

## ORIGINAL ARTICLE

# Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis: Reactivity to topical preservatives

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**Background:** Patients with atopic dermatitis (AD) have chronic dry skin to which they frequently apply skin care products containing preservatives, and they are predisposed to developing cutaneous delayed-type hypersensitivity.

**Objective:** We sought to compare the rates of positive patch test reactions to allergens on the North American Contact Dermatitis Group (NACDG) standard tray among patients with and without AD and to assess whether atopic patients in our database were more likely to patch test positive to preservatives.

**Methods:** A total of 2453 patients underwent patch testing to the NACDG standard screening series. The incidence of positive patch test reaction among patients with AD ( $n = 342$ ) and without AD ( $n = 2111$ ) was assessed. Statistical analysis was done using a  $\chi^2$  test.

**Results:** Compared with nonatopic patients, patients with AD were statistically more likely to have positive patch tests. AD was associated with contact hypersensitivity to quaternium-15, imidazolidinyl urea, DMDM hydantoin, and 2-bromo-2-nitropropane-1,3-diol but not to parabens, formaldehyde, or diazolidinyl urea.

**Limitations:** Only patients suspected of having allergic contact dermatitis were tested. Our population was geographically limited to metropolitan Kansas City, MO, and metropolitan New York City, NY.

**Conclusions:** Patients with AD should avoid the use of skin care products preserved with formaldehyde releasers. (J Am Acad Dermatol 10.1016/j.jaad.2013.08.046.)

**Key words:** allergy; atopic eczema; formaldehyde releasers; hypersensitivity; patch testing; preservatives.

Atopic dermatitis (AD), synonymous with atopic eczema, is clinically defined as inflamed, itchy skin that is chronically relapsing.<sup>1</sup> The dry, irritated skin of patients with AD necessitates frequent application of skin care products such as emollients, corticosteroids, and antibacterial creams.<sup>2</sup> In an earlier review of the database used in this study, patients with a history of AD were significantly more likely than nonatopic populations to develop cutaneous delayed-type hypersensitivity (CDTH) to at least 1 allergen on the North American Contact Dermatitis Group

## Abbreviations used:

|        |                                         |
|--------|-----------------------------------------|
| AD:    | atopic dermatitis                       |
| CDTH:  | cutaneous delayed-type hypersensitivity |
| NACDG: | North American Contact Dermatitis Group |

(NACDG) standard tray, most significantly to metal allergens including nickel, cobalt chloride, and potassium dichromate.<sup>3</sup>

As a follow-up to this earlier analysis, we were interested in examining 2 areas of study. First we

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wanted to confirm that another year of data from patients patch tested for suspected allergic contact dermatitis supported the conclusion that people with AD are more inclined to have a CDTH reaction than those without AD. Second, we wanted to investigate whether patients with AD are more likely to react to the preservatives paraben mix, formaldehyde, quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, and/or 2-bromo-2-nitropropane-1,3-diol, which are all tested on the NACDG standard tray.

## METHODS

Between July 1, 1994, and June 3, 2013, a total of 2453 patients, who presented with a clinical suspicion of allergic contact dermatitis, underwent patch testing to the NACDG standard allergen series by the senior author in Kansas City, KS, and New York, NY. Before patch testing, all patients completed a standardized questionnaire regarding demographic, medical, and occupational data. Atopic status (dermatitis, asthma, hay fever) was assessed in all patients; the diagnosis of AD was established using the criteria of Hanifin and Rajka.<sup>4</sup>

Patients were patch tested in a standardized manner using Finn Chamber (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Bard Medical, Covington, GA).<sup>5</sup> Patch tests were applied to areas of the back free of dermatitis. In general, patients with active dermatitis involving 25% or more of body surface area were not patch tested because of the enhanced possibility of false-positive (“angry back”) reactions. Test allergens were purchased from Chemotechnique Diagnostics AB, Malmö, Sweden (1994-2007) or from SmartPractice, Calgary, Alberta, Canada (2008-2013). Allergens were applied on Mondays, and patients were examined at days 2 and 4 after placement. Reactions were assessed based on morphology as previously described.<sup>5</sup> Reactions scored as 1+, 2+, or 3+ were considered a positive allergic response.

