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New positive patch test reactions on day 7—The additional value of the day 7 patch test reading

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Abstract
Background: Not performing a day (D) 7 patch test reading might result in positive patch test reactions being missed.
Objectives: To investigate the added value of the D7 patch test reading for individual allergens, and to identify patient characteristics and allergen groups associated with new positive D7 reactions.
Methods: Data from patients patch tested between 2008 and 2018 with the extended European baseline series were analysed. Patch test readings were performed on D3 and D7. Positive reactions were categorized into positive on D3 or new positive on D7.
Results: A total of 3292 patients were consecutively patch tested with at least 43 allergens of the TRUE Test panels 1 and 2 supplemented with investigator-loaded allergens. In total, 447 (13.6%) patients showed new positive D7 reactions. In univariable regression analysis, age between 18 and 30 years showed a negative association with new positive D7 reactions. Significantly more D7 positive reactions were seen for topicals (odds ratio [OR] 2.60, 95% confidence interval [CI]: 1.92-3.51) and corticosteroids (OR 1.87, 95%CI: 1.09-3.21). No associations were found between sex, atopic dermatitis and occupational dermatitis and a new positive D7 reaction.
Conclusion: A D7 reading to identify new positive patch test reactions is of added value, especially for topicals and corticosteroids.

KEYWORDS
allergic contact dermatitis, D7 reading, epidemiology, new positive D7 reactions, patch testing

1 INTRODUCTION

According to the European Society of Contact Dermatitis (ESCD) guideline for diagnostic patch testing, it is recommended to perform at least two readings, on day (D) 2, D3, or D4, and around D7. Most centres perform patch test readings on D2 to D4. A late patch test reading on D7 in addition to the D3 or D4 reading can identify new positive patch test reactions, ranging from 3% up to 34% in previous studies, which were found to be negative, doubtful or irritant on preceding readings. Multiple studies have reported the importance of an additional late patch test reading, especially for suspected contact allergies to metals, topicals, and corticosteroids. However, the...
allergens that have shown new positive reactions at an additional late patch test reading vary in the literature.\textsuperscript{7,10,11} It is unknown whether there are associated factors, for example, patient characteristics, that may enhance the tendency to develop new positive reactions at a D7 reading. Only one study evaluated sex and age as possible associated factors, and found a significantly higher rate of new positive D7 reactions in women than in men and in patients aged >40 years.\textsuperscript{7} The objectives of the current study were to evaluate the added value of the D7 patch test reading for individual allergens and allergen groups, and to identify factors associated with new positive D7 reactions.

2 | METHODS

2.1 | Study design and patch testing

We performed a retrospective data analysis on patch test data collected between January 2008 and July 2018 for consecutively patch tested patients who were routinely tested with our extended European baseline series. TRUE Test panels 1 and 2 (SmartPractice Europe, Reinbek, Germany) supplemented with additional investigator-loaded allergens (SmartPractice Europe, and Chemotechnique Diagnostics, Vellinge, Sweden) tested in Van der Bend square chambers (Van der Bend, Brielle, The Netherlands) were applied on the back for 48 hours under occlusion. Patch test readings were performed on D3 and D7. The readings were performed by experienced dermatologists according to the ESCD guideline.\textsuperscript{1} Weak (+), strong (+++) and extreme (++++) reactions were classified as positive reactions. Reactions reported as irritant, doubtful (?) or follicular were counted as negative reactions in addition to the negative results. In addition, patch test results reported as irritant, doubtful or follicular at the D3 reading that became positive on D7 were evaluated separately. Reactions were evaluated as irritant if margins were sharply demarcated and the surface of the test area showed a silk paper structure or a shiny skin. Reactions were considered to be doubtful if erythema and/or infiltration did not cover the whole test area.\textsuperscript{12}

2.2 | Data analysis

Positive reactions were categorized into positive on D3 or new positive on D7 (labelled as negative on D3). For patients who had been tested more than once, only the most recent patch test result was evaluated. To evaluate patient characteristics, three groups of patients were defined: patients with only D3 positive reactions and no new positive D7 reactions; patients with only new D7 positive reactions corresponding to D3 negative reactions; and patients with both D3 positive reactions and new D7 positive reactions. The patient characteristics that were analysed were age, sex, atopic dermatitis in the patient’s lifetime, and occupational dermatitis. Age was categorized into the following groups: <18, 19 to 30, 31 to 45, 46 to 60, and ≥61 years. To analyse the influence of type of allergen, allergens were grouped on the basis of chemical structure, cross-reactivity, and co-sensitization, resulting in seven groups: metals, preservatives, fragrances, rubbers, dyes, topical medicaments ("topicals"), and corticosteroids (Table 1).\textsuperscript{13,14} A positive reaction to at least one of the allergens in the group was counted as an overall positive group reaction.

