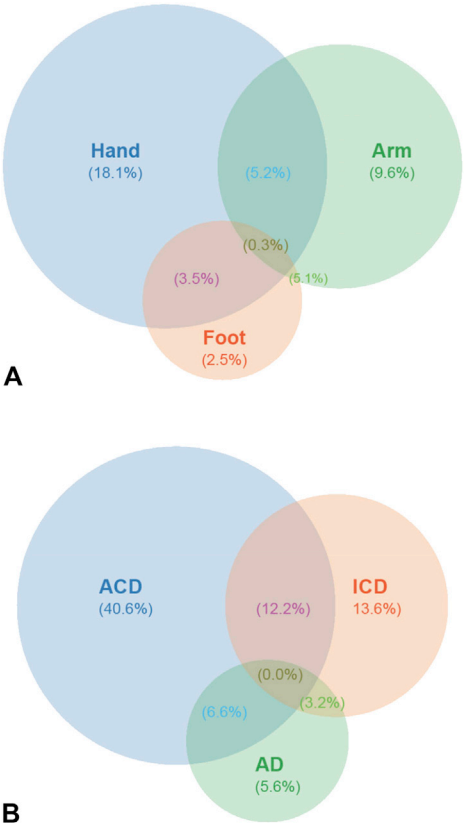

Fig 1. Overlap of dermatitis sites and diagnosis. Venn diagram of overlap between (**A**) dermatitis of the hands, feet and/or arms, in the NACDG database and (**B**) ACD, ICD and AD among adult patients with hand eczema in the NACDG database.

ACD, ICD, or AD diagnosed alone; 12.2% and 6.6% had concomitant ICD or AD with ACD, respectively (Fig 1, *B*).

Associations of HE and HE subsets

Overall, the proportion of patients referred for patch testing with HE appeared to decrease from 2003 to 2004 to 2011 to 2012 and increase again from 2015 to 2016 (supplemental Fig 1, *A* available at: https://data.mendeley.com/datasets/y3w52rk72y/1). This pattern was observed for primary HE and primary ACHE. In contrast, the proportion of patients with pompholyx increased in 2003 to 2004 then decreased until 2015 to 2016. Although the proportion of primary AHE steadily increased, primary irritant HE decreased over time. All HE subsets were most common at age 18 to 30 years and steadily decreased with older age (supplemental Fig 1, *B*).

In multivariable logistic regression models, being employed and having a history of eczema were associated with increased odds of any HE or primary HE (Table I). Whereas, ages 31-40, 41-50, 51-60 and ≥70 years, female sex, and non-white race/ethnicity were inversely associated with HE. Similar results were observed for ACHE, ICHE, and AHE (supplemental Table I available at: https://data.mendeley.com/datasets/y3w52rk72y/1).

Positive patch test reactions in adults with HE

Higher proportions of positive allergic reactions were observed in adults with HE (68.6%) and primary HE (67.8%) compared with those without HE (64.9%; χ^2; $P < .0001$ for both). Moreover, a higher mean plus or minus standard deviation number of positive allergic reactions were observed in adults with HE (2.2 ± 2.5) and primary HE (2.1 ± 2.5) compared with those without HE (1.8 ± 2.2; *t* test; $P < .0001$ for both).

The top 10 NACDG allergens for positive allergic reactions in adult HE patients included nickel sulfate hexahydrate (17.9%), methylisothiazolinone (17.0%), formaldehyde 2% (12.3%), quaternium-15 (11.3%), formaldehyde 1% (10.7%), thimerosal (10.2%), fragrance mix I (10.0%), gold sodium thiosulfate (9.3%), neomycin sulfate (9.3%) and bacitracin (8.9%) (Table II). Similar results were observed for primary HE (supplemental Table II available at: https://data.mendeley.com/datasets/y3w52rk72y/1).

Additionally, 2,222 (22.2%) adult HE patients had positive reactions to 1 or more non-NACDG screening allergen; 348 (3.5%) had reactions only to non-NACDG allergens, whereas 1874 (18.7%) had reactions to both NACDG and non-NACDG allergens.

