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A CORRELATION OF ALLERGIC CONTACT DERMATITIS WITH ALLERGEN TYPE AND PATIENT CATEGORICAL VARIABLES

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Allergic contact dermatitis is a very treatable disease once it is diagnosed. In this study, statistical analysis was done on 105 patients with allergic contact dermatitis and the data were correlated with allergen type and patient categorical variables. Once allergens were identified, patients were advised to practice avoidance of the identified allergens. Significant differences in gender and past history of allergy were noted. Improvement after avoidance of identified allergens was also tracked, and a significant negative correlation was observed between number of allergens and improvement of patients' conditions. Although not reaching a statistical level of significance, some interesting trends were found regarding age versus severity and age versus improvement, which should be explored in future studies. In addition, a larger study population would ensure the collection of more statistically significant data for future research.

Keywords: Allergic contact dermatitis; Patient characteristics; Allergies; Allergens

INTRODUCTION

Allergic contact dermatitis (ACD) is a form of eczematous dermatitis caused by exposure to some chemical substances in the environment in amounts that exceed an individual's threshold (1), and some studies also suggest that there may be genetic

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factors regarding an individual's susceptibility to particular allergens (2, 3). Risk factors include the inherent sensitizing potential of an allergen, an elevated concentration of the allergen (dose per unit area), a high frequency of exposure, occlusion of the skin, a long exposure time, the presence of penetration-enhancing factors, and an altered skin barrier function (4). Allergens are generally of low molecular weight (haptens of less than 500 Da) and lipophilic in nature. Most haptens are generally weak allergens, insufficient in size to act as a complete antigen, and require repeat exposure or conjugation with endogenous proteins to acquire antigenic activity (5, 6). The small size of these molecules allows for their penetration through the skin barrier, which otherwise is generally impermeable to larger molecules under normal conditions. These substances often act as irritants as well and may cause acute or chronic inflammation. Furthermore, elicitation of an allergic reaction depends on the duration and frequency of exposure, the region of application, and the presence of irritants. Certain allergens are ubiquitous in our environment, which can make total allergen avoidance impossible. Consequently, some patients develop chronic dermatitis, leading to sick leave as well as increased healthcare expenses (4). Systemic treatment with corticosteroids is usually reserved for severe cases with involvement of greater than 20% of the total body surface area (7). Early diagnosis of ACD is associated with improved quality of life, increased response to treatment, and prevention of developing the chronic phase of this disease (8, 9).

Determining the chemical responsible for ACD requires an evaluation of the clinical relevance of positive test reactions, that is, whether the identified allergen is the one causing the clinical problem. Clinical relevance and an assessment of all positive reactions on the basis of clinical history, physical examination, and provocative skin patch testing (10). Patch testing is a diagnostic tool for the evaluation of patients with suspected ACD, and is indicated for cases in which inflammation persists despite topical therapy. In this study, approximately 250 patient records were reviewed. All of the patients had ACD that did not respond to treatment, and underwent skin patch testing at the University of South Florida Dermatology Medical Clinic (USFDMC) from January 1, 2003, to December 31, 2003. Of the patients whose records were reviewed, 105 fit the inclusion criteria (specified in the Methods section, below). The primary objective was a reduction of ACD in the test population.

METHODS

Statistical analysis was performed on information gathered from 105 patients who were treated at USFDMC from January 1, 2003, to December 31, 2003. Inclusion criteria for all patients were as follows:

- Age above 18 and below 65 years
- A clinical diagnosis of ACD
- A negative response to topical therapy
- A skin patch test result of +1 or higher

Patch Test Allergen Series

The following is a list of the allergen series for which the study subjects were tested: cosmetic series, textile dyes, rubber and shoe series, preservative and vehicle

series, plastic and glue series, pesticide series, T.R.U.E. TEST (i.e., Thin-layer Rapid Use Epicutaneous Test; Allerderm, Phoenix, AZ, USA), standard data collection, hairdressing series, fragrance series, and corticosteroids series. T.R.U.E. TEST is a ready-to-use commercial patch test that consists of 24 allergen and allergen mixes that have been reported as being responsible for up to 80% of ACD cases (11). Testing for occupational allergic contact dermatitis (OACD) was beyond the scope of this study. The standard series are suitable only as screening tests or pre-employment screening in the diagnosis of OACD and are not adequate to recognize OACD. In order to screen for OACD, certain supplementary series should be administered, especially among workers who come in contact with special substances and materials (12). No supplementary series was used for this test population.

The interpretations of the tests were 48 hours to 1 week after removal of the patch. The skin patch tests were considered positive if they were +1 (non-vesicular erythematous reaction), +2 (vesicular erythematous reaction), or +3 (bullous reaction). USFDMC is a part of the University of South Florida Medical School and caters to patients with different types of skin diseases. ACD is highly preventable because it arises from man-made conditions and can be successfully treated by avoidance after identification of the condition or exposure through patch testing (13).

The diagnosis of contact allergy is mainly determined by the outcome of patch testing. However, a positive test reaction is not necessarily an indicator of clinical relevance, i.e., causative factor for the ACD, as the patch test measures only whether the individual is sensitized or not. Clinical relevance was considered either present, when related to the current clinical symptoms, or past, when associated with previous clinical events (10). It is generally acknowledged that the patch test holds some biological as well as technical limitations. Biological limitations include the occurrence of false-positive and false-negative reactions. Technical limitations include the different criteria that are used in the definition of a weak positive reaction. Study of the anatomical application site (regional variations) of patch test responses has shown that reactivity is weaker on the arm than on the back (1); in this study, the anatomical region used for testing of all cases was the back. In addition, the aspect of seasonal variations should be considered in this study because fewer positive reactions are observed during the summer months (1). This study was conducted in the Greater Tampa area of Florida, which has mild summer-like temperatures year round.

Data Management and Statistical Methodology

Data were collected on standardized forms developed by the investigator and entered into Microsoft Excel (Microsoft, Redmond, WA, USA). Every variable was given a name that identified its field in the data set; missing data (variables) were coded as 9. To evaluate the frequency/prevalence of allergens that cause ACD, categorical variables (age, gender, family or past history of dermatitis, ZIP code, allergen types, and results from avoiding the allergen) were compared. Criteria for past history of dermatitis included cases with positive past history of allergic rhinitis, asthma, or atopic eczema (8). A chi-square or Fisher's exact test, odds ratios (ORs), and 95% confidence intervals (CIs) were calculated. Significance was accepted at $p < .05$. Collected and coded data were entered into a Compaq (Hewlett-Packard,

Palo Alto, CA, USA)-compatible computer, using the SPSS version 12 for Windows (SPSS Inc., Chicago, IL, USA). Entered data were checked for accuracy, and then for normality, using Shapiro-Wilk tests. Qualitative variables were expressed as numbers and percentages, whereas quantitative variables were expressed as means and standard deviations.