2.3 | Statistics

Descriptive data are presented in tables as numbers with percentages and 95% confidence intervals (CIs). Prevalences are presented as both crude and age-standardized estimates with accompanying 95% CIs. The European standard population of 2013 was used as the reference for age and sex standardization.\textsuperscript{15} Univariable logistic regression was performed to analyse the association between patient characteristics and allergen groups on new positive D7 reactions, and these were expressed as odds ratio (ORs) with 95% CIs. Statistical analyses were performed with SPSS v.23 (IBM, Armonk, New York) and Excel 2013 (Microsoft, Redmond, Washington).

3 | RESULTS

3.1 | New D7 positive patch test reactions

A total of 3292 patients (67.0% female, 33.0% male, mean age 42.7 ± 16.9 years) were consecutively patch tested with at least 43 allergens of the TRUE Test panels 1 and 2 supplemented with investigator-loaded allergens. The sociodemographic characteristics of the total patch tested group and the subgroup of patients with at least...
one positive reaction are shown in Table 2. A total of 1653 patients (50.2%) had at least one positive reaction on D3 and/or D7. Of the total 3292 patch tested patients, 189 (5.7%) showed only new positive D7 reactions (ie, read as negative, doubtful or irritant on D3) and another 258 (7.8%) patients showed positive D3 reactions with additional new positive D7 reactions. Thus, in total, 447 (13.5%) of the patch tested patients had new positive D7 patch test reactions. Both crude and age-standardized and sex-standardized prevalences of the total number of positive reactions on D3 and D7 are shown together with 95%CIs in Table 3. The allergens with the highest proportions of new positive D7 reactions (new positive D7 reactions/total positive reactions) in order of frequency were neomycin sulfate (81.5%, 22/27 patients), 2-bromo-2-nitropropane-1,3-diol (50%, 11/22 patients), budesonide (42.3%, 11/26 patients) and diazolidinyl urea (41.4%, 12/29 patients). For groups of allergens, the proportions of new positive D7 reactions were, in order of decreasing frequency, most frequent for topicals (33.3%, 72/216 patients), corticosteroids (28.4%, 19/67 patients), dyes (20.2%, 53/263 patients), fragrances (16.6%, 95/572), metals (16.3%, 147/904), preservatives (15.1%, 113/749), and rubber additives (7.6%, 23/304).

### 3.2 | Regression analysis

A univariable logistic regression analysis was performed to investigate patient characteristics and allergen groups possibly associated with the occurrence of new positive D7 reactions. The results are shown in Table 4. For age, a significant negative association was found in the age group 18 to 30 years as compared with the age group >61 years (OR 0.58, 95% CI: 0.36-0.93). No significant associations were found for sex, atopic dermatitis in the patient’s lifetime and occupational dermatitis and a new positive D7 reaction. Significant associations were found for the allergen groups of topicals (OR 2.60, 95% CI 1.92-3.51) and corticosteroids (OR 1.87, 95% CI 1.09-3.21) and a new positive D7 reaction. Rubbers showed the lowest prevalence (7.6%) of new positive D7 reactions, and were significantly negatively associated with new positive D7 reactions (OR = 0.37, 95% CI: 0.24-0.57).

Table S1 shows the prevalence of new positive D7 reactions in each age group for each allergen group.

### 3.3 | Reaction strength

The reaction strength of the new positive D7 reactions and patch test results of the D3 reading are shown in Table 3. Of the 595 new positive D7 reactions in 189 patients, 548 (92.1%) were weak positive (+) and 46 (7.7%) were strong positive (++), especially to nickel sulfate, parthenolide, methylchloroisothiazolinone/methylisothiazolinone, colophonium, and epoxy resin. Only one extreme positive (+++) reaction was seen, namely, to epoxy resin. Of all new positive D7 reactions, 164 of 595 (27.6%) were regarded as doubtful and 4 of 595 (0.7%) were regarded as irritant at the D3 reading. Besides irritant and/or doubtful reactions, follicular reactions were seen to nickel sulfate (18 of 104 positive D7 reactions), cobalt chloride (2 of 25 positive D7 reactions), and ethylenediamine dihydrochloride (1 of 3 positive D7 reactions).