HE was associated with significantly higher odds of positive patch test reactions in 13 of the 25 most common allergens, including methylisothiazolinone, formaldehyde 1% and 2%, quaternium-15, bacitracin, cobalt, carba mix, thiuram mix, methylchloroisothiazolinone/methylisothiazolinone, methyldibromoglutaronitrile/phenoxyethanol, potassium dichromate, diphenylguanidine, and 2-hydroxyethyl methacrylate (Table II). Similarly, primary HE was associated with 14 of the top 25 allergens, including all of the above-mentioned allergens, as well as diazolidinyl urea (supplemental Table II).

Allergen relevance in adults with HE

Among adults with HE, the five allergens with highest proportion of current relevance (definite, probable, and possible) were methylisothiazolinone, nickel sulfate hexahydrate, formaldehyde, quaternium-15, and fragrance mix I (Table III). HE was associated with higher odds of relevance in 16 of the top 25 most relevant allergens but lower odds of relevance in 2 allergens.

Table II. Most common positive allergic reactions in adult patients with a primary or secondary site for HE

Allergen	No HE			Primary/secondary HE			Adjusted OR (95% CI)	*P* value
	No. of patients tested	Allergic reaction, n (%)	Rank order	No. of patients tested	Allergic reaction, n (%)	Rank order		
Nickel sulfate hexahydrate, 2.5% pet.	26976	4845 (18)	1	9986	1784 (17.9)	1	1.016 (0.953-1.083)	.6797
Methylisothiazolinone, 0.2% aq. (2000 ppm)	7509	820 (10.9)	3	2586	440 (17.0)	2	**1.756 (1.541-2.001)**	**<.0001**
Formaldehyde, 2.0% aq.	3904	285 (7.3)	9	1411	174 (12.3)	3	**1.968 (1.597-2.426)**	**<.0001**
Quaternium 15, 2.0% pet.	27038	1604 (5.9)	13	10020	1134 (11.3)	4	**2.237 (2.054-2.436)**	**<.0001**
Formaldehyde, 1.0% aq.	27041	1700 (6.3)	11	10022	1071 (10.7)	5	**1.96 (1.798-2.136)**	**<.0001**
Thimerosal 0.1% pet.	3372	333 (9.9)	4	1354	138 (10.2)	6	0.987 (0.792-1.232)	.9163
Fragrance mix I, 8.0% pet.	27014	2970 (11)	2	10024	1003 (10.0)	7	1.058 (0.977-1.146)	.2187
Sodium gold thiosulfate, 0.5% pet.	6803	654 (9.6)	6	2861	265 (9.3)	8	1.082 (0.92-1.273)	.4185
Neomycin sulfate, 20.0% pet.	27021	2589 (9.6)	6	10008	920 (9.2)	9	1.079 (0.992-1.173)	.1072
Bacitracin, 20.0% pet.	27021	2073 (7.7)	8	10020	892 (8.9)	10	**1.279 (1.173-1.396)**	**<.0001**
Myroxylon pereirae resin (Balsam of Peru), 25.0% pet.	27048	2662 (9.8)	5	10028	857 (8.5)	11	0.956 (0.877-1.042)	.3810
Cobalt (ii) chloride hexahydrate, 1.0% pet.	27022	1846 (6.8)	10	10014	831 (8.3)	12	**1.179 (1.078-1.289)**	**.0005**
Carba mix, 3.0% pet.	27046	987 (3.6)	18	10020	726 (7.2)	13	**2.039 (1.836-2.265)**	**<.0001**
Thiuram mix, 1.0% pet.	27039	668 (2.5)	30	10021	711 (7.1)	14	**3.225 (2.875-3.617)**	**<.0001**
Methylchloroisothiazolinone/ methylisothiazolinone, 0.02% aq. = 200 ppm	27005	890 (3.3)	20	10016	644 (6.4)	15	**2.145 (1.921-2.395)**	**<.0001**
Methyldibromoglutaronitrile/ phenoxyethanol, (Euxyl K 400), 2.0% pet.	27015	1289 (4.8)	15	10023	517 (5.2)	16	**1.183 (1.058-1.323)**	**.0050**
4-phenylenediamine, 1.0% pet.	27005	1628 (6)	12	10008	512 (5.1)	17	0.901 (0.81-1.003)	.0810
Fragrance mix II, 14.0% pet.	17193	876 (5.1)	14	5880	279 (4.7)	18	1.002 (0.868-1.158)	.9730
Potassium dichromate, 0.25% pet.	27053	717 (2.7)	28	10023	458 (4.6)	19	**1.553 (1.366-1.766)**	**<.0001**
Diphenylguanidine, 1% pet.	7511	214 (2.8)	27	2587	115 (4.4)	20	**1.542 (1.209-1.967)**	**.0008**
2-Hydroxyethyl methacrylate, 2.0% pet.	17180	381 (2.2)	36	5880	228 (3.9)	21	**2.156 (1.808-2.571)**	**<.0001**
Benzalkonium chloride, 0.1% aq.	3364	153 (4.5)	16	1354	53 (3.9)	21	0.861 (0.613-1.209)	.4672
Propylene glycol, 100%	7512	251 (3.3)	20	2587	99 (3.8)	23	1.158 (0.906-1.481)	.3132
Iodopropynyl butylcarbamate, 0.5% pet.	20196	831 (4.1)	17	7154	237 (3.3)	24	0.98 (0.838-1.145)	.8396
Lanolin alcohol (Amerchol L101), 50% pet.	27045	814 (3)	24	10024	328 (3.3)	24	1.057 (0.922-1.211)	.5088