The following statistical tests were used:

1. Independent-sample *t*-test was used as a parametric test of significance for comparison between 2 sample means, after performing Levene's test for equality of variances.
2. The χ^2 test was used as a non-parametric test of significance for comparison between the distributions of 2 qualitative variables.
3. Fisher's exact test was used as a non-parametric test of significance for comparison between the distributions of 2 binary variables whenever the χ^2 test was not appropriate. It gives a *p*-value directly.
4. The Mann-Whitney test (Z-value) was used as a non-parametric test of significance for comparison between 2 samples' means when the independent *t*-test was not appropriate.
5. The Kruskal-Wallis (K-W) test (χ^2 value) was used as a non-parametric test of significance for 1-way comparison between more than 2 samples' means when the 1-way analysis of variance (ANOVA) test was not appropriate. One way ANOVA to analyzing the variation in the data due to difference between groups and variation due to error.
6. Spearman's rank correlation coefficient (*r*) was used as a non-parametric measure of the mutual relationship between 2 non-normally distributed quantitative or ordinal variables.

A 5% level of significance was used in all of the above-mentioned statistical testing.

RESULTS

One hundred five cases were included in the study, among which 71 allergens were tested. Out of the total sample, there were more women (59.1%) than men (40.9%). Ages ranged from 21 to 63 years, with a mean of 47.25 ± 10.78 years for the total sample. The women were slightly older than the men (47.60 ± 10.68 and 46.74 ± 11.02 years, respectively); however, the difference was not significant ($p = .692$). Past history of allergy was positive among 38 participants, representing 36.2% of the test population. The majority of participants were white ($n = 102$), whereas the other participants were black ($n = 2$) and Asian ($n = 1$). Thirteen ZIP codes were identified from which participants came to the USFDMC.

Frequency, Prevalence, and Severity of Allergens

In Table 1, the frequencies (and corresponding severities) of allergens were tabulated and sorted in descending order according to the incidence of ACD. Incidence of ACD, as revealed by each allergen, was classified into 3 groups: *group 1—high incidence* ($\geq 9\%$ or ≥ 10 cases); *group 2—medium incidence* ($4\% - < 9\%$ or 4–9 cases); and *group 3—low incidence* ($< 4\%$ or 1–3 cases).

Table 1 Rank order frequency of allergens according to prevalence/severity

Allergen	Severity			Allergen frequency			
				Yes		No	
	+ 1	+ 2	+ 3	<i>n</i>	%	<i>n</i>	%
Balsam of Peru	23	2	1	26	24.76	79	75.24
Potassium dichromate	21	1	2	24	22.86	81	77.14
Nickel sulfate	10	6	3	19	18.10	86	81.90
Carba mix	11	2		13	12.38	92	87.62
Neomycin sulfate	4	7	1	12	11.43	93	88.57
Thiomersal	6	4	2	12	11.43	93	88.57
Cinnamaldehyde	11			11	10.48	94	89.52
Cetylpyridinium chloride	10			10	9.52	95	90.48
Cocobetaine	8	2		10	9.52	95	90.48
Diphenylguanidine	9		1	10	9.52	95	90.48
Formaldehyde	7	3		10	9.52	95	90.48
Quaternium 15	6	1	1	8	7.62	97	92.38
Oak moss	6	1		7	6.67	98	93.33
Ethylenediamine dihydrochloride	5	1		6	5.71	99	94.29
Para-phenylenediamine	3	2	1	6	5.71	99	94.29
Cinnamyl alcohol	3	2		5	4.76	100	95.24
Cobalt dichloride	3	2		5	4.76	100	95.24
Fragrance mix	4	1		5	4.76	100	95.24
Ammonium persulfate	4			4	3.81	101	96.19
Coconut diethanolamide	3	1		4	3.81	101	96.19
Euxyl K400	4			4	3.81	101	96.19
Glutardialdehyde	4			4	3.81	101	96.19
Kathon CG	3	1		4	3.81	101	96.19
Tetramethylthiuram disulfide	3		1	4	3.81	101	96.19
Benzoyl peroxide	3			3	2.86	102	97.14
Butylphenol formaldehyde resin	1	1	1	3	2.86	102	97.14
Chlorquinaldol	2		1	3	2.86	102	97.14
Clobetasol	2		1	3	2.86	102	97.14
Colophony	1		2	3	2.86	102	97.14
Sorbitan sesquioleate	3			3	2.86	102	97.14
Thiuram mix	1	1	1	3	2.86	102	97.14
Triethylenetetramine	3			3	2.86	102	97.14
Benzalkonium chloride	1	1		2	1.90	103	98.10
Black rubber mix	1	1		2	1.90	103	98.10
Bronopol	2			2	1.90	103	98.10
Captan	2			2	1.90	103	98.10
Epoxy resin	2			2	1.90	103	98.10
Eugenol	2			2	1.90	103	98.10
Hexamethylenetetramine	2			2	1.90	103	98.10
Hydroxycitronellal	2			2	1.90	103	98.10
Imidazolidinyl urea	1	1		2	1.90	103	98.10
Isopropylaminodiphenylamine	2			2	1.90	103	98.10
Mercapto mix	2			2	1.90	103	98.10
Mercaptobenzothiazole	1	1		2	1.90	103	98.10
Negative control	1		1	2	1.90	103	98.10
Octyl gallate	1	1		2	1.90	103	98.10

(Continued)

Table 1 Continued

Allergen	Severity			Allergen frequency			
				Yes		No	
	+ 1	+ 2	+ 3	n	%	n	%
Paraben mix		1	1	2	1.90	103	98.10
Propyl gallate	1	1		2	1.90	103	98.10
Sorbic acid	2			2	1.90	103	98.10
Triclosan	2			2	1.90	103	98.10
Wool alcohol	2			2	1.90	103	98.10
Isoeugenol	2			2	1.90	103	98.10
Alpha amyl cinnamaldehyde	1			1	0.95	104	99.05
Ammonium thioglycolate	1			1	0.95	104	99.05
Budesonide	1			1	0.95	104	99.05
<i>Chamomilla romana</i>	1			1	0.95	104	99.05
Cyclohexylbenzothiazl Sulfenamide	1			1	0.95	104	99.05
Dexamethasone phosphate	1			1	0.95	104	99.05
Edetic acid	1			1	0.95	104	99.05
Ethyleneglycol dimethacrylate		1		1	0.95	104	99.05
Formaldehyde resin	1			1	0.95	104	99.05
Geraniol	1			1	0.95	104	99.05
Hydrocortisone	1			1	0.95	104	99.05
Irgasan dp300	1			1	0.95	104	99.05
Lanolin alcohol	1			1	0.95	104	99.05
Phenoxycyclo-paraphenylenediamine	1			1	0.95	104	99.05
Phenylmercuric acetate		1		1	0.95	104	99.05
Tixocortol pivalate	1			1	0.95	104	99.05
Triamcinolone	1			1	0.95	104	99.05
Triethanolamine stearate	1			1	0.95	104	99.05
Toluene diamine sulfate	1			1	0.95	104	99.05

