Changing Trends and Allergens in the Patch Test Standard Series


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Objective: To present and interpret results of patch testing with the Mayo Clinic standard series over 5 years.

Design: Retrospective study. A standardized patch testing technique was used. Data were recorded on a standardized computer program from January 1, 2001, to December 31, 2005, and analyzed.

Setting: Tertiary referral center.

Patients: Patients who were referred for patch testing.

Intervention: Patch testing with the “standard series,” ie, a standard series of allergens used by most clinicians to identify the most common offending allergens in patients with allergic contact dermatitis.

Main Outcome Measures: Number of patients patch tested, allergens used over this period, and rates of allergic patch test reactions to allergens.

Results: A total of 3854 patients (mean age, 55.1 years; age range, 6.2-99.4 years; 2576 female [66.8%]) were tested. All dermatologists in the department performed patch testing. The mean number of allergens included was 69.3 (range, 6-87). There were 2664 patients with at least 1 positive reaction (69.1%) and 1933 with 2 or more positive reactions (50.2%). Metals, fragrances, topical antibiotics, preservatives, and individual allergens used in hair-care products, topical corticosteroids, glues, plastics, and rubber were still the most common allergen groups associated with allergic patch test reactions.

Conclusions: We describe the structure of the patch testing service at our referral center. Ongoing analysis of our patch test reaction rates allows us to recommend broad, clinically relevant, and up-to-date allergens for testing.

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Patch testing is the primary diagnostic tool used to identify allergens that cause allergic contact dermatitis (ACD). To identify the most common offending allergens in patients with ACD, most clinicians use a standard series of allergens (the “standard series”) that may be augmented by patch testing with other series specifically chosen on the basis of the patient’s contact and occupational history. Thus, the standard series forms the core series of allergens used to test every patient undergoing patch testing. It represents the allergens that most commonly cause ACD in the population being patch tested.

The term standard is perhaps a misnomer because the standard series is far from standardized. Specifically, the number of allergens and the specific allergens in the series vary enormously from country to country, region to region, and practitioner to practitioner, and often vary based on the referral center. For example, the European standard series contains 25 allergens, whereas the North American Contact Dermatitis Group (NACDG) uses a series of 65 allergens. The True-Test (Allerderm, Phoenix, Arizona) series consists of 24 allergens, whereas Mayo Clinic has reported using a mean of 60 allergens. Other standard series include those developed in Belgium, Finland, Hungary, Italy, Korea, and Sweden—all series of allergens judged to be appropriate for the population being tested.

Furthermore, it is important to note that the standard series is constantly in flux. Contact dermatitis groups have published their experience with the standard series. The importance of these reports is that they provide clinically rel-
evant information on new and old allergens, including trends in allergenicity rates and variations in patch test reactions among populations.

We now update our group’s previous report (1998-2000) with the results of patch testing in the subsequent 5-year period. What is the value in providing yet another report of patch testing with a standard series? First, we describe the results of patch testing with our standard series and draw attention to allergens added to or deleted from our standard series over the past 5 years. Second, we describe the patch testing service at Mayo Clinic, which is organized somewhat differently from that of other patch testing centers in the United States.

METHODS

PATIENTS

After approval by the institutional review board of Mayo Clinic, we identified patients who underwent patch testing for suspected ACD at Mayo Clinic from January 1, 2001, to December 31, 2005. The patients were identified from the patch test database into which data from all patients who have had patch testing are entered. Patients who denied research authorization were excluded from the analysis.

INTERPRETATION OF PATCH TEST REACTIONS

Patch testing was conducted in a standardized fashion using the same methods as described by the NACDG and in the previous report. Patients generally were not patch tested if they applied topical corticosteroids to patch test sites, took immunosuppressive drugs (including oral corticosteroids), or had medical conditions that could compromise the evaluation of skin responsiveness. Testing was performed with Finn chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster Aksjeselskap, Vennesla, Norway); patches were applied to the upper backs of patients and removed after 48 hours. Most allergens were purchased from Chemotechnique Diagnostics AB (Vellinge, Sweden). The other allergens were compounded by the Mayo Clinic pharmacy. Reactions were evaluated initially at 48 to 72 hours and again at 96 to 168 hours after application of the patch. Final patch test reading, interpretation of results, and assessment of relevancy were performed by the ordering physician. A return visit with the ordering physician sometime after patch testing was completed was encouraged to further assess relevancy.

