

Physician-Patient Agreement in the Assessment of Allergen Relevance

Katrina A. Gipson, Sean W. Carlson, and Susan T. Nedorost

Background: The efficacy of patch testing may be enhanced by data allowing the physician to estimate the likelihood that results of a patch-test reading are relevant to a patient's dermatitis.

Objective: The goal of this study was to compare the rates of agreement between the physician's assessment of relevance at the time of final reading and the patients' report 3 months to 3 years later in regard to whether avoidance of an allergen was needed to remain free of dermatitis. We hypothesize that the agreement rates between the physician and patient relevance assessments will vary based on properties both intrinsic and extrinsic to the allergen in question.

Methods: We mailed 407 Institutional Review Board–approved questionnaires to patients and analyzed results for the 92 patients reporting greater than 80% improvement of their dermatitis. Cross-reacting allergens tested on the same patient were combined for analysis. Percent agreement was used to assess interrater concordance.

Results: Percent agreement regarding relevance for each allergen or group of allergens was as follows: formaldehyde and formaldehyde-releasing preservatives, 88%; neomycin sulfate, 78%; nickel sulfate hexahydrate, 71%; fragrance mix and related products, 65%; and gold sodium thiosulfate, 56%.

Conclusion: Relevance varies between allergens. Physician assessment of relevance at the time of final reading is not the ideal method for determining allergen relevance. This has implications for when best to determine the relevance of certain allergens. For allergens with lower agreement, in particular, extended follow-up is recommended to accurately determine an allergen's contribution to a patient's allergic contact dermatitis, especially in those circumstances in which a patient's condition has not improved.

CERTAIN SUBSTANCES that contact the skin may produce a delayed type IV hypersensitivity reaction, resulting in allergic contact dermatitis (ACD). Patch testing remains the primary diagnostic tool for identifying allergens responsible for ACD. The series of allergens applied to patients depends on patient history, practitioner preference, region, and country.^{1,2} Practitioners' reading schedules vary as well.³

In this study, the physician used an extended reading schedule; the physician's initial reading was done 72 to 96 hours after patch application (day 3 or 4), and the final reading was done at approximately 168 hours after application (day 7). At the final reading, allergen relevance was determined with the standard scale (Table 1).

From the Department of Dermatology, University Hospitals Case Medical Center, Cleveland, OH.

Address correspondence to Susan T. Nedorost, MD, Department of Dermatology, University Hospitals Case Medical Center, 11100 Euclid Avenue, Lakeside 3500, Cleveland, OH 44106. E-mail: susan.nedorost@uhhospitals.org

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The nature of allergens applied to the patient's skin (eg, their prevalence in the patient's environment and the anatomic location to which they are applied) affects the physician's ability to accurately assess the relevance of patch-test readings. Because of the variability among the type of allergens used in a single series, we hypothesized that the physician's assessment of the relevance of an allergen at the time of final reading might differ from the patient's assessment, after a trial of allergen avoidance, as to which allergen is actually responsible for the patient's ACD. To test this hypothesis, we surveyed patients 30 days to 3 years after the final reading of their patch tests, asking which allergens they felt they needed to avoid to maintain an 80% or greater improvement in their ACD. The patients' survey results were then compared to the physician's determination of relevance at the time of final reading.

Methods

Via standard mail, 407 Institutional Review Board–approved questionnaires were sent to patients whose patch tests were applied and interpreted between January 2005 and

Table 1. Physician Assessment of Patch-Test Reactions

IR	Irritant or Nonallergic Reaction
0	No relevance
1	Definite relevance
2	Probable relevance
3	Past relevance

February 2008. An extended North American Contact Dermatitis Group standard series was used for all patch testing, with Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Actavis Norway AS, Vennesla, Norway). A specialty series was used for select patients. All patients included in this study removed their own patch tests at home 48 hours after application. The physician's initial reading was done at 72 to 96 hours after application (day 3 or 4), and the final reading was done at approximately 168 hours after application (day 7).

Each questionnaire asked the following questions:

1. Is your rash more than 80% better compared to before patch testing?
2. Have you avoided contact with [allergen]?
3. Do you feel it is important to avoid [allergen] over the long term?