### 4 | DISCUSSION

The present analysis provided estimates of the prevalence of new positive D7 patch test reactions in patients consecutively patch tested

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**TABLE 2** Sociodemographic characteristics of the patch tested population

<table>
<thead>
<tr>
<th></th>
<th>Total tested (N = 3292)</th>
<th>Reacted positively on D3 and/or D7 (N = 1653)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Female</td>
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<td>67.0</td>
</tr>
<tr>
<td>Age (y)</td>
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<tr>
<td>&lt;18</td>
<td>112</td>
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<tr>
<td>18-30</td>
<td>918</td>
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<tr>
<td>31-45</td>
<td>787</td>
<td>23.9</td>
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<tr>
<td>46-60</td>
<td>912</td>
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</tr>
<tr>
<td>≥61</td>
<td>563</td>
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<td>Atopic dermatitis (lifetime prevalence)</td>
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<td>Yes</td>
<td>1409</td>
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<td>No</td>
<td>1883</td>
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<tr>
<td>No</td>
<td>2577</td>
<td>78.3</td>
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CI, confidence interval.
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<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
<th>n</th>
<th>%</th>
<th>—</th>
<th>?</th>
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<th>+</th>
<th>++</th>
<th>+++</th>
<th>%</th>
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<td>3172</td>
<td>607</td>
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<td>424</td>
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<td>104</td>
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<td>64</td>
<td>22</td>
<td>18</td>
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<td>0.7-1.4</td>
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<td>0.1</td>
<td>1</td>
<td>1</td>
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<td>3</td>
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<td>1.8-2.8</td>
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<td>0.2% aq</td>
<td>466</td>
<td>32</td>
<td>0.9</td>
<td>31</td>
<td>7.2</td>
<td>4.4-8.9</td>
<td>3</td>
<td>0.6</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>9.4</td>
</tr>
</tbody>
</table>
### TABLE 3 (Continued)