Patch test reactions were interpreted with the following criteria: negative reaction, macular erythema or weak reaction (non-vesicular erythema, infiltration, and possibly papules), strong reaction (edematous or vesicular), and extreme reaction (spreading, bullous, ulcerative lesions). Reactions (including macular erythema) were further interpreted as relevant or irrelevant on the basis of a history of known contact with substances containing the allergen or a history of circumstances of likely contact with substances containing the allergen. Relevancy for each reaction was recorded as follows: I, irritant; N, allergic, not relevant (no exposure to products that contain the allergen); Q, allergic, unquestionably relevant (current exposure to products likely to contain the allergen); P, allergic, formerly relevant (past exposure to products likely to contain the allergen); and R, allergic, relevant (use test or patch test with the product containing the allergen is positive, or ingredient verified in patient's product and use of that product is verified). For this study, a positive allergic patch test result was defined as a weak, strong, or extreme reaction at the last reading or as a macular erythema reaction if the result was relevant after irritant reactions had been excluded.

STATISTICAL ANALYSIS

Patient data were entered into a clinical database. The application was client server written in Uniface (Compuware Corp, Detroit, Michigan), and the database was Sybase (Sybase, Inc, Dublin, California). All statistical analyses were performed using the Statistical Analysis System software package, version 8.8 (SAS Institute, Inc, Cary, North Carolina).

We also compared the present rates with those our group reported previously and with the results from the largest comparable group in the United States (NACDG), particularly in the most recent report of patch testing from 2001-2002. Specifically, we used a 2-tailed χ² test or the Fisher exact test, as appropriate, to compare positive rates of reactions to our standard series with those reported by the NACDG. P < .05 indicated a statistically significant difference.

ORGANIZATIONAL STRUCTURE

Unlike many other patch test centers where patch testing is performed only by a physician who specializes in patch testing, the patch testing service at Mayo Clinic is structured to support all dermatologists in the department to do patch testing at any time. All dermatologists, including staff physicians, fellows, residents, and physician assistants, are expected to, and do, use this service. Staff dermatologists with a special interest in patch testing examine the patients specifically referred for patch testing.

A patch test nurse reviews the patch testing procedure with the patient, obtains consent before the patches are applied to the back, assists the physician during the grading and documentation of the reactions, and assists with patient education through discussions about allergen avoidance sheets and often with a printout from the Contact Allergen Replacement Database (CARD). The CARD is an electronic tool designed to generate a “shopping list” of skin care products free of the patient’s allergens identified with the patch test. It is available to members of the American Contact Dermatitis Society at www.contactderm.org.

The physician ordering the patch test is responsible for interpreting and communicating the results to the patient. To aid with grading relevancy, the patient completes a questionnaire that describes his or her contact and occupational history.

SUPERVisory RESOURCES

The Mayo Clinic Contact Dermatitis Group (MCCDG) currently consists of 9 dermatologists (4 physicians and 1 fellow at Mayo Clinic Rochester, 2 at Mayo Clinic Arizona, 1 at Mayo Clinic Jacksonville, and 1 in private practice) in addition to the patch test coordinators at all 3 Mayo Clinic sites with a special interest in contact dermatitis and patch testing. The MCCDG meets formally once annually and communicates frequently via e-mail to revise and develop, as appropriate, all aspects of patch testing and, in particular, to update the series used for patch testing. A quality assurance program is in place to ensure that patients receive appropriate education for the allergens identified and that relevancy is assessed.