Bold indicates statistical significance.

In adults with HE, the allergens with highest mean SPIN across all testing cycles included methylisothiazolinone, nickel, methylchloroisothiazolinone/ methylisothiazolinone, quaternium-15, formaldehyde, fragrance mix I, and balsam of Peru (Fig 2).

DISCUSSION

This study had several important findings. Adult HE patients had a high proportion of positive patch test reactions with both statistically and clinically significantly more reactions compared with adults without HE. These results are consistent with those of previous studies that found high rates of positive patch tests in HE patients referred for patch testing.[8,9,20] HE was associated with higher odds of positive patch tests and relevant allergic reactions to a variety of different allergens, including preservatives, metals, topical medications, and rubber accelerators. The top 5 NACDG currently relevant allergens included methylisothiazolinone, nickel, formaldehyde, quaternium-15, and fragrance mix I in adults.

Table III. Most common relevant allergens in adults with HE

Allergen	Rank order of allergen relevance in HE	HE	Relevance of allergens—freq. (%)					Adjusted OR (95% CI)*	*P* value
			Not relevant allergen	Definite	Probable	Possible	Past		
Methylisothiazolinone, 0.2% aq. (2000 ppm)	1	No	6684 (89.7)	58 (0.8)	380 (5.1)	314 (4.2)	17 (0.2)	1.00 [ref]	-
		Yes	2143 (83.8)	30 (1.2)	225 (8.8)	147 (5.7)	11 (0.4)	**1.743 (1.522-1.996)**	**<.0001**
Nickel sulfate hexahydrate, 2.5% pet.	2	No	22225 (84.3)	75 (0.3)	809 (3.1)	1710 (6.5)	1535 (5.8)	1.00 [ref]	-
		Yes	8217 (84)	38 (0.4)	331 (3.4)	659 (6.7)	539 (5.5)	**1.092 (1.006-1.185)**	**.0516**
Formaldehyde, 2.0% aq.	3	No	3601 (94)	3 (0.1)	76 (2)	148 (3.9)	4 (0.1)	1.00 [ref]	-
		Yes	1232 (89.5)	2 (0.1)	31 (2.3)	106 (7.7)	5 (0.4)	**1.986 (1.574-2.507)**	**<.0001**
Quaternium-15, 2.0% pet.	4	No	25425 (94.5)	42 (0.2)	480 (1.8)	901 (3.3)	59 (0.2)	1.00 [ref]	-
		Yes	8873 (89.7)	32 (0.3)	294 (3)	648 (6.5)	48 (0.5)	**2.157 (1.97-2.363)**	**<.0001**
Formaldehyde, 1.0% aq.	5	No	25309 (94.5)	15 (0.1)	480 (1.8)	935 (3.5)	41 (0.2)	1.00 [ref]	-
		Yes	8923 (90.6)	16 (0.2)	222 (2.3)	657 (6.7)	26 (0.3)	**1.972 (1.796-2.166)**	**<.0001**