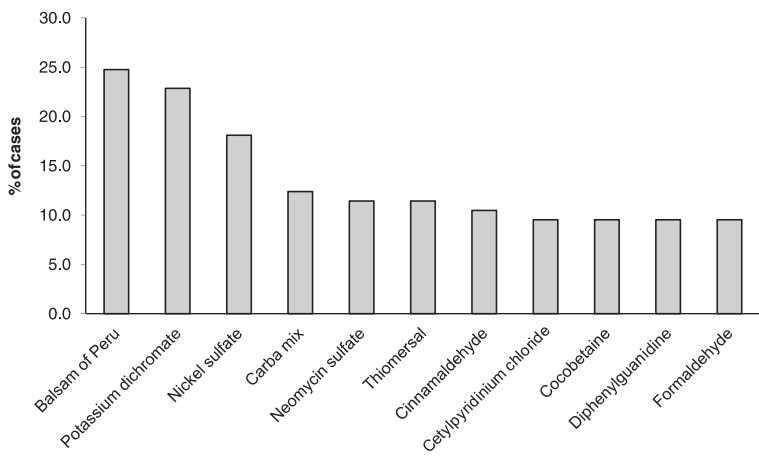


Figure 1 Rank order frequency of the high-incidence allergens of the study cases.

Of all the 71 allergens tested, 15.5% were in group 1, which included 11 allergens sorted in descending order as follows (Fig. 1): balsam of Peru (24.76%), potassium dichromate (22.86%), nickel sulfate (18.10%), carba mix (12.38%), neomycin sulfate (11.43%), thiomersal (11.43%), and cinnamaldehyde (10.48%). Cetylpyridinium chloride, cocobetaine, diphenylguanidine, and formaldehyde all had the same percentage of cases (9.52%).

Three grades of severity (+1/+2/+3) were observed among patients exposed to balsam of Peru, potassium dichromate, nickel sulfate, neomycin sulfate, and thiomersal; diphenylguanidine showed +1 and +3 grades of severity; and the rest of group 1 allergens showed either +1 and +2 grades or only +1 grade of severity.

Group 2 allergens showed frequency of ACD ranging from 4 to 8 cases (3.81%–7.62%); these included 13 allergens sorted in descending order as follows: quaternium, oak moss, ethylenediamine dihydrochloride, para-phenylenediamine (PPD), cinnamyl alcohol, cobalt dichloride, fragrance mix, ammonium persulfate, coconut diethanolamide, Euxyl K400, glutardialdehyde, Kathon CG, and tetramethylthiuram disulfide. The highest incidences were observed with quaternium 15 and oak moss (7.62% and 6.67%, respectively). Only quaternium 15 and PPD showed 3 grades of severity, whereas tetramethylthiuram disulfide had +1 and +3 grades; the other allergens in group 2 had +1 or +1 and +2 grades of severity.

Group 3 allergens, representing almost two-thirds of the substances tested (47 allergens), had ranges between 1 and 3 cases (0.95%–3.84%). Only thiuram mix showed 3 grades of severity (equally distributed) and paraben mix had only +2 and +3 grades. The other 45 allergens showed either +1 or +2 grades, or +1 and +2 grades.

Age, Severity, and Gender

As determined by Spearman's correlation, no significant correlation was observed between age and severity ($p > .05$) among all allergens, except for benzalkonium chloride, which revealed a significant negative correlation ($p < .05$). The first 11 allergens in Table 2, which had the most frequent allergic effects, indicated that nickel sulfate, carba mix, and neomycin sulfate showed a negative correlation trend (predilection to younger age groups), whereas the other 8 allergens indicated the reverse, i.e., older patients were more frequently affected; however, none reached the appropriate level of significance ($p > .05$). There was no significant correlation between age and number of allergens per person, where Spearman's correlation was -0.066 , $p = .504$. There were no significant gender differences regarding age; women were slightly older than men for the total sample (47.60 ± 10.68 and 46.74 ± 11.02 years, respectively, $t = 0.397$ and $p = .692$).

Improvement after Non-Exposure to Offending Allergens (Table 3)

Of the 105 patients in the study, 50 improved, 13 did not improve, and the status of 42 was unknown (Fig. 2). The majority of the 42 patients with unknown status failed to make follow-up appointments after the original diagnosis and instructions; 3 patients were from outlying areas and decided to have follow-up done at clinics closer to their homes. Percentage improvement varied among different allergens.

Table 2 Distribution of allergens according to age group

Allergen	Age group (Yr)					Total	<i>r</i>	<i>p</i>
	18–27	28–37	38–47	48–57	≥ 58			
Balsam of Peru	1	1	5	12	7	26	0.171	.081
Potassium dichromate	1	2	8	8	5	24	0.045	.647
Nickel sulfate	1	4	5	5	4	19	−0.062	.532
Carba mix		3	4	3	3	13	−0.011	.913
Neomycin sulfate	1	4	2	3	2	12	−0.088	.370
Thiomersal		1	5	3	3	12	0.072	.468
Cinnamaldehyde		1	5	3	2	11	0.089	.365
Cetylpyridinium chloride	1	2	1	3	3	10	0.041	.676
Cocobetaine	1	1	2	4	2	10	0.015	.881
Diphenylguanidine		1	4	3	2	10	0.012	.906
Formaldehyde	1		3	2	4	10	0.124	.208
Quaternium 15	2		3	2	1	8	−0.068	.488
Oak moss		1	5		1	7	−0.101	.303
Ethylenediamine dihydrochloride			1	2	3	6	0.147	.134
Para-phenylenediamine			4	1	1	6	−0.018	.856
Cinnamyl alcohol		2	2	1		5	−0.145	.140
Cobalt dichloride	1	1	1	2		5	−0.078	.429
Fragrance mix			1	1	3	5	0.168	.088
Ammonium persulfate	1		2		1	4	−0.045	.647
Coconut diethanolamide		1		1	2	4	0.087	.378
Euxyl K400	2			1	1	4	−0.068	.490
Glutardialdehyde				3	1	4	0.156	.112
Kathon CG			2	1	1	4	0.074	.450
Tetramethylthiuram disulfide		2		1	1	4	−0.012	.904
Benzoyl peroxide	1		1	1		3	−0.081	.410
Butylphenol formaldehyde resin			1		2	3	0.141	.152
Chlorquinaldol			1	1	1	3	0.097	.325
Clobetasol		2			1	3	−0.065	.511
Colophony		1		1	1	3	0.070	.479
Sorbitan sesquioleate	1	1		1		3	−0.165	.092
Thiuram mix		1	1	1		3	−0.062	.530
Triethylenetetramine		2			1	3	−0.001	.992
Benzalkonium chloride	1	1				2	−0.196	.045
Black rubber mix			1		1	2	0.071	.470
Bronopol			1	1		2	0.002	.981
Captan			1	1		2	−0.005	.963
Epoxy resin		1			1	2	0.005	.963
Eugenol		1	1			2	−0.143	.147
Hexamethylenetetramine				1	1	2	0.184	.060
Hydroxycitronellal				1	1	2	0.167	.089
Imidazolidinyl urea				1	1	2	0.103	.294
Isopropylaminodiphenylamine			1	1		2	0.040	.683
Mercapto mix	1			1		2	−0.043	.666
Mercaptobenzothiazole				2		2	0.121	.219
Negative control				1	1	2	0.150	.127
Octyl gallate			2			2	−0.061	.539
Paraben mix	1			1		2	−0.058	.555
Propyl gallate			1		1	2	0.042	.674

