

Patch-Testing with the Standard Series at the Massachusetts General Hospital, 1998 to 2006

Lilla Landeck, Peter C. Schalock, Lynn A. Baden, Konrad Neumann, and Ernesto Gonzalez

Background: The diagnostic tool to detect allergic contact sensitization is patch testing.

Objective: Results of patch testing performed from January 1998 to December 2006 at the Massachusetts General Hospital (MGH) are analyzed and compared to our 1990–1997 data as well as to data from North American and European contact dermatitis societies.

Methods: Data were collected from retrospective chart reviews and analyzed, focusing on the Hermal standard tray.

Results: The most common sensitizers were fragrance mix (18.3%) and nickel (16.7%). Significant increases over time were seen for balsam of Peru ($p < .0005$; CI, 1.34–2.76) and wool alcohols ($p = .002$; CI, 1.38–4.38) while gender-related statistical predominance was seen for nickel in females ($p < .0005$; CI, 2.92–8.20) and for epoxy resin in males ($p < .0005$; CI, 0.14–0.58). Our findings are similar to those of the North American and European contact dermatitis societies. The retrospective study sample was drawn from a selected group of referred patients that may not be representative of the general population. Analysis of data focused on the Hermal standard tray and might not reflect trends resulting from additional allergens in supplemental trays.

Conclusion: Sensitization rates and the most important allergens at MGH have been stable over the past 17 years.

AMONG INDUSTRIALIZED COUNTRIES, allergic contact dermatitis (ACD) is one of the frequent dermatologic diseases presenting for treatment. Data from the 2006 National Ambulatory Medical Care Survey¹ revealed an estimated 9.5 million outpatient visits yearly to American physicians for “contact dermatitis and other eczema,” of which 20% are likely allergic in nature,² the remaining cases being classified as irritant. This suggests that approximately 2 million visits per year are related to allergy.

Both the American and European contact dermatitis societies recommend patch testing as the “gold standard” for confirmation of ACD.^{3,4} The vast majority of patients suspected of having contact allergy are tested with a standard series. The goal of a standard series is to identify allergens that react at rates of greater than 0.5 to 1.0%.⁵

Because of the significant socioeconomic impact of ACD, especially in the realm of occupational dermatology,⁶ it is important to examine population trends.

Epidemiologic data on contact dermatitis collected from several patch test clinics across the United States and Europe have been combined to characterize these trends. The North American Contact Dermatitis Group (NACDG) provides significant pooled epidemiologic data used to determine the prevalence of contact allergens among the patch-tested population. The European Surveillance System on Contact Allergies (ESSCA) is a similar group that conducts epidemiologic research on contact allergy for European countries.

The objective of this study is to describe and compare patch-test results collected during a 9-year period from the Contact Dermatitis Clinic at the Massachusetts General Hospital with our previously collected data from 1990 to 1997 and to data reported by NACDG and ESSCA.^{7–9} The focus of our investigation was allergens from the Hermal standard tray (Hermal, Reinbek, Germany).

Materials and Methods

Patch-test results and patient information regarding age, sex, date of testing, occupation, and final diagnosis after testing were collected by reviewing paper (1998–2003) and electronic (2004–2006) records for patients who underwent patch testing between January 1998 and December 2006 at the Massachusetts General Hospital Contact Dermatitis Clinic. Institutional review board approval was obtained. Individuals referred to the clinic with

From the Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; Centre Dermatology and Aesthetic Medicine, Newton, MA; and the Department of Biometry and Clinical Epidemiology, Charité-Universitätsmedizin Berlin, Berlin, Germany.