Fragrance mix I, 8.0% pet.	6	No	23973 (89.8)	70 (0.3)	888 (3.3)	1642 (6.1)	126 (0.5)	1.00 [ref]	-
		Yes	8989 (91)	14 (0.1)	235 (2.4)	598 (6.1)	41 (0.4)	1.023 (0.938-1.115)	.6619
Myroxylon pereirae resin (Balsam of Peru), 25.0% pet.	7	No	24323 (91)	37 (0.1)	803 (3)	1476 (5.5)	92 (0.3)	1.00 [ref]	-
		Yes	9140 (92.5)	9 (0.1)	192 (1.9)	516 (5.2)	29 (0.3)	0.927 (0.844-1.017)	.1447
Carba mix, 3.0% pet.	8	No	26017 (97)	22 (0.1)	228 (0.9)	464 (1.7)	76 (0.3)	1.00 [ref]	-
		Yes	9275 (93)	82 (0.8)	255 (2.6)	325 (3.3)	34 (0.3)	**2.552 (2.273-2.866)**	**<.0001**
Thiuram mix, 1.0% pet.	9	No	26360 (98)	29 (0.1)	162 (0.6)	261 (1)	85 (0.3)	1.00 [ref]	-
		Yes	9301 (93.1)	71 (0.7)	255 (2.6)	312 (3.1)	54 (0.5)	**4.149 (3.642-4.726)**	**<.0001**
Methylchloroisothiazolinone/methylisothiazolinone, 0.02% aq. = 200 ppm	10	No	26107 (96.9)	68 (0.3)	375 (1.4)	351 (1.3)	30 (0.1)	1.00 [ref]	-
		Yes	9366 (93.9)	45 (0.5)	294 (2.9)	243 (2.4)	26 (0.3)	**2.181 (1.942-2.449)**	**<.0001**
Bacitracin, 20.0% pet.	11	No	24984 (93.8)	121 (0.5)	380 (1.4)	286 (1.1)	859 (3.2)	1.00 [ref]	-
		Yes	9139 (92.6)	73 (0.7)	228 (2.3)	149 (1.5)	278 (2.8)	**1.691 (1.493-1.915)**	**<.0001**
Cobalt (ii) chloride hexahydrate, 1.0% pet.	13	No	25190 (95.1)	12 (0)	133 (0.5)	667 (2.5)	473 (1.8)	1.00 [ref]	-
		Yes	9169 (93.7)	10 (0.1)	95 (1)	303 (3.1)	207 (2.1)	**1.287 (1.133-1.462)**	**.0001**
Fragrance mix II, 14.0% pet.	13	No	16283 (95.1)	22 (0.1)	352 (2.1)	437 (2.6)	25 (0.1)	1.00 [ref]	-
		Yes	5596 (95.7)	5 (0.1)	73 (1.2)	167 (2.9)	9 (0.2)	0.955 (0.82-1.112)	.6189
Diphenylguanidine, 1% pet.	15	No	7281 (98.1)	2 (0)	25 (0.3)	99 (1.3)	18 (0.2)	1.00 [ref]	-
		Yes	2464 (96)	15 (0.6)	24 (0.9)	59 (2.3)	4 (0.2)	**2.274 (1.712-3.019)**	**<.0001**
Methyldibromoglutaronitrile/phenoxyethanol, (Euxyl K 400), 2.0% pet.	15	No	25647 (96.3)	23 (0.1)	311 (1.2)	594 (2.2)	62 (0.2)	1.00 [ref]	-
		Yes	9460 (96)	17 (0.2)	95 (1)	256 (2.6)	24 (0.2)	**1.149 (1.007-1.311)**	**.0562**
Propylene glycol, 100%	16	No	7249 (96.9)	16 (0.2)	132 (1.8)	77 (1)	4 (0.1)	1.00 [ref]	-
		Yes	2480 (96.3)	6 (0.2)	54 (2.1)	35 (1.4)	0 (0)	1.253 (0.972-1.614)	.1127
Neomycin sulfate, 20.0% pet.	17	No	24464 (92.4)	87 (0.3)	320 (1.2)	284 (1.1)	1311 (5)	1.00 [ref]	-