(Continued)

Table 2 Continued

Allergen	Age group (Yr)					Total	<i>r</i>	<i>p</i>
	18–27	28–37	38–47	48–57	≥ 58			
Sorbic acid		1			1	2	0.013	.898
Triclosan		2				2	−0.196	.046
Wool alcohol				2		2	0.064	.514
Isoeugenol				1	1	2	0.130	.186
Alpha amyl cinnamaldehyde		1				1	−0.131	.182
Ammonium thioglycolate			1			1	−0.028	.780
Budesonide		1				1	−0.139	.157
<i>Chamomilla romana</i>		1				1	−0.131	.182
Cyclohexylbenzothiazyl Sulfenamide				1		1	0.097	.324
Dexamethasone phosphate		1				1	−0.139	.157
Edetic acid					1	1	0.138	.162
Ethyleneglycol dimethacrylate			1			1	−0.096	.332
Formaldehyde resin					1	1	0.120	.224
Geraniol		1				1	−0.131	.182
Hydrocortisone			1			1	−0.070	.480
Irgasan dp300		1				1	−0.144	.143
Lanolin alcohol				1		1	0.063	.522
Phenylcyclohexyl-p-phenylenediamine			1			1	−0.083	.402
Phenylmercuric acetate		1				1	−0.131	0.182
Tixocortol pivalate				1		1	0.034	0.731
Triamcinolone		1				1	−0.139	0.157
Triethanolamine stearate					1	1	0.138	0.162
Toluene diamine sulfate			1			1	−0.028	0.780

Group 1 allergens showed a range of improvement between 50% for cocobetaine and 92.3% for potassium dichromate; the other 9 allergens were within that range. In group 2 allergens, improvement was between 25% for quaternium 15 and 100% for 3 allergens (cobalt dichloride, coconut diethanolamide, and Euxyl K400). Group 3 allergen showed 68.5% improvement and 31.5% have no improvement, representing 68.5% of known results for different allergens in this group.

A significant difference was observed regarding mean number of allergens; patients with improved conditions showed a significantly lower number of allergens compared with those who did not show improvement (2.70 ± 1.87 and 4.0 ± 1.83 allergens, respectively, where the Mann-Whitney test result was 2.526, $p = .012$). The mean age of patients who showed improvement was lower than that for those who did not show improvement, although this difference was not statistically significant (47.40 ± 10.36 and 51.77 ± 8.16 years, respectively, where $t = 1.408$, $p = .203$).

Gender, Past History of Allergy, and ZIP Codes

There was a significant level of difference in the mean number of allergens related to gender (Fig. 3). The mean number of allergens was significantly higher among men compared with women (3.51 ± 2.36 and 2.65 ± 1.78 allergens, respectively) in which

Table 3 Distribution of allergens according to improvement after non-exposure to the offending allergen

Allergen	No improvement	Improvement	Unknown	Total	Total known	% Improvement/ known
Balsam of Peru	5	9	12	26	14	64.3
Potassium dichromate	1	12	11	24	13	92.3
Nickel sulfate	2	11	6	19	13	84.6
Carba mix	1	5	7	13	6	83.3
Neomycin sulfate	1	8	3	12	9	88.9
Thiomersal	3	6	3	12	9	66.7
Cinnamaldehyde	2	5	4	11	7	71.4
Cetylpyridinium chloride	2	4	4	10	6	66.7
Cocobetaine	3	3	4	10	6	50
Diphenylguanidine	1	5	4	10	6	83.3
Formaldehyde	4	4	2	10	8	50
Quaternium	3	1	4	8	4	25
Oak moss	3	4	0	7	7	57.1
Ethylenediamine dihydrochloride	1	3	2	6	4	75
Para-phenylenediamine	2	2	2	6	4	50
Cinnamyl alcohol	1	3	1	5	4	75
Cobalt dichloride	0	3	2	5	3	100
Fragrance mix	1	3	1	5	4	75
Ammonium persulfate	2	2	0	4	4	50
Coconut diethanolamide	0	2	2	4	2	100
Euxyl K400	0	1	3	4	1	100
Glutardialdehyde	1	0	3	4	1	0
Kathon CG	3	1	0	4	4	25
Tetramethylthiuram disulfide	1	2	1	4	3	66.7
Benzoyl peroxide	0	3	0	3	3	100
Butylphenol formaldehyde resin	2	1	0	3	3	33.3
Chlorquinaldol	0	1	2	3	1	100
Clobetasol	0	1	2	3	1	100
Colophony	1	1	1	3	2	50
Sorbitan sesquioleate	0	1	2	3	1	100
Thiuram mix	0	1	2	3	1	100
Triethylenetetramine	0	1	2	3	1	100
Benzalkonium chloride	0	0	2	2	0	0
Black rubber mix	1	0	1	2	1	0
Bronopol	0	1	1	2	1	100
Captan	0	0	2	2	0	0
Eugenol	0	0	2	2	0	0
Epoxy resin	0	0	2	2	0	0
Hexamethylenetetramine	1	1	0	2	2	50
Hydroxycitronellal	0	2	0	2	2	100
Imidazolidinyl urea	1	1	0	2	2	50
Isopropylaminodiphenylamine	2	0	0	2	2	0
Mercapto mix	0	1	1	2	1	100
Mercaptobenzothiazole	0	1	1	2	1	100
Negative control	0	2	0	2	2	100
Octyl gallate	0	2	0	2	2	100

(Continued)

Table 3 Continued

Allergen	No improvement	Improvement	Unknown	Total	Total known	% Improvement/ known
Paraben mix	0	1	1	2	1	100
Propyl gallate	0	1	1	2	1	100
Sorbic acid	0	2	0	2	2	100
Triclosan	0	1	1	2	1	100
Wool alcohol	0	1	1	2	1	100
<i>Isoeugenol</i>	0	0	2	2	0	0
Alpha amyl cinnamaldehyde	0	0	1	1	0	0
Ammonium thioglycolate	0	1	0	1	1	100
Budesonide	0	0	1	1	0	0
<i>Chamomilla romana</i>	0	1	0	1	1	100
<i>Cyclohexylbenzothiazl</i>	0	1	0	1	1	100
<i>Sulfenamide</i>						
<i>Dexamethasone phosphate</i>	0	0	1	1	0	0
Edetic acid	1	0	0	1	1	0
Ethyleneglycol dimethacrylate	0	0	1	1	0	0
Formaldehyde resin	0	0	1	1	0	0
Geraniol	0	0	1	1	0	0
Hydrocortisone	0	1	0	1	1	100
Irgasan dp300	0	0	1	1	0	0
Lanolin alcohol	0	1	0	1	1	100
Phenylcyclohexyl-p-phenylenediamine	1	0	0	1	1	0
Phenylmercuric acetate	0	1	0	1	1	100
Tixocortol pivalate	0	0	1	1	0	0
Triamcinolone	0	0	1	1	0	0
Triethanolamine stearate	1	0	0	1	1	0
Toluene diamine sulfate	0	1	0	1	1	100