<table>
<thead>
<tr>
<th>Haptens</th>
<th>Concentration (μg/cm²)</th>
<th>Total patch tested patients (n = 3292)</th>
<th>Total crude positives on D3 and/or D7 (n = 1653)</th>
<th>Total age-standardized and sex-standardized positives on D3 and/or D7</th>
<th>Reaction strength at D3 reading (n)</th>
<th>Reaction type at D3 reading (n)</th>
<th>Reaction strength on D7 (n)</th>
<th>Proportion of total positive reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragrance mix II</td>
<td>14% pet.</td>
<td>3275</td>
<td>246 7.5</td>
<td>181 6.0</td>
<td>4.7-6.3</td>
<td>33 1.0</td>
<td>14 18 1</td>
<td>133 0 0</td>
</tr>
<tr>
<td>HICC</td>
<td>5% pet.</td>
<td>3242</td>
<td>98 3.0</td>
<td>72 2.4</td>
<td>1.7-2.7</td>
<td>22 0.7</td>
<td>17 5 0</td>
<td>22 0 0</td>
</tr>
<tr>
<td>Sesquiterpene lactone mix</td>
<td>0.1% pet.</td>
<td>3277</td>
<td>43 1.3</td>
<td>40 1.3</td>
<td>0.8-1.6</td>
<td>13 0.4</td>
<td>10 3 0</td>
<td>11 2 0</td>
</tr>
<tr>
<td>Parthenolide</td>
<td>0.1% pet.</td>
<td>3233</td>
<td>42 1.3</td>
<td>37 1.2</td>
<td>0.8-1.5</td>
<td>14 0.4</td>
<td>12 2 0</td>
<td>9 5 0</td>
</tr>
<tr>
<td>MDBGN</td>
<td>0.5% pet.</td>
<td>3247</td>
<td>127 3.9</td>
<td>134 4.5</td>
<td>3.4-4.8</td>
<td>17 0.5</td>
<td>7 10 0</td>
<td>17 0 0</td>
</tr>
<tr>
<td>Budesonide</td>
<td>0.1% pet.</td>
<td>3276</td>
<td>26 0.8</td>
<td>22 0.7</td>
<td>0.4-1.0</td>
<td>11 0.3</td>
<td>7 4 0</td>
<td>9 2 0</td>
</tr>
<tr>
<td>Tioctortol-21-pivalate</td>
<td>0.1% pet.</td>
<td>3277</td>
<td>27 0.8</td>
<td>29 1.0</td>
<td>0.6-1.2</td>
<td>4 0.1</td>
<td>2 2 0</td>
<td>4 0 0</td>
</tr>
<tr>
<td>Hydrocortisone-17-butyrate</td>
<td>1% eth.</td>
<td>3250</td>
<td>14 0.4</td>
<td>12 0.4</td>
<td>0.2-0.6</td>
<td>4 0.1</td>
<td>2 2 0</td>
<td>4 0 0</td>
</tr>
<tr>
<td>Textile dye mix</td>
<td>6.6% pet.</td>
<td>991</td>
<td>52 5.2</td>
<td>47 5.0</td>
<td>3.4-6.1</td>
<td>12 1.2</td>
<td>8 4 0</td>
<td>11 1 0</td>
</tr>
<tr>
<td>Disperse Blue 106</td>
<td>1% pet.</td>
<td>3250</td>
<td>31 1.0</td>
<td>27 0.9</td>
<td>0.5-1.1</td>
<td>9 0.3</td>
<td>8 1 0</td>
<td>9 0 0</td>
</tr>
<tr>
<td>Disperse Blue 124</td>
<td>1% pet.</td>
<td>3274</td>
<td>27 0.8</td>
<td>23 0.8</td>
<td>0.4-1.0</td>
<td>10 0.3</td>
<td>10 0 0</td>
<td>10 0 0</td>
</tr>
<tr>
<td>Toluene-2,5-diamine</td>
<td>1% pet.</td>
<td>2333</td>
<td>48 2.1</td>
<td>35 1.6</td>
<td>1.0-2.0</td>
<td>9 0.4</td>
<td>7 2 0</td>
<td>8 1 0</td>
</tr>
<tr>
<td>Sodium disulfite</td>
<td>1% pet.</td>
<td>395</td>
<td>35 8.9</td>
<td>35 9.6</td>
<td>6.1-11.7</td>
<td>6 1.5</td>
<td>2 4 0</td>
<td>6 0 0</td>
</tr>
<tr>
<td>2-Bromo-2-nitropropane-1,3-diol</td>
<td>0.5% pet.</td>
<td>3250</td>
<td>22 0.7</td>
<td>22 0.7</td>
<td>0.4-1.0</td>
<td>11 0.3</td>
<td>7 4 0</td>
<td>11 0 0</td>
</tr>
<tr>
<td>Diazolidinyl urea</td>
<td>2% pet.</td>
<td>3250</td>
<td>29 0.9</td>
<td>21 0.7</td>
<td>0.4-0.9</td>
<td>12 0.4</td>
<td>9 3 0</td>
<td>11 1 0</td>
</tr>
<tr>
<td>Imidazolidinyl urea</td>
<td>2% pet.</td>
<td>3250</td>
<td>26 0.8</td>
<td>20 0.7</td>
<td>0.3-0.9</td>
<td>7 0.2</td>
<td>3 4 0</td>
<td>6 1 0</td>
</tr>
<tr>
<td>1,2-Benzoisothiazolin-3-one</td>
<td>0.05% pet.</td>
<td>3230</td>
<td>21 0.7</td>
<td>25 0.8</td>
<td>0.5-1.1</td>
<td>2 0.1</td>
<td>0 2 0</td>
<td>2 0 0</td>
</tr>
<tr>
<td>Amerchol L 101</td>
<td>50% pet.</td>
<td>606</td>
<td>19 3.1</td>
<td>14 2.5</td>
<td>1.3-3.5</td>
<td>2 0.3</td>
<td>1 1 0</td>
<td>2 0 0</td>
</tr>
</tbody>
</table>

Abbreviations: HICC, hydroxylisohexyl-3-cyclohexene carboxaldehyde (Lyral); IR, irritant reaction; MCI, methylchloroisothiazolinone; MDBGN, methyldibromo glutaronitrile (dibromodicyanobutane); MI, methylisothiazolinone; PTBP-FR, p-tert-butylphenol formaldehyde resin.