Continued

Table III. Cont'd

Allergen	Rank order of allergen relevance in HE	HE	Relevance of allergens—freq. (%)					Adjusted OR (95% CI)*	*P* value
			Not relevant allergen	Definite	Probable	Possible	Past		
		Yes	9092 (92.4)	53 (0.5)	159 (1.6)	145 (1.5)	391 (4)	**1.547 (1.348-1.774)**	**<.0001**
Sodium gold thiosulfate, 0.5% pet.	18	No	6116 (95)	4 (0.1)	79 (1.2)	176 (2.7)	61 (0.9)	1.00 [ref]	-
		Yes	2588 (95.9)	3 (0.1)	21 (0.8)	65 (2.4)	22 (0.8)	0.923 (0.705-1.208)	.6199
Potassium dichromate, 0.25% pet.	19	No	26279 (98.5)	12 (0)	92 (0.3)	227 (0.9)	72 (0.3)	1.00 [ref]	-
		Yes	9547 (96.5)	20 (0.2)	110 (1.1)	176 (1.8)	44 (0.4)	**2.057 (1.738-2.436)**	**<.0001**
4-phenylenediamine, 1.0% pet.	21	No	25361 (94.9)	55 (0.2)	659 (2.5)	343 (1.3)	309 (1.2)	1.00 [ref]	-
		Yes	9484 (96)	29 (0.3)	151 (1.5)	97 (1)	120 (1.2)	**0.734 (0.638-0.845)**	**<.0001**
Lanolin alcohol (Amerchol L101), 50% pet.	21	No	26212 (97.3)	43 (0.2)	306 (1.1)	362 (1.3)	28 (0.1)	1.00 [ref]	-
		Yes	9680 (97)	22 (0.2)	113 (1.1)	149 (1.5)	11 (0.1)	1.048 (0.906-1.213)	.6064
Diazolidinyl urea (Germall II), 1.0% pet.	23	No	26370 (97.7)	35 (0.1)	196 (0.7)	357 (1.3)	21 (0.1)	1.00 [ref]	-
		Yes	9717 (97.2)	20 (0.2)	83 (0.8)	175 (1.7)	7 (0.1)	**1.468 (1.257-1.714)**	**<.0001**
Iodopropynyl butylcarbamate, 0.5% pet.	23	No	19261 (96.3)	20 (0.1)	287 (1.4)	407 (2)	14 (0.1)	1.00 [ref]	-
		Yes	6884 (97.2)	10 (0.1)	64 (0.9)	119 (1.7)	8 (0.1)	0.907 (0.764-1.076)	.3327
2-Hydroxyethyl methacrylate, 2.0% pet.	24	No	16800 (98.3)	7 (0)	86 (0.5)	98 (0.6)	92 (0.5)	1.00 [ref]	-
		Yes	5650 (96.5)	7 (0.1)	90 (1.5)	59 (1)	45 (0.8)	**2.95 (2.353-3.697)**	**<.0001**
Propylene glycol, 30.0% aq.	25	No	26137 (97.2)	106 (0.4)	321 (1.2)	322 (1.2)	11 (0)	1.00 [ref]	-
		Yes	9742 (97.6)	31 (0.3)	108 (1.1)	95 (1)	5 (0.1)	**0.792 (0.679-0.925)**	**.0050**

Bold indicates statistical significance.