All deidentified Health Insurance Portability and Accountability Act–compliant data were entered, retrieved, and evaluated using a computer database (Access 2010, Microsoft Corp, Seattle, WA), and this study was therefore considered exempt from institutional review board approval at Columbia

University Medical Center, New York, NY. The incidence of contact sensitization to any allergen, to paraben mix, to formaldehyde, and to formaldehyde releasers (quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, and/or 2-bromo-2-nitropropane-1,3-diol) among patients with AD ( $n = 342$ ) and without AD ( $n = 2111$ ) was

assessed. A  $\chi^2$  test was conducted to test whether the difference between observed and expected frequencies was statistically significant, using statistical software (R, Version 3.0.1, R Foundation for Statistical Computing, Vienna, Austria.)

## RESULTS

Of the 2453 patients patch tested, 13.94% ( $n = 342$ ) had a history of AD. Of the 870 males tested, the incidence of AD was 9.20% ( $n = 80$ ); among the 1581 females, the incidence of AD was 16.57% ( $n = 262$ ). As seen in [Fig 1](#),

among patients with a history of AD, 72.51% had a positive patch test to at least 1 allergen, whereas 64.71% of those with no history of AD had at least 1 positive patch test response ( $P = .006$ ). Subanalysis by gender showed 73.2% of females with a history of AD had a positive patch to at least 1 allergen, whereas 66.3% of females with no history of AD had at least 1 positive patch test response ( $P = .032$ ). Subanalysis for men was not statistically significant, most likely because of the small sample size.

When examining paraben mix and formaldehyde, there was no statistically significant difference in the incidence of positive responses between atopic and nonatopic patients. These results held true when analyzed by gender. However, an interesting finding was that no atopic patients reacted positively to paraben mix ([Table I](#) and [Fig 2](#)).

Among the formaldehyde releasers, there was a significantly higher incidence of positive patch test reactions to 4 of the 5 releasers analyzed among those persons with a history of AD as compared with the nonatopic population ([Table I](#) and [Fig 2](#)). For quaternium-15, imidazolidinyl urea, and 2-bromo-2-nitropropane-1,3-diol, patients with AD were statistically more likely to have a positive patch test response than those patients with no history of AD; when analyzed by gender, the above findings held true in women but lost statistical significance in men. For DMDM hydantoin, patients with AD were

## CAPSULE SUMMARY

- Atopic individuals have chronic dry skin and are predisposed to developing cutaneous delayed-type hypersensitivity.
- Atopic individuals were significantly more likely to exhibit cutaneous delayed-type hypersensitivity to quaternium-15, imidazolidinyl urea, DMDM hydantoin, and 2-bromo-2-nitropropane-1,3-diol but not to parabens, formaldehyde, or diazolidinyl urea.
- Atopic patients should minimize cutaneous contact with products containing formaldehyde releasers.

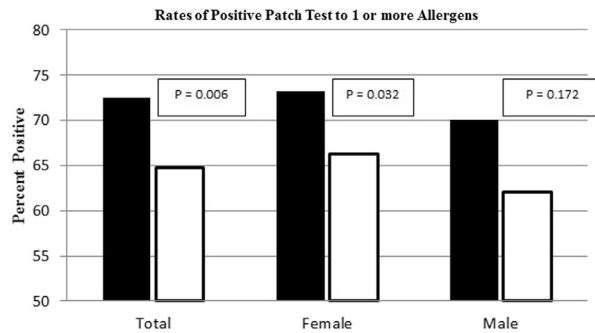


**Fig 1.** Cutaneous delayed-type hypersensitivity. Percentage of atopic (■) and nonatopic (□) patients who had a positive patch test reaction to any allergen.