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persistent eczematous dermatitis who were suspected of having contact allergy were included; 627 patients aged 9 to 89 years (mean, 47.6 years) were screened at least with the Hermal standard tray, which included 29 common allergens. Additionally tested customized supplemental allergen series were not included in this study. For descriptive characterization of the patient population, the MOAHLFA index¹⁰ was used (MOAHLFA is an acronym for male; occupational, atopic, hand, leg, or face dermatitis; and age > 40 years) (Table 1). Patch testing and reading was conducted by standardized technique in accordance with international recommendations, applying Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) affixed with Scanpor tape (Norgesplaster A/S, Vennessla, Norway) to the upper back.¹¹ Allergens were purchased from Hermal. Patch tests remained in place for 48 hours, and test sites were initially evaluated after 48 and 72 hours and (in a few cases) again at 96 hours or 7 days following placement. In this analysis, only 48- and 72-hour readings were incorporated.^{12–14}

All interviews and interpretations of patch-test reactions over the 9-year study period were performed by a single observer (E.G.). Patch-test readings were classified as allergic (+, ++, +++), questionable (?), irritant (i), or negative (n). Questionable, irritant, and negative reactions were considered nonallergic.

Statistical analysis was performed for allergens with sensitization rates greater than or equal to 0.5% and carried out by contingency tables, using the chi-square test and Fisher exact test where appropriate. Odds ratios with two-sided 95% confidence intervals (CIs) are reported. The multiple level of significance was $\alpha = 0.05$. Because 21 tested allergens showed a rate of sensitization greater than or equal to 0.5%, the single level of significance was adjusted to $\alpha = 0.0024$ (Bonferroni correction of factor 21). All statistical analyses were carried out with SPSS v. 15.0 software (SPSS Inc., Chicago, IL).

Table 1. MOAHLFA Index for the Investigated Population (N = 627)

MOAHLFA	%	N
Male	29.2	183
Occupational dermatitis	4.0	25
Atopic dermatitis	11.2	70
Hand dermatitis	24.2	152
Leg dermatitis	14.7	92
Face dermatitis	29.5	185
Age > 40 years	67.3	422

Results

Patch tests were performed on a total of 627 patients during the 1998–2006 study period; 444 (70.8%) were females. The average age was 48.1 years (range, 12–89 years) for females and 46.6 years (range, 9–81 years) for males. Seventy patients (11.2%) had a past history of atopic dermatitis. One or more positive reactions were observed in 387 patients (61.7%). The frequency of response to test substances with a sensitization rate greater than or equal to 0.5% is shown in Table 2 and is compared with sensitization rates from the authors' previous study period and surveys done by the NACDG⁷ and ESSCA.⁹ The five most frequently positive allergens were fragrance mix (18.3%), nickel sulfate (16.7%), balsam of Peru (14.9%), para-phenylenediamine (7.3%), and wool alcohols (6.6%). A statistically significant increase ($p \leq .0024$) of sensitization over the two study periods was seen for balsam of Peru ($p < .0005$) and wool alcohols ($p = .002$). There appeared to be a trend of an increase of sensitization for fragrance mix and potassium dichromate, although neither trend showed statistical significance.

Analyzing patch-test results with regard to gender-related differences (detailed data not presented) in positive reactions showed that only nickel sulfate was significantly more frequent in women ($p < .0005$; CI, 2.92–8.20). Men showed predominance in sensitization to epoxy resin ($p < .0005$; CI, 0.14–0.58). As seen in Table 3, the most frequent primary diagnoses according to the single reader after testing were ACD (42.3%) and atopic dermatitis (23.0%). In 13.1% of the patient population tested, no primary diagnosis was established. The most common occupation reported was “professional/office,” representing 28.9% of tested patients, followed by “medical/dental” (10.4%). The group designated as “home/retired/unemployed” represented 23.8% of the population. For a complete breakdown of the occupations represented, see Table 4.