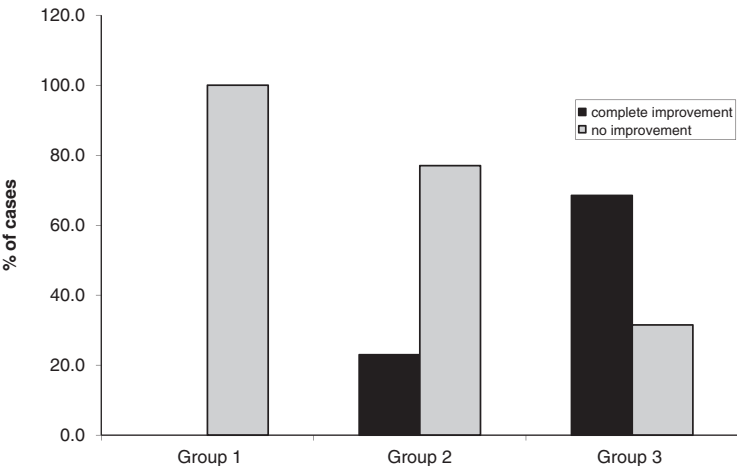


Figure 2 Distribution of different subgroups according to complete improvement after avoidance of exposure to the offending allergen.

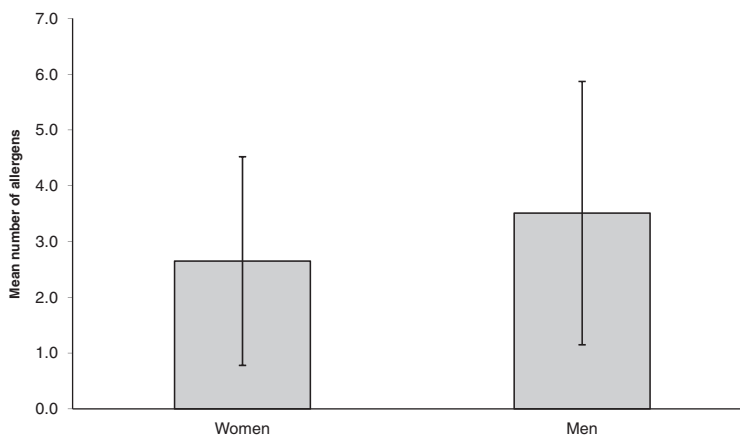


Figure 3 Mean and standard deviation of the number of allergens per case according to gender.

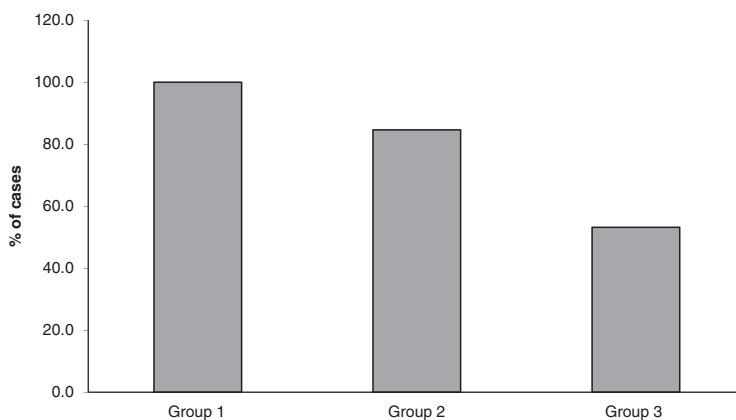


Figure 4 Distribution of subgroups according to presence of past history of allergic diseases.

the Mann-Whitney test result was 1.967, $p = .05$. In group 1 allergens, men predominated over women, except for potassium dichromate, nickel sulfate, and neomycin sulfate; however, no significant difference was observed as revealed by χ^2 values and Fisher's exact test ($p > .05$). The same result occurred for group 2 and group 3; no consistent/significant gender differences could be detected.

Almost one-third ($n = 38$) of total cases (36.2%) had previous positive past history of allergy, regardless of type of allergen, whereas the rest were negative (Fig. 4). It was found that those with past history of allergy were significantly older than those with negative history (49.10 ± 10.19 and 43.97 ± 11.13 years, respectively, where $t = 2.397$, $p = 0.018$). Although the mean number of allergens was slightly higher among patients who had positive past history compared with those who had negative past history, a significant level of difference was not reached (3.10 ± 2.27 and 2.82 ± 1.84 allergens, respectively) in which the Mann-Whitney test result was 0.297, $p = 0.767$.

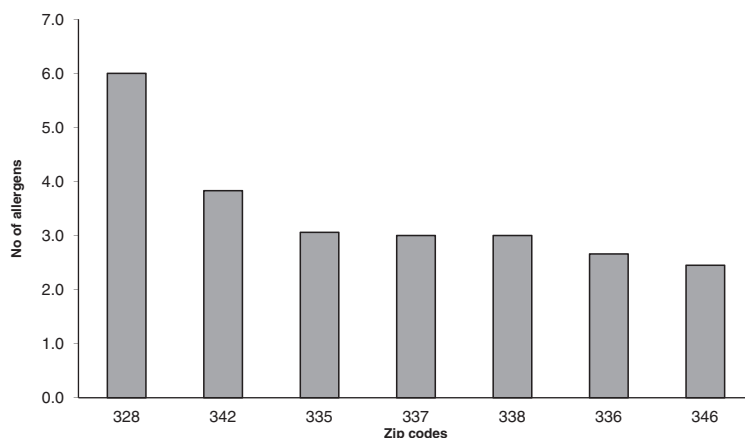


Figure 5 Mean number of allergens per case according to highly affected ZIP codes.

All group 1 allergens showed positive past history, with the highest observed in potassium dichromate ($\sim 46\%$), whereas the lowest proportion was observed with carba mix ($\sim 8\%$). For group 2, 11 of 13 allergens showed positive past history, with a range of 14.29% to 100% among cases. Group 3, 22 allergen out of 47 allergen showed negative past history representing 46.8% of allergen, the other 25 allergen representing 53.2% showed positive past history.