**Table I.** Common preservatives and their rates of positive patch tests among atopic and nonatopic populations, stratified by gender

|                                 | Atopic eczema + |       | Atopic eczema – |      | P value |
|---------------------------------|-----------------|-------|-----------------|------|---------|
|                                 | No.             | %     | No.             | %    |         |
| Paraben mix                     | 0/342           | 0.00  | 10/2111         | 0.47 | .413    |
| Female                          | 0/262           | 0.00  | 5/1319          | 0.38 | .692    |
| Male                            | 0/80            | 0.00  | 5/790           | 0.63 | 1.000   |
| Formaldehyde                    | 22/342          | 6.43  | 123/2111        | 5.83 | .751    |
| Female                          | 16/262          | 6.11  | 71/1319         | 5.38 | .748    |
| Male                            | 6/80            | 7.50  | 52/790          | 6.58 | .938    |
| Quaternium-15                   | 38/342          | 11.11 | 151/2111        | 7.15 | .015    |
| Female                          | 29/262          | 11.07 | 93/1319         | 7.05 | .036    |
| Male                            | 9/80            | 11.25 | 58/790          | 7.34 | .303    |
| Imidazolidinyl urea             | 13/342          | 3.80  | 41/2111         | 1.94 | .048    |
| Female                          | 10/262          | 3.82  | 20/1319         | 1.52 | .025    |
| Male                            | 3/80            | 3.75  | 21/790          | 2.66 | .834    |
| Diazolidinyl urea               | 13/342          | 3.80  | 60/2111         | 2.84 | .426    |
| Female                          | 10/262          | 3.82  | 31/1319         | 2.35 | .250    |
| Male                            | 3/80            | 3.75  | 29/790          | 3.67 | 1.000   |
| DMDM hydantoin                  | 14/342          | 4.09  | 41/2111         | 1.94 | .022    |
| Female                          | 10/262          | 3.82  | 25/1319         | 1.90 | .089    |
| Male                            | 4/80            | 5.00  | 16/790          | 2.03 | .194    |
| 2-Bromo-2-nitropropane-1,3-diol | 16/342          | 4.68  | 42/2111         | 1.99 | .004    |
| Female                          | 14/262          | 5.34  | 27/1319         | 2.05 | .004    |
| Male                            | 2/80            | 2.50  | 15/790          | 1.90 | 1.000   |

statistically more likely to have had a positive response when compared with patients with no history of AD; however, the above findings lost statistical significance when analyzed by gender. Among the formaldehyde releasers, only for diazolidinyl urea was there no statistically significant difference between atopic and nonatopic patients in the rate of positive reactions (Table I and Fig 2).

## DISCUSSION

In an earlier study, patients with severe AD were less likely sensitized to dinitrochlorobenzene than

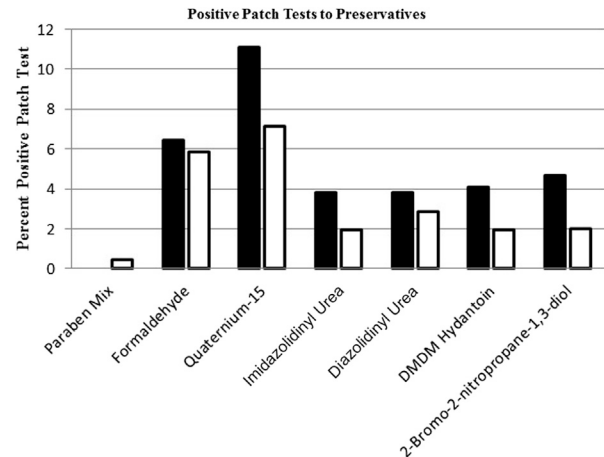


**Fig 2.** Cutaneous delayed-type hypersensitivity to the preservatives of interest among patients with atopic dermatitis (■) and those without (□).

those with moderate or mild disease. In this study, of 20 patients with severe or moderate disease unresponsive to the initial dinitrochlorobenzene challenge, 18 reacted to a second challenge when the dermatitis was well controlled.<sup>6</sup> In contrast, our data, collected from individuals with dermatitis covering 25% or less of body surface area, show that persons with a history of AD are significantly more likely than the non-AD population to have a positive allergic patch test reaction to at least 1 allergen. Thus, although the induction of CDTH (at least to dinitrochlorobenzene, a potent allergen) may be dampened in atopics with “active” disease,<sup>6,7</sup> in the aggregate, patients with AD are more likely than nonatopic patients to acquire and manifest CDTH responses over time.