Follicular reactions: nickel sulfate, n = 18; ethylenediamine dihydrochloride, n = 1; cobalt chloride, n = 2.
This is in agreement with our findings, in which neo-
mycin sulfate has been the most frequently
reported allergen associated with new positive reactions at a late
patch test reading. In multiple studies addressing the added value of a late
reading, neomycin sulfate was significantly associated with new positive D7
reactions, and gave a proportion of 28.4% new positive D7 reactions
for all positively tested patients. A recent study by Chaudry et al
reported that readings after D5 provided limited information, as no
new reactions were seen to 0.01% budesonide, 1% clotetasol-17-pro-
pionate, 1% hydrocortisone-17-butyrate alcohol and 1% triamcinol-
one acetonide in 298 evaluated patients. It is interesting to note
that budesonide was tested at a higher concentration of 0.1% in our
baseline series. Davis et al evaluated 135 patients, and only two
patients showed positive patch test reactions to corticosteroids, on
D7 and D9. In their experience, the extended reading was of limited
value.

There have been conflicting results of studies on corticosteroids
and the association with new positive D7 reactions. In our patients,
corticosteroids were significantly associated with new positive D7
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and the association with new positive D7 reactions. In our patients,
metals, especially for gold sodium thiosulfate, which showed the highest prevalence of new positive reactions after D5. In our regression analysis, the group metals was not significantly associated with new positive D7 reactions as compared with other groups of allergens. However, our metal group consisted only of nickel sulfate, potassium dichromate and cobalt chloride from the European baseline series.

In the current analysis, the rubbers group was the only allergen group that was significantly less associated with new positive D7 reactions. Literature reports on the prevalence of rubbers showing new positive reactions at additional (late) patch test readings are scarce. A study by Madsen et al evaluated a second patch test reading on D6/D7 in patients who were tested with at least TRUE Test panels 1 and 2. Mercaptobenzothiazole and carba mix (together with paraben mix) were the only allergens that did not show new positive reactions at an additional reading, which is in agreement with our findings.

4.1 | Associated factors

In general, contact allergies may be associated with several patient characteristics. These include sex, age, and occupational dermatitis. Women tend to have a higher prevalence of contact allergies than men. Furthermore, several studies have evaluated the effect of age on the elicitation of contact allergy. Kwangsuksith et al reported a decrease in reactivity upon primary exposure to new antigens in older individuals, owing to senescence of the immune system. In our study, sex was not significantly associated with a higher prevalence of new positive reactions on D7. A study by Madsen et al reported significantly more new positive reactions in women and in patients aged >40 years. In the current study, an age of 18 to 30 years were significantly less associated with new positive D7 reactions than an age of 61 years. However, allergens could be a confounding factor. The allergens with the highest proportion of new D7 reactions was neomycin sulfate. The use of neomycin sulfate in topicals in The Netherlands was reduced years ago. Consequently, it was mainly the elderly who were exposed, which could explain the lower proportion of new positive reactions in the age group 18 to 30 years. Logistic regression analysis was controlled for age and sex. Nevertheless, we found a significant association for age in all subgroups of allergens analysed. Thus, the effect of age can be only partly moderated by the exposure to allergens. For patients suffering from occupational dermatitis, it could be hypothesized that sensitization occurs earlier because of a high probability of impaired barrier function of the skin resulting from concomitant exposure to irritants, allowing for more rapid penetration of the contact allergen. In the current analysis, no differences were observed for the presence of occupational dermatitis between patients with new positive D7 reactions and patients with positive D3 reactions. Concerning the overall prevalence of contact allergy in atopic vs non-atopic dermatitis patients, Johansen et al concluded that there were no significant differences. In the current analysis, the prevalence of new positive D7 reactions was also comparable between atopic and non-atopic dermatitis patients.

4.2 | Strength and limitations

The added value of a D7 reading has been underscored by previous studies, but these investigations have mostly been performed on small populations, whereas the current study was performed on a large sample. A novel aspect was the investigation of patient characteristics in relation to late positive reactions. One limitation is the retrospective nature of the study. Furthermore, it is challenging to compare publications about new (delayed) positive patch test reactions at additional (late) patch test readings. Patch test materials and concentrations, vehicles, techniques and patch test interpretation differ between studies. Furthermore, variations in terminology and day of the additional patch test reading (D5-D9) do not always match in the compared studies.

5 | CONCLUSION

The results of the present analysis support the importance of an additional late patch test reading on D7. Especially for topicals and corticosteroids, the share of new D7 reactions is high. Our results show that, in patients tested with True Test panel 1 and 2 and additional allergens, 13.5% of positive reactions are missed if no D7 reading is performed. Therefore, it is recommended to perform a D7 patch test reading to detect new, clinically relevant positive patch test reactions.

CONFLICTS OF INTEREST

There was no funding and the authors have no conflicts of interest to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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