In general, clusters of effects of allergens were seen in areas with the following ZIP codes: 335, 336, 337, 338, 342, 346, and 339 (Fig. 5). Group 1 allergens, which had the most frequent dermatological effects, had the highest share in areas with ZIP codes 335, 336, 337, and 338, especially among the following 7 allergens: balsam of Peru, potassium dichromate, nickel sulfate, carba mix, neomycin sulfate, thiomersal, and cinnamaldehyde. For the remaining allergens, random distribution was observed, with no specific inference. Analyzing the number of allergens by ZIP code indicated that the highest mean number of allergens was observed in ZIP code 328 (6.0 ± 4.36 allergens), whereas the lowest was observed in ZIP code 346 (2.45 ± 1.15 allergens). No significant difference could be detected, as revealed by K-W χ^2 , where $p = .781$.

DISCUSSION AND RECOMMENDATIONS

The superficial inflammatory process known as dermatitis is categorized by chronicity of the condition as acute, subacute, or chronic. Contact dermatitis is further identified as either *irritant* or *allergic*, the distinction being based on immunological mediation (14). Irritant contact dermatitis (ICD), which is the second most common occupational illness, is divided into 2 forms, acute and cumulative contact dermatitis. Acute ICD presents the classic symptoms of irritation such as localized and superficial erythema, edema, and chemosis; it occurs as a result of a single exposure to an acute irritant. Cumulative ICD presents similar symptoms, but occurs when exposure to a less potent irritant is persistent or repeated until signs and symptoms develop over weeks, years, or decades. The severity of symptoms depends on exogenous and endogenous

factors. Exogenous factors include the irritant's chemical and physical properties, the vehicle, and the frequency of application. Endogenous factors include age, gender, pre-existing skin diseases, skin sensitivity, genetic background, and ethnicity (15). In a study by Shenefelt with a university student population, contact dermatitis represented a relatively large proportion of visits for dermatitis. Slightly more ACD than ICD was found, which was at variance with findings in industrial settings, in which ICD was generally more common than ACD (16).

In this study, results showed that the top 3 allergens frequently responsible for ACD among cases (65.7%) were balsam of Peru, potassium dichromate, and nickel sulfate. Balsam of Peru sensitization is common in healthcare workers and hair-dressers. Common consumer products that contain balsam of Peru include cosmetics, topical medications, flavors, and spices (17). Potassium dichromate is deemed a carcinogenic chemical, and exposure can occur in industrial settings such as battery manufacturing, painting, printing and dyeing, and leather tanning, and also while using disinfectants (18). Since the 1970s, trends show a decrease in reaction positivity, although in this study it presented as the second most frequent allergen. Potassium dichromate's classification as cancerous may have led to more cautious use of the chemical and may account for the decrease of reaction positivity seen in the early North American Contact Dermatitis Group (NACDG) results (18, 19).

Nickel, one of the most prolific metal allergens in the general population, can be found in industry (welding, petroleum refining, and steel production) and in households (costume jewelry, clothing zippers and snaps, coins, keys, tools, batteries, etc.) (20, 21). Nickel is a hard, silvery white metal that resists corrosion, even at high temperatures. It was first identified in 1751 and is used in many industrial and consumer products, including stainless steel, magnets, metal plating, coinage, and special alloys. In the 1970s, metal buttons and zippers in blue jeans most frequently caused nickel dermatitis, whereas in the 1980s, it was most frequently caused by jewelry (1). Interestingly, patients with a positive reaction to nickel sulfate were likely to have an additional positive reaction to fragrance mix, which unequivocally and progressively increased with the strength of nickel reaction, and vice versa. Patients with a positive reaction to fragrance mix also had an additional reaction to nickel sulfate. These associations were found to be statistically significant (22).

In 1994, legislation was passed in the European Union (EU) prohibiting trade with products that released more than 0.5 mg/cm^2 per week of nickel. Despite these regulations, nickel remains the most common allergen in patch test clinics all over Europe. In the United States, where no nickel regulation has been introduced, nickel continues to be responsible for clinical disease among younger patients (4, 19). The proportion of nickel allergy out of all contact allergens has increased significantly over the past 4 decades. Hand eczema, heavy smoking, and pierced ears are strong risk factors for nickel allergy. The frequency of nickel allergy in women increased with the number of piercings, i.e., having 3 or more ear piercings led to a 4-fold increase (1).

As mentioned previously, patch testing was performed for 71 allergens (Table 1). The following are brief descriptions of select allergens from groups 1, 2, and 3. Neomycin sulfate (ranked fifth, group 1) in previous study results had trended upward in prevalence of allergic reaction, possibly because it was readily prescribed as a topical antibiotic by physicians in the 1970s, but more recently has declined, suggesting that physicians may have limited their prescription regimen of this antibiotic (19).

Formaldehyde (ranked tenth, group 1) is used as a preservative in household products, such as detergents, topical medications, and cosmetics; it is also used in industrial products such as paints, cutting fluids, lacquers, and disinfectants. Today, formaldehyde-releasing preservatives have replaced formaldehyde in most cosmetics and industrial products, as they are less frequent sensitizers. Occupational sensitization to formaldehyde is widespread and has been reported among hairdressers, medical personnel, paper manufacturers, shoe manufacturers, embalmers, and especially among industrial workers exposed to metalworking fluids (4). Quaternium 15 (ranked 11th, group 1) is found in many common household products including cosmetic, self-hygiene, and pharmaceutical products; many mainstream brands may include this chemical. The recent surge in reaction positivity may be due to an increase in use of such well-known, affordable products (19).

PPD (ranked 14th, group 2) has been used as a fur and textile dye and is found in black rubber, but today it is mainly used for permanent hair dyeing and is an ingredient in almost every permanent hair color product on the market, regardless of brand. Sensitization by PPD was considered a significant health risk and prohibited in Germany in 1906. Today, hair dyeing is widely applied, with 75% of American women reportedly dyeing their hair, and an increasing number of men following their lead (19). Euxyl K400 (ranked 20th, group 2) is a combination of 2 preservatives, methyl dibromoglutaronitrile (MDBGN) and 2-phenoxyethanol (PE), in a 1:4 ratio. Euxyl K400 was introduced as a potent alternative to other sensitizing preservatives. ACD to Euxyl K400 is almost exclusively due to sensitization with MDBGN and only rarely due to PE. ACD has been reported from MDBGN in different products such as soap, cleansing milk, shampoos, moisturizers, ultrasonic gel, moistened toilet paper, sunscreen lotion, detergents, and eye gel (4). Thiuram sensitivity appears to be decreasing in sensitivity according to the most recent set of data. In this study, only 3 patients were sensitive to thiuram (ranked 30th, group 3), which is consistent with the recent trends reported by Nguyen et al. This decrease could be the result of greater use of vinyl and non-natural rubber latex gloves in the healthcare professions (19).