Table 1 lists the reaction rates to individual allergens used over the 5-year study period and compares our
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>Patients Tested,</td>
<td>Reaction,</td>
<td>Allergic Reaction, %</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Allergens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>Relevance of Allergic Reaction, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dermatophagoides mix, 20%</strong></td>
<td>839 27.4</td>
<td>10.8</td>
<td>14.8</td>
</tr>
<tr>
<td><strong>Nickel sulfate hexahydrate, 2.5%</strong></td>
<td>3833 11.1</td>
<td>1.4</td>
<td>43.2</td>
</tr>
<tr>
<td><strong>Balsam of Peru, 25%</strong></td>
<td>3837 15.7</td>
<td>1.2</td>
<td>64.5</td>
</tr>
<tr>
<td><strong>Gold sodium thiosulfate, 0.5%</strong></td>
<td>3646 13.5</td>
<td>2.7</td>
<td>28.5</td>
</tr>
<tr>
<td><strong>Neomycin sulfate, 20%</strong></td>
<td>3318 11.8</td>
<td>0.8</td>
<td>50.2</td>
</tr>
<tr>
<td><strong>Fragrance mix, 8%</strong></td>
<td>3844 11.3</td>
<td>1.4</td>
<td>71.0</td>
</tr>
<tr>
<td><strong>Thimerosal, 0.1%</strong></td>
<td>1747 10.5</td>
<td>1.2</td>
<td>39.7</td>
</tr>
<tr>
<td><strong>Cobalt chloride, 1%</strong></td>
<td>3818 10.3</td>
<td>1.8</td>
<td>97.8</td>
</tr>
<tr>
<td><strong>Formaldehyde, 1% aq</strong></td>
<td>3836 9.0</td>
<td>0.7</td>
<td>75.6</td>
</tr>
<tr>
<td><strong>Benzalkonium chloride, 0.1% aq</strong></td>
<td>3833 8.3</td>
<td>1.6</td>
<td>39.0</td>
</tr>
<tr>
<td><strong>Bacitracin, 20%</strong></td>
<td>3844 8.1</td>
<td>0.6</td>
<td>51.6</td>
</tr>
<tr>
<td><strong>Quaternium-15, 1%</strong></td>
<td>3841 8.1</td>
<td>0.7</td>
<td>75.1</td>
</tr>
<tr>
<td><strong>Potassium dichromate, 0.25%</strong></td>
<td>3335 8.7</td>
<td>2.6</td>
<td>42.4</td>
</tr>
<tr>
<td><strong>Disperse Blue 106, 1%</strong></td>
<td>3839 6.1</td>
<td>1.8</td>
<td>54.0</td>
</tr>
<tr>
<td><strong>Imidazolidinyl urea, 2%</strong></td>
<td>3740 2.9</td>
<td>0.4</td>
<td>87.5</td>
</tr>
<tr>
<td><strong>2-Hydroxy-4-methoxybenzophenone, 3%</strong></td>
<td>3845 0.7</td>
<td>0.4</td>
<td>48.0</td>
</tr>
</tbody>
</table>

Table 1. Rates of Allergic Patch Test Reaction to Allergens Ranked According to Frequency of Reaction.

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current results with the results in our group’s previous report and in the most recent NACDG report. Allergens in our current series are boldfaced.

The mean age of the 3854 patients tested during the 5-year period was 55.1 years (median, 56.2 years; range, 6.2-99.4 years; 25th percentile, 43.0 years; 75th percentile, 70.5 years). Female patients made up 66.8% of our study group (n=2576).

The mean (SD) number of allergens included in the standard series was 69.3 (0.1) (median, 69.0; range, 6-87; 25th percentile, 43.0; 75th percentile, 72). Overall, 2664 patients (69.1%) had at least one positive allergic patch test reaction and 1933 (50.2%) had 2 or more positive reactions. A total of 963 patients (25.0%) had 1 or more irritant reactions; 503 (13.1%) had 2 or more irritant reactions; and 2891 (75.0%) had no irritant reactions. Among the 963 patients who had at least 1 irritant reaction, there were 2349 (75.0%) with no allergic reactions. Among the 963 patients (25.0%) had 1 or more irritant reactions; 503 (13.1%) had 2 or more irritant reactions; and 2891 (75.0%) had no irritant reactions. Among the 963 patients who had at least 1 irritant reaction, there were 2349 (75.0%) with no allergic reactions.

Compared with the previous report, we have noted significantly higher allergic patch test rates (P<.05) for the following allergens: Dermatophagoides mix, 20%; nickel sulfate hexahydrate, 2.5%; balsam of Peru, 25%; benzalkonium chloride, 0.1%, aqueous; methylidibromo glutaronitrile/phenoxethanol, 1.5%; hexylresorcinol, 0.25%; 1,3-dimethylol-5,5′-dimethyl (DMDM) hydantoin, 1%; and DMDM hydantoin, 1%, aqueous. Significantly lower rates were observed for potassium dichromate, 0.25%; hexachlorophene, 1%; and mixed dialkyl thioureas, 1%.

We also compared the MCCDG results from the 2001-2005 period (data not shown) with the NACDG results from the same period. Significantly higher reaction rates for MCCDG patients were found for balsam of Peru, 25%; cobalt chloride, 1%; potassium dichromate, 0.25%; glutaraldehyde, 1%; benzalkonium chloride, 0.1%, aqueous; and methylidibromo glutaronitrile/phenoxethanol (MCI/MI), 100 ppm, aqueous. The largest relative differences were observed for cobalt chloride, 1%...
(MCCDG, 12.4% positive; NACDG, 7.4% positive), and benzalkonium chloride, 0.1%, aqueous (MCCDG, 8.9% positive; NACDG, 4.3% positive). Significantly lower reaction rates were found among Mayo Clinic patients for DMDM hydantoin, 1%, aqueous.