*Multivariable logistic regression models were constructed with specific allergen relevance (definite/probable/possible vs not relevant; excluding past or unknown relevance) as the dependent variable and hand eczema (yes vs no) as the independent variable, and age (continuous), race/ethnicity (white, non-Hispanic/black/Hispanic/Asian/other), sex and employment.

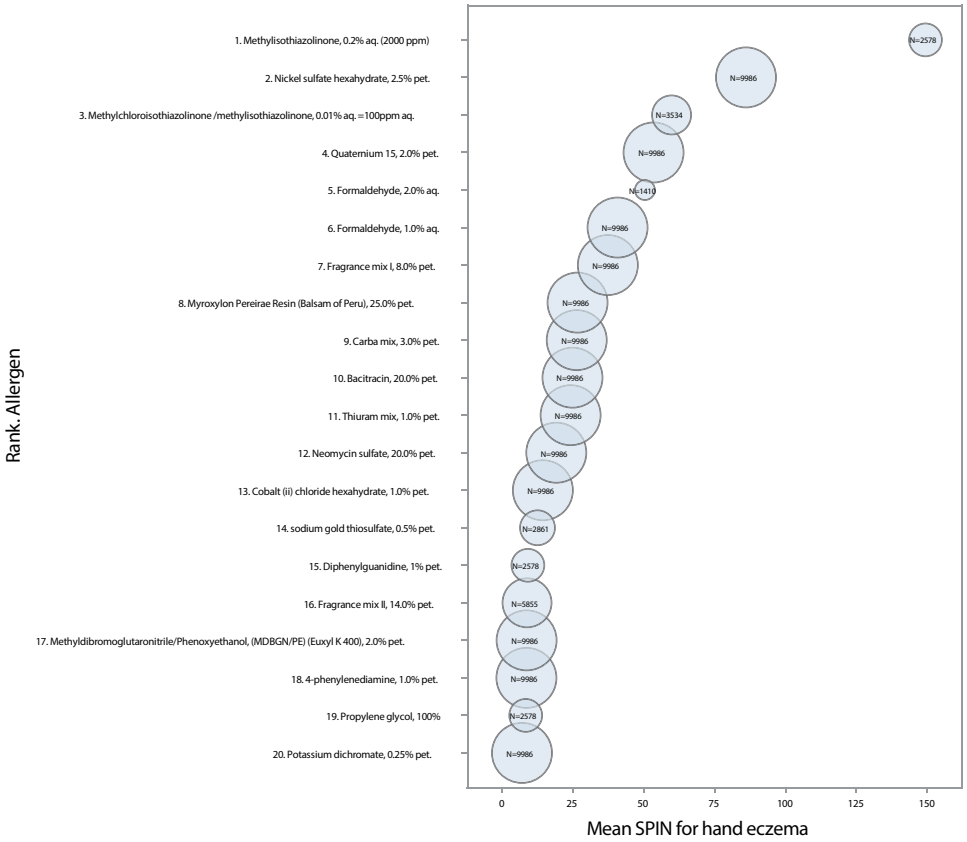

Fig 2. Allergens with highest SPIN in adults with HE. SPIN was calculated at each 2-year cycle by: (proportion of population allergic) * (1*percentage with definite relevance + 0.66*percentage with probable relevance + 0.33*percentage with possible relevance) * 100.