Our findings of an increased incidence of CDTH in atopic patients are consistent with the findings of Gittler et al<sup>8</sup> in their recent exhaustive review of the literature. As outlined by these authors, there are multiple possible mechanisms accounting for enhanced CDTH in atopic patients. However, which of these factors, or what combination thereof, might account for our finding that atopics are more likely than nonatopics to react to formaldehyde-releasing preservatives is unclear. Moreover, it is possible that enhanced rates of reactivity to formaldehyde releasers in atopic patients are merely the result of a greater exposure to emollients and other personal care products preserved with these potential allergens.

Products with low water content, such as ointments, are self-preserved. Many cosmetics, topical medications, and hygiene products including liquid soaps, shampoos, and conditioners have a high water content that requires chemical

**Table II.** Consumer products containing preservatives

| Preservative                    | CIR    | EWG    |
|---------------------------------|--------|--------|
| Total paraben                   | 21,584 | 43,204 |
| Methyl                          | 8786   | 17,143 |
| Ethyl                           | 2679   | 5195   |
| Propyl                          | 7118   | 15,264 |
| Butyl                           | 3001   | 5602   |
| Formaldehyde                    | 77     | 14     |
| Total formaldehyde releaser     | 4232   | 2345   |
| Quaternium-15                   | 487    | 223    |
| Diazolidinyl urea               | 756    | 760    |
| DMDM hydantoin                  | 963    | 1050   |
| Imidazolidinyl urea             | 2025   | 274    |
| 2-Bromo-2-nitropropane-1,3-diol | 1      | 38     |

Data collected from the EWG<sup>11</sup> and the CIR<sup>12-17</sup> on the prevalence of different preservatives in consumer products.

CIR, Cosmetic Ingredient Review; EWG, Environmental Working Group.

preservation.<sup>9,10</sup> Parabens, formaldehyde, and formaldehyde releasers are commonly used as preservers.<sup>9</sup> The Cosmetic Ingredient Review and the Environmental Working Group collect data on the prevalence of the different preservatives in consumer products (Table II).<sup>11-17</sup>

Parabens including methyl, ethyl, propyl, and butyl paraben used alone or in combination are the most common preservative. They have been frequently used over the last 70 years.<sup>10</sup> In a study of patch-tested individuals, the rate of sensitization to a paraben mix of methyl, ethyl, propyl, and butyl paraben was 0.6%.<sup>18</sup> Given their long-term and expansive use along with their low rate of sensitization, parabens seem to be stable, effective, and relatively nonsensitizing preservatives.<sup>10</sup>

Formaldehyde has been reported to be a strong skin sensitizer, irritant, and potential carcinogen.<sup>19-21</sup> Because of this, the use of formaldehyde has been predominantly replaced by formaldehyde releasers. Formaldehyde is still used in some hair care products and nail hardeners.<sup>10</sup> In a past study, the rate of sensitization to formaldehyde in patch-tested individuals was 8.4%.<sup>18</sup> A study of pathologists who were frequently exposed to formaldehyde showed no tendency for atopic patients to be more sensitive to formaldehyde than nonatopic patients.<sup>22</sup> Although the scope of this study is to focus on the relationship between AD and a CDTH response to formaldehyde, it is worthwhile to note that 1 study found formaldehyde exposure may be associated with an increased prevalence of atopic eczema in Japanese pregnant women.<sup>23</sup>

Formaldehyde releasers release formaldehyde through hydrolysis to keep the amount of free

formaldehyde low but sufficient to prevent bacterial growth.<sup>21,24</sup> Well-known formaldehyde releasers include quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, and 2-bromo-2-nitropropane-1,3-diol.<sup>19</sup> In a study of patch-tested patients, positive allergic reactions for formaldehyde releasers were 9.3% for quaternium-15, 3.0% for imidazolidinyl urea, 3.1% for diazolidinyl urea, 2.8% for DMDM hydantoin, and 3.3% for 2-bromo-2-nitropropane-1,3-diol.<sup>18</sup> These allergic reactions may be caused by released formaldehyde or by the structure of the formaldehyde releaser itself.<sup>20,21</sup>

Our study agrees with the previous finding that there is no significant difference in prevalence of allergic reactions to formaldehyde between atopic and nonatopic populations.<sup>22</sup> We suspect this is because formaldehyde is infrequently used as a preservative in personal care products (Table II); and its greatest use is in rinse-off hair care products and nail hardeners<sup>13</sup> where it is unlikely to sensitize.