Although balsam of Peru, potassium dichromate, and nickel were the 3 allergens most frequently observed, study results indicated that frequency of sensitization did not correlate with severity of sensitization, as measured by +1, +2, or +3 grades of reaction. For example, although balsam of Peru was the most frequent allergen observed, only 1 patient had a +3 reaction, whereas 2 patients had +3 reactions to thiomersal (ranked sixth according to frequency). In the entire sample population, 20% had +3 reactions. Patients with +3 reactions to 1 allergen are statistically more likely to have reactions to unrelated allergens than patients with weaker (+1/+2) reactions (3, 22). In an interesting case study from Canada, a patient developed facial ACD to nickel from cell phone use; this in turn led to a study of cell phones, which found that many cell phones' exterior casings contain free nickel, especially those with more fashionable designs (23). According to Brasch et al., it would be appropriate for the patient with ACD to nickel to be cross-patch tested for reaction to fragrance mix (22).

Regarding gender, the results of this study are consistent with other gender studies (24, 25); Modjtahedi et al. found that there were no fundamental skin differences between men and women, although the study indicated that women might show

more skin sensitivity to certain allergens because of an increase in skin exposure patterns to the allergen itself, or to wet work and other irritants. In another study conducted in Israel, positive reactions to nickel sulfate were more common among women under 40 years of age, whereas positive reactions to balsam of Peru were more common in men over 40 years of age (9). In the Modjtahedi study, the most frequent contact allergen was nickel, which was seen more frequently in women who wore jewelry, especially earrings (24).

Brasch et al. observed that the proportion of patch test patients who were women was higher than the proportion who were men, and that there was a higher positivity ratio (PR) in women than in men. The PR is defined as the percentage of weak positive (+) reactions out of all positive reactions elicited by a certain allergen. The mostly higher PR in women may, therefore, indicate that women are more likely to develop only weak positive (+) reactions to common contact allergens than are men, who appear to have a slightly higher tendency to show stronger positive reactions. Furthermore, a higher reaction index (RI) in women than in men was found. The RI relates the number of irritant and questionable reactions to the number of positive reactions obtained with a certain allergen. A high RI reflects a higher proportion of positive as compared with irritant and/or questionable reactions than a low RI. Therefore, Brasch et al. found that the higher RI in women than in men indicates that women tend to have less questionable and/or irritant reaction to common patch test allergens than men. In contrast to the current study, Brasch et al.'s study supported the idea that some constitutive difference in responsiveness to contact allergens between men and women might exist (25).

In this study, no significant difference could be observed in the race variable because only 2 patients were black (positive to 3 and 4 different allergens, respectively) and 1 was Asian (positive to 8 allergens), while the remaining patients were white. The high percentage of white participants can be accounted for by 2 factors: 1) According to other studies regarding ethnicity (namely, between white and black individuals), even though the studies were directly comparing 2 ethnicities, a much higher percentage of whites (88.5% and 89.5%, respectively) underwent patch testing than blacks (11.5% and 10.5%, respectively). Incidentally, these studies found that the prevalence of ACD among black and white individuals in North America was the same; however, there were differences in response to specific allergens (26,27). 2) According to demographic data in the studied region, the counties surrounding USFDMC, where most of the study participants reside (~83%), are in an area that has a higher white population and a lower black population compared with other regions in the United States (28–31).

Age was another variable affected by demographics in the region. Analysis of age by ZIP codes (after excluding areas with 1 case) showed significant differences in mean age, where the oldest (55.40 ± 5.74 years) was observed in ZIP code 337 and the youngest (42.67 ± 8.62 years) was observed in ZIP code 328 ($\chi^2 = 23.201$, $p = .026$). The median age in this region is higher than the national average, and the distribution of age may be due in part to clustering in "over 50" communities (28–31). Age did not have a clear relation with severity or number of allergens; the difference regarding ZIP codes may be related to residential distribution of cases.

Of all the patients studied, 50.5% were 50 years of age or older and 29.5% were 55 years of age or over. According to Scalf and Shenefelt, dermatitis, not otherwise

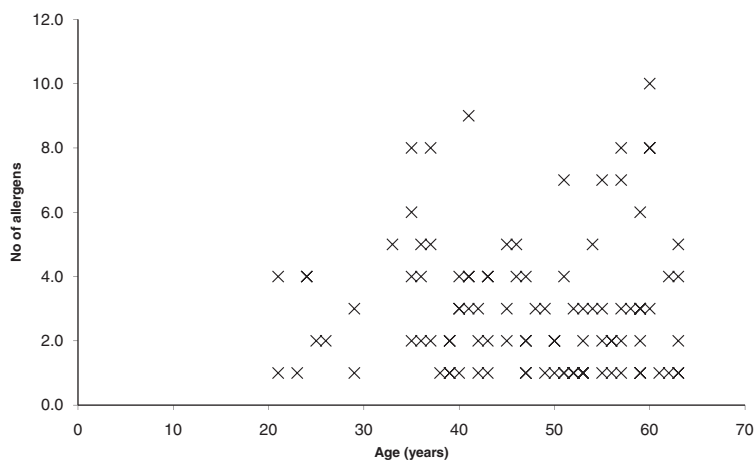


Figure 6 Scatterplot of the relationship between age and number of allergens per case for all studied cases.

specified (NOS), was the sixth most frequently coded dermatological diagnosis for adults aged 55 years and older (32). Diminished chemical dermal clearance in the aged skin, due to altered dermal circulation and dermal structure changes, may result clinically in contact dermatitis (33). It is important to tell older patients with ACD that it may take as long as 3 months of strict allergen avoidance to see improvement (32).

Multiple contact allergies (polysensitized) are instances in which patients have 3 or more contact allergens and can be observed in both children and adults (1, 3). In this study, 69.5% of patients had 2 or more contact allergens and 50.5% of patients had 3 or more contact allergens (Fig. 6). Many synchronous reactions occur to chemically unrelated allergens (nickel sulfate and fragrance mix) that neither are cross-reacting nor have common sources of exposure; this not only indicates a strong sensitization to a particular antigen, but also can also be related to an outstanding disposition for contact allergy in general. In the study by Brasch et al., patients with a strong patch test reaction to 1 allergen were more likely to have reactions to additional allergens than were patients with only weak patch test reactions (22). Development of multiple contact allergies is the result of interplay among environmental exposure, individual susceptibility (genetic factors), and cross-reaction. Genetic markers associated with multiple contact allergens are polymorphism of NAT2, IL 16-295, TNF- α -308 (2, 3).

Genetic factors seem to be an important contributor to the increased susceptibility for non-high-risk environmental exposure patients with multiple contact allergies. An increased susceptibility lowers the threshold for induction. In the study by Carlsen et al., strong patch test reactions were shown to be associated with additional allergies and with strong reactivity to the additional contact allergens. Concomitant exposures and cross-reactivity were excluded as explanation, supporting an antigen-independent association. Therefore, patients who respond with strong patch test reactions, which occurred with 20% of this study's participants, might exhibit a general increased susceptibility. Cross-reaction as a mechanism explains only a minor proportion of all patients with multiple contact allergies (3).