Discussion

Comparison of the epidemiologic data in our study with data from 1990 to 1997 revealed essentially no changes. The percentage of female patients stayed constant at approximately 70%, as did the rate of patients with at least one sensitization ($\approx 60\%$). A slightly higher rate of sensitization of 67% for the latter group was reported by the NACDG in their 2001–2002 pooled data,⁷ whereas the ESSCA indicated sensitization rates between 26% and 64%, depending on the participating center.⁹ Variations in the European data were attributed to different levels of

Table 2. Positive Patch-Test Reactions for Allergens with a Sensitization Rate $\geq 0.5\%$ *

Allergen [†]	(%)	Authors' 1998–2006 Study, n = 627 (%)	Authors' 1990–1997 Study, n = 610 (%)	p Value [‡] (Recent vs Previous Study)	Odds, Recent/Odds, Previous (OR [95% CI])	NACDG 2001–2002 (%)	ESSCA 2002–2003 (%)
1. Fragrance mix	8.0	18.3	13.3	0.016	1.46 (1.07–1.99)	10.4	7.1
2. Nickel sulfate	5.0	16.7	12.8	n.s.	1.36 (0.99–1.87)	16.7	18.0
3. Balsam of Peru	25.0	14.9	8.4	< .0005	1.92 (1.34–2.76)	11.6	6.1
4. para-Phenylenediamine	1.0	7.3	5.4	n.s.	1.38 (0.72–2.63)	4.8	3.3
5. Wool alcohols	30.0	6.6	2.8	.002	2.46 (1.38–4.38)	2.2	3.0
6. Cobalt chloride	1.0	6.4	8.7	n.s.	0.72 (0.47–1.10)	7.4	7.8
7. Formaldehyde	1.0 aq	5.8	6.2	n.s.	0.92 (0.58–1.48)	8.4	2.0
8. Quaternium-15	1.0	5.1	8.0	.041	0.62 (0.39–0.98)	9.3	1.3
9. Potassium dichromate	0.5	5.0	2.3	.012	2.22 (1.17–4.22)	4.3	5.3
10. Neomycin sulfate	20.0	4.7	4.9	n.s.	0.94 (0.56–1.59)	11.6	2.9
11. Thiuram mix	1.0	4.3	5.7	n.s.	0.74 (0.45–1.25)	4.5	2.1
12. Colophony	20.0	4.3	3.9	n.s.	1.12 (0.63–1.94)	2.6	3.6
13. MCI/MI (3:1 in water)	100 ppm aq	3.4	0	n.s.	n.a.	2.3	2.2
14. Carba mix	3.0	3.3	2.5	n.s.	1.34 (0.67–2.66)	4.9	n.a.
15. Paraben mix	15.0	2.2	4.1	n.s.	0.54 (0.28–1.05)	0.6	1.2
16. p-tert-Butylphenol formaldehyde resin	1.0	2.2	1.3	n.s.	1.72 (0.72–4.14)	1.9	1.5
17. Epoxy resin	1.0	2.1	3.4	n.s.	0.60 (0.30–1.21)	2.3	1.3
18. Imidazolidinylurea	2.0	1.7	2.5	n.s.	0.69 (0.31–1.55)	1.8	n.a.
19. Benzocaine	5.0	1.4	2.0	n.s.	0.73 (0.31–1.75)	1.7	0.8
20. Mercapto mix	1.0	1.3	1.5	n.s.	0.87 (0.33–2.27)	0.7	0.8
21. Clioquinol	5.0	0.6	1.5	n.s.	0.43 (0.13–1.41)	n.a.	0.4

aq = aqueous; CI = confidence interval; ESSCA = European Surveillance System on Contact Allergies; MCI = methylchloroisothiazolinone; MI = methylisothiazolinone; n.a. = not available; NACDG = North American Contact Dermatitis Group; n.s. = not significant; OR = odds ratio.

*Italic values denote significant results after Bonferroni adjustment.

[†]Vehicle: petrolatum unless otherwise noted.