Four of the 5 formaldehyde releasers (quaternium-15, imidazolidinyl urea, DMDM hydantoin, and 2-bromo-2-nitropropane-1,3-diol) demonstrated significantly higher allergic responses in patients with AD than in nonatopic patients. These results of sensitization to the majority of the formaldehyde-releasing preservatives, but not for formaldehyde itself, suggest that it is the structure of the formaldehyde releasers causing an allergic response, and this response is not caused by their low release of formaldehyde.<sup>20,21</sup> When stratified by gender, quaternium-15, imidazolidinyl urea, and 2-bromo-2-nitropropane-1,3-diol were found to be significantly more likely to elicit a positive reaction in females with AD, but no significant difference was found for males. This may simply be a result of a loss of power because of the relatively small number of males with AD included in the study. However, it may be caused by higher rates of exposure to products containing formaldehyde releasers, such as cosmetics and lotions, in the female, compared with the male, population.

In our study, parabens had the lowest rate of positive allergic response with 0.47% in the nonatopic group and 0% in the atopic group with no significant difference between the 2 groups. Parabens appear in the highest number of consumer products (Table II). Although we are unable to account for the frequency of use of the products containing parabens compared with products containing other preservatives, we assume that their presence in such a high percentage of products equates to their being the most frequent

preservatives encountered. This supports past studies finding parabens to be relatively nonsensitizing preservatives,<sup>10</sup> even in the atopic population.

All known preservatives cause allergic contact dermatitis in some users.<sup>25</sup> Past studies have found persons with AD more likely to develop CDTH than persons without AD.<sup>3</sup> It has also previously been noted that atopics may experience more adverse reactions to topical preparations because of impaired barrier function than nonatopics.<sup>25-27</sup> However, it is a novel finding that people with AD are more likely than nonatopics to have a CDTH response to the formaldehyde releasers quaternium-15, imidazolidinyl urea, DMDM hydantoin, and 2-bromo-2-nitropropane-1,3-diol. Possible mechanisms for this enhanced CDTH to formaldehyde-releasing preservatives in atopic populations could include some combination of barrier disruption, increased exposure, cutaneous/systemic immunologic abnormalities, and genetic factors,<sup>8</sup> but the exact mechanism(s) is (are) still unknown.

In summary, our patients with AD are more likely to have a CDTH reaction than those without AD. We did not find atopics to be more likely to react to parabens, formaldehyde, or diazolidinyl urea than nonatopics. We did observe significantly higher rates of allergic reaction in all the tested formaldehyde releasers besides diazolidinyl urea in patients with AD compared with patients without AD. Based on our findings, we strongly recommend that health care practitioners counsel their atopic patients to minimize cutaneous contact with products that contain formaldehyde releasers. Diazolidinyl urea shares a common chemical backbone with imidazolidinyl urea. A past study found that 90% of people who reacted to imidazolidinyl urea also reacted to diazolidinyl urea, and 47% of people who reacted to diazolidinyl urea reacted to imidazolidinyl urea.<sup>20</sup> Even though our data showed no significant difference between atopic and nonatopic populations in their reactivity to diazolidinyl urea, we still recommend that atopic patients avoid products with diazolidinyl urea given its high rate of cross-reactivity with imidazolidinyl urea.

Atopic patients should be advised to treat their skin with ointments, which are unlikely to contain antimicrobial preservatives. When using creams, lotions, and other products containing biocides, atopic patients should preferentially use products preserved with parabens, which rarely sensitize the atopic and nonatopic populations. Although we are aware of reports of a putative link between parabens and endocrine disruption, this issue has been thoroughly reviewed by the Cosmetic Ingredient

Review and found not to be relevant to parabens as used in cosmetics.<sup>12</sup>

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