The profile of most common allergens in HE appears to have shifted over time. Previous analysis of data from the NACDG database between 1994 and 2004 found the 5 most common relevant allergens (in adults and children) with HE to be quaternium-15, formaldehyde, nickel, fragrance mix I, and thiuram mix.[8] Although these allergens continue to be relevant, methylisothiazolinone has emerged as one of the most commonly relevant allergens in adult HE, consistent with the ongoing epidemic of methylisothiazolinone contact allergy.[21] Methylisothiazolinone had the highest HE-specific SPIN of all allergens tested, indicating both high prevalence and relevance. Formaldehyde and formaldehyde releasers were more commonly positive and relevant in HE. Previous studies found myriad potential sources of formaldehyde and releasers in HE, including occupational dermatitis,[22,23] gloves,[24] skin cleansers,[25] and even cigarettes.[26] Carba mix and thiuram mix were both common and significantly increased in HE, which is relevant for guidance on glove alternatives. Other common rubber sources include tires, tubes, footwear, hoses, belting, gaskets, packing, and sealing devices.[27] Although nickel allergic reactions were not significantly more common in HE patients, nickel was still the most common positive allergic reaction in HE patients and had a high proportion of relevance and SPIN score. Common sources of nickel exposure to the hands include electronic devices and protective cases, coins, pots and pans, musical instruments, tools, and jewelry.[28] Dietary intake of nickel has been reported as a less common cause of HE.[29] It is noteworthy that some allergens, such as gold, were common in HE patients but were not more likely to be positive or relevant in HE. This finding is consistent with previous findings of high proportions of positive reactions to gold but mixed results regarding its relevance to the underlying dermatitis.[30,31]

These results have important clinical ramifications. First, they highlight the importance of patch testing in HE patients. The European Society of Contact Dermatitis guidelines recommend that patch

testing be performed in chronic HE regardless of the location or morphology of lesions.[7] Second, some of the most common and relevant allergens in HE would be missed by Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) test, including benzalkonium chloride, iodopropynyl butylcarbamate, and lanolin. Thus, use of an expanded patch test series should be encouraged over a T.R.U.E. test in the workup of HE patients. Third, approximately 1 in 5 adults with HE had a positive reaction to 1 or more allergens not present on the NACDG screening series. These results underscore the importance of testing HE patients to supplemental allergens in both children and adults, including patient's own products, workplace materials, and/or other suspected allergens. Finally, there was considerable overlap between ACD and ICD on the hands, consistent with previous studies. Thus, even HE patients with relevant positive allergic reactions and a diagnosis of ACD should be counseled about irritant avoidance to address overlapping ICD.

Associations of HE

HE was more common in patients who were male, young adults, and employed. HE has consistently been found in population-based studies to be more common in females.[32,33] The observed male predilection may be related to increased occupational exposures, as males are more likely to work in the manufacturing and metalworking industries.[34] Previous studies also found higher rates of other occupational dermatoses[35,36] and HE subtypes associated with increased manual labor, such as hyperkeratotic HE,[37] in males. Future studies will specifically examine the associations of occupational HE. HE was less likely to occur with older age or in females or in black, Asian, and other patients but not in Hispanics. These demographic differences may be caused by differences of occupation, culture, and/or access to care; however, these factors were not examined.

Temporal trends of HE

Different temporal trends were observed across HE subsets. Although the proportion of patients with ACHE in the NACDG database fluctuated, AHE increased and ICHE decreased over time. Of note, the NACDG database is not a population-based study and cannot estimate disease prevalence per se. However, the observed trends may reflect evolving population trends of HE in North America. There has also been a steady decline in manufacturing jobs in the United States,[38] which may be accompanied by lower rates of occupational HE. As such, the proportion of ACD may be increasing as a cause of HE over time.

Limitations

The NACDG database does not distinguish between specific HE phenotypes (eg, hyperkeratotic vs vesicular, unilateral vs bilateral). Names of non-NACDG allergens are not recorded (only sources of those allergens). Data on HE onset, longitudinal course, and treatment history were not collected. Finally, long-term follow-up data are lacking, precluding assessment of whether patients improved with allergen or irritant avoidance.

CONCLUSIONS

HE is associated with heterogeneous clinical presentation and multiple classes of allergens. ACD was the most common diagnosis in adults with HE who were referred for patch testing. HE was associated with a heterogeneous profile of allergic reactions and relevant allergens. Patch testing remains an important tool in the evaluation of patients with HE.

Conflicts of interest

None disclosed.

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