[‡]p Values shown for allergens reaching $p \leq .05$.

sensitization in the countries and also to the specialization of certain centers' seeing a more select group of patients at the end of a referral process.⁹

Both of our studies at the Massachusetts General Hospital over the past 17 years showed fragrance mix and nickel sulfate as the most frequent sensitizers. In the NACDG and ESSCA data, these allergens were also among the top three allergens. The stable prevalence of these allergens likely illustrates their extensive distribution in industry and in everyday life. The high ratio of diagnoses of ACD among patients seen in our study (42.3%) and also in the NACDG data (43.5%) is evidence that patch testing is an important diagnostic tool for accurate dermatologic diagnosis. Hence, the number of diagnosed patients with ACD in our study is in accordance with Rietschel, who stated that the appropriate use of patch testing should yield positive test results 30 to 65% of the time.¹⁵

Selected Allergens in Detail

Fragrance mix, the sensitizer yielding the most positive test reactions in our study, was introduced by Larsen¹⁶ in 1977 and consists of a mixture of seven chemicals and one natural extract. The composition of the original formulation was 2% of each constituent, totaling 16% in petrolatum. Because of the high incidence of irritant reactions with this formulation, the percentage of each constituent was lowered to 1% in 1984 for an overall combined concentration of 8% in petrolatum.¹⁷ To reduce the potential for false-positive reactions to fragrance mix in our study, positive allergic results were rated, as were all other readings as well, based on a minimum of erythematous infiltration, vesiculation, or both. Macular erythema was not considered positive. The rate of fragrance sensitization seen in our 1998–2006 study

Table 3. Final Diagnosis after Patch Testing (*N* = 627)

<i>Final Primary Diagnosis</i>	<i>%</i>	<i>N</i>
ACD	42.3	265
AD	23.0	144
Rule out contact dermatitis	13.1	82
Other eczema	3.6	23
Irritant contact dermatitis	2.6	16
Psoriasis	2.4	15
AD with relevant ACD	2.0	13
Urticaria	1.1	7
Nummular dermatitis	1.1	7
Seborrheic dermatitis	1.0	6
Perioral dermatitis	1.0	6
Rosacea	0.8	5
Prurigo	0.3	2
Hypersensitivity reaction	0.3	2
Dyshidrotic eczema	0.2	1
Other	5.2	33

ACD = allergic contact dermatitis; AD = atopic dermatitis.

(18.3%) was higher than the rates shown by the 2001–2002 data from the NACDG⁷ (10.4%) and by the ESSCA⁹ data (7.1%). In view of our previous data (1990–1997), there is a clear (although not statistically significant) trend in overall fragrance sensitization ($p = .016$). This trend is in contrast to that found by the NACDG investigators, who reported a decrease as compared to the 1994–1996 trend.

Table 4. Occupational Categories (*N* = 627)

<i>Occupational Category</i>	<i>%</i>	<i>N</i>
Professional/office	28.9	181
Home/retired/unemployed	23.8	149
Medical/dental	10.4	65
Industrial	7.0	44
“Wet work”	5.1	32
Student	3.2	20
Teaching	2.7	17
Laboratory	2.7	17
Sales	2.4	15
Other/unknown	13.8	87

Earlier publications suggested that fragrance sensitization increases with age.^{18–20} It is possible that our test population, with 67.3% of individuals 40 or more years of age, may have been older than the other groups to which it was compared. The higher levels of fragrance sensitization seen in our study might also reflect a higher rate of use of these fragrance-containing products among our patient population in Massachusetts.

This hypothesis would be supported by the high sensitization rates also seen to balsam of Peru, an allergen with partial cross-reactivity to fragrance mix owing to an overlap of certain constituents.²¹ Up to 40% of patients who had positive reactions either to fragrance mix or to balsam of Peru may have concomitant sensitization to the other agent.^{22,23} Concordant with high positive rates for fragrance mix in our population, rates of sensitization to balsam of Peru, were also higher than those reported by the NACDG⁷ and the ESSCA.⁹ In addition, we saw over time a statistically significant increase ($p < .0005$) in sensitization to balsam of Peru, whereas the NACDG described only a slight increase since 1994 to 1996.