Regarding polysensitization among cases in this study, Fregert brings up a very good point about cross-sensitivity, which means that a subject, allergic to a primary allergen, reacts to a chemically related secondary allergen to which he or she did not react before sensitization to the primary allergen. Fregert's premise is that patch test substances should be clear and free from secondary allergen. However, the release of chemically related substance from the vehicle may vary and therefore give weaker or stronger test reactions; if the purity of the primary allergen and/or simultaneously reacting substances is unknown, the conclusions drawn concerning cross-sensitivity must be limited because it cannot then be established whether the labeled substance is the allergen or not (34). In this study, the antigens were all purchased pre-prepared from reliable commercial sources, and none were prepared at USFDMC, allowing for consistency in test substances.

The standard approach to help patients avoid further sensitization is to inform them of the name of the offending allergen, including its chemical name, any synonyms, and the names of any cross-reacting chemicals. Patients are then counseled to read the labels of any product for use on their skin to make sure it is free of this allergen. This works with single-allergen sensitization, but can be a very challenging task with multiple sensitivities. As mentioned previously, 70.5% of patients in this study were sensitive to 2 or more allergens. In regard to alleviating this problem, a useful tool is available to practitioners. Since 1999, the Mayo Clinic has used the Contact Allergen Replacement Database (CARD), which contains the ingredient list of more than 2,000 topical skin care products, to assist patients in avoidance of specific allergens; the patient-identified allergens are entered into CARD and a list of products that the patient can safely use is generated. These products are free of any offending allergens or any cross- or co-reactants. CARD is now available as an on-line tool at www.contactderm.org for members of the American Contact Dermatitis Society (4, 35).

Although an appropriate level of significance was not met regarding percentage improvement and age, there was a trend toward better outcomes for younger patients. According to Kadyk et al., quality of life in patients with ACD seemed to be improved by early diagnosis in the natural history of the condition (8). Education about allergens is very important, and assessment of appropriate levels of exposure is the best way to reduce the incidence of sensitization.

Overall, environmental exposure is the most important factor in development of contact allergy; without it, contact allergy cannot be induced (3). It is difficult to assess contact allergy in children, but it is generally believed that the prevalence of contact sensitization gradually increases through childhood and adolescence because of increased environmental exposure to contact allergens (1). The fact that a chemical is a contact allergen does not mean that it cannot be formulated into a consumer product at levels well tolerated by most individuals. All allergens show dose-response and threshold characteristics; therefore, one should be able to incorporate these chemicals into products at levels that produce acceptably low incidences of skin sensitization under foreseeable conditions of exposure (6). Certain sensitizing chemicals can be applied in various products without inducing contact allergy, as long as the concentration is low. However, if the concentration of a sensitizing chemical is too high, the risk of sensitization is increased. The purpose of preservation is to eliminate microbial growth, but often a higher concentration than necessary is applied. This increases the risk of sensitization (4).

On the macro level, several countries have implemented legislations to reduce the populations' exposure to known sensitizers. Common sensitizers studied include nickel, chromate, and thiuram. Overall, the evidence suggests a decreasing trend of ACD with appropriate formulation changes following toxicological and epidemiological information. However, exposure to the allergens via small manufacturers or imported products that do not follow regulations may still exist (36). The key steps of quantitative risk assessment (QRA) are establishing human exposure, identifying a no-observed-adverse-effect level (NOAEL), applying appropriate uncertainty factors (UFs), establishing an acceptable dermal exposure level (sensitization reference dose; S-Rfd), and comparing consumer exposure with the acceptable exposure level (37, 38). For example, it was recommended that household and other consumer products should not contain more than 5 ppm of nickel, chromium, or cobalt and that, for an even greater degree of protection, the ultimate target level should be 1 ppm (38). Interestingly, contact allergy epidemics most often start with cases of OACD, whereas consumer cases seem to appear later. Regrettably, safety data do not always reach scientific journals and meetings. Data from industries as well as public research institutions should be easily accessible to investigators to enhance future risk assessment and early detection (4).

CONCLUSION

Statistical analysis indicated a significant level of difference in the mean number of allergens related to gender, with men having more allergens than women, i.e., men were more likely than women to suffer from ACD (and polysensitization, in particular) (Fig. 3). Therefore, special care must be taken, especially in occupational exposure (i.e., pre-employment testing). Positive past history of allergy was frequently observed in the first 2 groups of allergens; in group 1—high incidence, 100% of patients affected by these allergens had positive past history; in group 2—medium incidence, 84.62% were affected, and in group 3—low incidence, 53.2% were affected (Fig. 4). Also, patients with positive past history were significantly older than those with negative history. These factors (number of allergens according to gender and positive past history) suggest that possible future research should focus on both of these variables.

Another direction of future research should be number of allergens and improvement, since patients whose conditions improved showed a significantly lower number of allergens compared with those whose conditions did not improve (Fig. 2). According to groups, group 1 showed 100% non-improvement compared with group 2, in which 23% showed complete improvement. Group 3 had the best outcome, with 68.5% experiencing complete improvement. In addition, although not statistically significant, younger patients trended toward better improvement compared with older patients. In the future, having a sufficiently larger population would help determine whether the above-mentioned trend would in fact become statistically significant. In general, having a larger population would have increased the power of this study.

Cases with severe patch test reactions did not undergo further testing for cross-reactions to other allergens, which would be an appropriate measure in future studies. However, severity, as measured by 3 grades, does not always correlate with frequency.

Damage to the skin can be repaired, when the interval between the individual damaging processes is sufficiently long and when the damage is not too extensive (39). Therefore, future studies should use further statistical analysis to see if susceptibility to one allergen indicates a significant susceptibility to another allergen (22). Clustering of some allergens and the occurrence of ACD could be observed in some areas, namely, ZIP codes 328, 335, 336, 337, 338, and 342, which raised interesting questions regarding location and allergen exposure. Geographical areas must be considered in the study of ACD, and environmental samples could be of help to identify the presence of any allergen. A future avenue of study should include cluster analysis, with more finely parsed areas within each ZIP code. In this study, some of the allergens trended the same as those in Nguyen et al.'s study, whereas others did not. New chemicals and old chemicals combined in different ways emerge onto the market consistently (19). Past risk-assessment failures teach us that regulatory steps should be enhanced to prevent long-term contact allergy epidemics (for example, nickel products). It is essential that dermatologists, scientists, and administrators organize and structure known regulatory methods to accelerate the control of emerging contact allergens (4).

Identification of patients at risk of developing multiple contact allergies is needed for primary prevention (3). Patients with strong patch test reactions should be advised not only to strictly avoid their known allergen, but also to minimize exposure to further contact allergens (22). In this study, patients who did not show improvement through avoidance were not patch tested for other allergens; in future research, subsequent patch testing would provide valuable data. In general, interpreting trends in the results of patch testing and statistically comparing the results and data monitoring will—in the end—provide stimulus for preventive interventions and public health opportunities (4).

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