**COMMENT**

Herein, we report our experience with a large group of patients patch tested with the standard series over a 5-year period. With some exceptions, rates of reactions to specific allergens have not changed dramatically since our group’s previous report, and the rates of allergic patch test reaction are broadly similar to those reported by the NACDG. Our standard series is large (69 allergens); there are abundant data that a larger series permits identification of clinically meaningful allergens that would not be identified with a smaller screening standard series.

The demographic features of the present patients are similar to those described in previous reports. Two-thirds of the patients were female, and the age range was broad.

Although our method of patch testing is for the most part identical to that published by others, there are some differences in the way our rates are calculated and in our organizational structure. First, reactions graded as macular erythema that were judged to be relevant were included in our calculations. We have recently drawn attention to the importance of these macular erythema reactions, which we find in more than 50% of readings.

Second, our organizational structure of patch testing is different from that of other patch test centers in that all physicians (45 at Mayo Clinic Rochester, 17 at Mayo Clinic Arizona, and 17 at Mayo Clinic Jacksonville) can order and interpret patch testing. The system of interpretation of patch tests at our institution is both a strength (permitting flexibility for patients and physicians) and a potential weakness (physicians with modest patch testing experience are free to perform and interpret patch tests). Members of MCCDG are available for specialized consultation and for any specific questions the physicians may have when interpreting patch test reactions. In addition, the patch test nurse aids in reading of patch test results, thus ensuring consistency of readings.

**NEW ALLERGENS ADDED OR DELETED SINCE LAST REPORT**

Multiple allergens have been added or deleted since the last report, illustrating that the standard series is in flux. The following allergens were deleted because of very low rates of reaction detected: 4-chloro-3-m-cresol (PCMC), 1%; polysorbate (Tween) 85, 2.5%; and sorbitol sesquioleate, 20%. Steroid mixes were deleted because we now test corticosteroids separately, finding separate testing to be more effective.

The following allergens were added: cocamidopropyl betaine, 1%, aqueous; amidoamine, 0.1%, aqueous; compositae mix, 5%; dimethylol dihydroxyethylene urea, 4.5%, aqueous; Disperse Blue 124, 1%; Disperse Blue 106, 1%; Disperse Orange 3, 1%; natural fragrance mix, 2%; coconut diethanolamide (cocamide DEA), 0.5%; and gold sodium thiosulfate, both 0.5% and 0.25%.

We increased the number of corticosteroid allergens in our standard series to 5 (hydrocortisone-17-butyrate, 1% alcohol, and clobetasol-17-propionate, 1%, were added). These corticosteroid screens on our standard series detect 74% of corticosteroid allergies when compared with a specialized corticosteroid series.

**INCREASED ALLERGIC PATCH TEST REACTION RATES**

Table 1 summarizes the rates of reaction found in the present report compared with those of the previous report. Currently, allergic patch test rates are significantly higher for nickel, markers of fragrance allergy, and some preservatives than in the previous report.

**Table 2. Rationale for Allergens Used at Mayo Clinic at Concentrations Different From Those of the NACDG**

<table>
<thead>
<tr>
<th>Allergen Concentration at Mayo Clinic (NACDG)</th>
<th>Allergen Group</th>
<th>Reason for Inclusion in Standard Series at This Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutaraldehyde, 0.2% (1%)</td>
<td>Sterilization</td>
<td>We now patch test at 0.2% because 1% was thought to be irritant and may be irritant in higher concentration (0.5%); we test both 0.25% and 0.5% to compare</td>
</tr>
<tr>
<td>Gold sodium thiosulfate, 0.25% and 0.5% (0.5%)</td>
<td>Metal</td>
<td>Lower concentration used to avoid irritant reactions</td>
</tr>
<tr>
<td>Propylene glycol, 10% (30% aq)</td>
<td>Preservative</td>
<td>Lower concentration used to avoid irritant reactions; commercially available concentration. In 1999, Chemotechnique changed the concentration to 1.5%</td>
</tr>
<tr>
<td>Methylidibromo glutaronitrile/phenoxethanol, 1.5% (Euxyl K400; Chemotechnique, Vellinge, Sweden), hydrocortisone-17-butyrate, 0.5%</td>
<td>Preservative</td>
<td>The higher concentration is thought to detect a higher percentage of relevant allergic reactions. In 1999, Chemotechnique changed the concentration to 16%</td>
</tr>
<tr>
<td>Paraben mix (Chemotechnique), 16% (12%)</td>
<td>Preservative</td>
<td>Used in clinical practice at this concentration (as in patches), therefore tested at this concentration</td>
</tr>
<tr>
<td>Lidocaine, 5% (15%)</td>
<td>Topical anesthetic</td>
<td>Lower concentration used to avoid irritant reactions</td>
</tr>
<tr>
<td>Quaternium-15, 1% (2%)</td>
<td>Preservative</td>
<td>Lower concentration used to avoid irritant reactions</td>
</tr>
<tr>
<td>2-Bromo-2-nitroprop-1,3-diol, 0.25% (0.5%)</td>
<td>Preservative</td>
<td>Lower concentration used to avoid irritant reactions</td>
</tr>
</tbody>
</table>