Other substances to which a significant increase ($p = .002$) in sensitization was shown over time in comparison to our previous data were wool alcohols, which are the preferred patch-test reagent to detect lanolin allergy.²⁴ Lanolin is a common ingredient in topically applied materials such as cosmetics and creams and also in furs, leather products, and textile finishes. The clinical relevance of positive test reactions has been controversial.^{25,26} Kligman concluded that, despite high positive rates in view of its overall widespread exposure, lanolin is likely an insignificant allergen.²⁵

Analysis of gender-related predominance in sensitization revealed two allergens that reached a level of statistical significance. Reactions to nickel sulfate were seen more often in females ($p < .0005$) whereas the majority of reactions to epoxy resin occurred in men ($p < .0005$). Sensitization to epoxy resin, a common occupational allergen,^{27,28} is seen predominantly in individuals who handle unhardened epoxy resin such as is found in certain paints, adhesives, and insulating materials.^{27,29} Because the occupations connected with such products have been traditionally populated by males, there would be an above-average proportion of males at risk, compared to females.

In a retrospective European analysis of 47,626 patch-tested patients between 1997 and 2006, Brasch and colleagues reported significantly higher sensitization to nickel and cobalt chloride among females and to epoxy resin among men.³⁰ Female predominance among those sensitized to nickel was explained by a tendency of this

population subset to wear pierced earrings and other nickel-containing jewelry. Due to its extensive distribution, not only in jewelry but also in a multitude of metal products, nickel is a leading allergen in patch-test clinics.^{7,9}

Nickel sulfate was the second most common allergen in our recent study (with a value of 16.7%) and was also the second most common allergen in our previous study. Both the NACDG⁷ and the ESSCA⁹ rank nickel as the top allergen. Data presented by the NACDG showed an increase of sensitization to nickel between the 1994–1996 and 2001–2002 periods (14.3% and 16.7%, respectively).⁷ Similarly, data from another European study indicates the trend of a slight increase between 2001 and 2004.³¹ The European observation is somewhat unexpected since legislation by the European Union in 1994³² has attempted to decrease nickel sulfate exposure. Further observation and patch-test analysis are necessary to determine if these interventions are effective enough to decrease sensitization rates.

Limitations of this Study

The study sample was drawn from a selected group: referred patients to the patch-test clinic. Results may therefore not be representative of the general population. Data analysis is focused on the Hermal standard tray and might not reflect trends resulting from sensitization to additional important allergens from supplemental trays.

Conclusion

Rates of sensitization and the most important allergens from the standard screening tray at the Massachusetts General Hospital have been stable over the past 17 years. Our general findings were similar to results seen in North America and Europe during similar time periods (see Table 2). The most important cause of contact sensitization is a group of allergens in the standard screening tray. Nickel sulfate, balsam of Peru, and fragrance mix are typical examples.

A standard series is a screening tool only and often needs to be complemented with customized allergen series, depending on the individual patient's situation. For comparison of data between various regional and international centers, a higher level of standardization than currently exists with regard to a basic screening tray and materials is necessary. Moreover, through the MOAHLFA index, each clinic could characterize their patch-test population and correlate this with patterns of sensitization. Limiting factors for the comparison of patch-test data

between various regional and international clinics include heterogeneity in the use of test materials from different manufacturers, number and type of tested allergens, and interval dates of patch-test readings. As a means to this goal, Lachapelle and colleagues proposed the launch of a minimal international standard series of 20 allergens combined with an "extended" international standard series of 14 allergens, to balance regional requirements.³³ Agreement on the number of test allergens and uniformity in allergen concentration could help to make data from different studies more comparable. With this type of system, the comparison of data from different clinics might better reveal emerging demographic factors associated with new or newly important allergens, so that patients can be advised on which allergens to avoid.

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