Abbreviations: aq, aqueous; NACDG, North American Contact Dermatitis Group; TADC, tested at a different concentration.

a Designated TADC; for reaction rates, see Table 1.
MAYO CLINIC ALLERGENS NOT USED IN OTHER STANDARD SERIES OR USED IN DIFFERENT OR MULTIPLE CONCENTRATIONS

We patch test with several allergens at Mayo Clinic that are not used by NACDG. Many of these are included in our patch test series because they are commonly used in skin-care products, including preservatives, emulsifiers, emollients, excipients, lubricants, antifoaming agents, flavorings, and dyes. Although the percentage of positive reactions is relatively low, they may be clinically relevant.

For several years, we patch tested with a Dermatophagoides mix: initially 20%, then 0.1% concentration. (The dust mite antigen Dermatophagoides has been proposed as a major factor in provoking or perpetuating atopic and other forms of dermatitis; patch testing has been advocated as a means of determining reactivity to Dermatophagoides.) The results were disappointing: a high rate of reactivity was found in all populations tested (both atopic and nonatopic) to both the 20% mix and the 0.1% mix, and generally, the reactions were thought to be either irritant or allergic, and if allergic, not to be of relevance; they did not correlate with the presence or absence of atopy or atopic dermatitis.12 Considering these factors, we discontinued testing with the Dermatophagoides mix.

The allergens used by Mayo Clinic at 2 concentrations and the rationale for this dual use are listed in Table 2.

REGIONAL VARIATION

The rates of allergic reaction vary among the 3 Mayo Clinic sites in Minnesota, Florida, and Arizona (data not shown), thus illustrating that patch testing with the same allergens can show different reaction rates in different parts of the United States. Thompson and Belsito reported differing reaction rates from individual centers and ascribed this variation to regional demographic and occupational differences; it might also reflect variations in referral patterns.

MCCDG RESULTS VS NACDG RESULTS

The percentage of our patients with at least 1 positive allergic reaction (69.1%) was the same as that in the NACDG (69%). The overall rate of irritant patch test reactions was 25.0%, which is higher than that reported by NACDG (15.4%).3 Our patch test results for allergens in common with the NACDG generally are similar to those reported previously2 and similar to those reported by NACDG and others.

In summary, we present the results of patch testing at Mayo Clinic during the past 5 years. Our standard series has evolved as new allergens of clinical importance have been recognized and added to our standard tray and as other allergens not thought to be clinically relevant have been deleted. We also describe the organizational structure of the patch testing service at our referral center, which is somewhat different from that of other institutions. For optimal patient care, we have educated all our dermatologists (staff, residents, and fellows) to identify and interpret reactions to relevant contact allergens. We hope that the data, which emphasize the importance of using a broad and dynamic standard patch test series, will help others to initiate or modify a patch test service in an academic or private practice setting.

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Analysis and interpretation of data: Davis, Scalf, Yiannias, el-Azhary, Rohlinger, Farmer, Fett, and Connolly.

Drafting of the manuscript: Davis, Scalf, and Schroeter.

Critical revision of the manuscript for important intellectual content: Davis, Scalf, Yiannias, Cheng, el-Azhary, Rohlinger, Farmer, Fett, Johnson, Nordberg Linehan, Richardson, and Connolly.

Statistical analysis: Davis, Rohlinger, and Farmer.

Obtained funding: Davis.

Administrative, technical, and material support: Davis, Scalf, Cheng, el-Azhary, Johnson, Nordberg Linehan, Richardson, and Schroeter.

Study supervision: Davis and Yiannias.

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REFERENCES