Questions 2 and 3 above were repeated for each allergen that elicited a positive allergic reaction (allergen reactions graded as ?+, +, ++, or +++ at either an early or late reading and felt to be allergic in nature). A doubtful reaction (?+) was defined as erythema without induration or as induration not filling the entire chamber area.

Of the 407 questionnaires, 121 were returned. Questionnaires eligible for interpretation included those of patients who reported greater than 80% improvement of their dermatitis due to the avoidance of identified allergens. Cross-reacting allergens tested on the same patient were combined for analysis (Table 2). Each survey included all cross-reacting allergens listed separately.

We considered an allergen "relevant" from the patient's perspective if the patient indicated that it was important to avoid the allergen over the long term to remain dermatitis free (as interpreted in a previous study based on the same questionnaire).⁴ Conversely, an allergen was not considered relevant if the patient did not feel it necessary to avoid the allergen over the long term to remain dermatitis free. The patients' observances of relevance were compared to the physician's assessment at the time of the final reading. Furthermore, physician assessment coding (see Table 1) was dichotomized so that

Table 2. Cross-Reacting Allergens Combined for Analysis

<i>Fragrance Mix and Related Products</i>	<i>Formaldehyde and Formaldehyde Releasers</i>
Fragrance mix I and II	Formaldehyde
Cinnamic aldehyde	Quaternium-15
<i>Myroxilon pereirae</i> (balsam of Peru)	Imidazolidinylurea
Narcissus absolute	2-Bromo-2-nitropropane-1, 3-diol (bronopol)
Isoeugenol	Dimethylol dimethyl (DMDM) hydantoin
	Ethyleneurea/melamine formaldehyde mix
	Diazolidinylurea

a physician assessment of 0 (no relevance) correlated to the patient's feeling no need to avoid the allergen over the long term. For the purpose of this study, a physician assessment of 1, 2, or 3 was equivalent to a relevant patch-test result. Percent agreement for the most prevalent allergens was calculated.

Results

Among the 121 questionnaires that were returned, 92 patients reported that their dermatitis had improved by at least 80%.

Percent agreement regarding relevance for each allergen or group of allergens was as follows: formaldehyde and formaldehyde-releasing preservatives, 88%; neomycin sulfate, 78%; nickel sulfate hexahydrate, 71%; fragrance mix and related products, 65%; and gold sodium thiosulfate, 56% (Table 3, Table 4, Table 5, Table 6, and Table 7, respectively). Table 8 summarizes the data.

Discussion

Assignment of relevance at the time of final reading may result in several outcomes. Patients with positive patch-test results may (1) avoid an allergen the physician felt was relevant and get better, (2) avoid an allergen the physician

Table 3. Ratings of Reactions to Formaldehyde and Formaldehyde-Releasing Preservatives

<i>Patient Rating</i>	<i>Physician Rating</i>	
	<i>Relevant</i>	<i>Irrelevant</i>
Relevant	21	0
Irrelevant	3	0

Table 4. Ratings of Reactions to Neomycin Sulfate

<i>Patient Rating</i>	<i>Physician Rating</i>	
	<i>Relevant</i>	<i>Irrelevant</i>
Relevant	14	2
Irrelevant	2	0

felt was not relevant and get better, or (3) not avoid an allergen the physician felt was relevant but still get better. The first outcome is illustrated by Table 3, Table 4, and Table 5—the preponderance of patients agreed with the physician's assessment of relevance (they were told to avoid the allergen as instructed, and most of them felt it was necessary to remain dermatitis free), reinforcing the impact of the allergen on the patients' condition. The latter two outcomes are illustrated by Table 6 and Table 7. In the case of gold sodium thiosulfate, relevance was underestimated by the physician as the patients who reacted to gold sodium thiosulfate felt it was important to avoid it to remain dermatitis free. In the case of fragrance mix and related products, the physician overestimated relevance as the patients felt it was not as necessary to avoid the allergen to remain dermatitis free (ie, they were instructed to avoid the allergen, but they did not feel it necessary to do so). The outcomes illustrated by Table 6 and Table 7 both indicate that the attribution of relevance was flawed.

This study did not address the analysis of the relevance of positive patch-test results of patients who did not show improvement in their dermatitis. However, when the physician assigns relevance to an allergen and asks the patient to avoid the allergen but the patient's dermatitis does not improve, then (1) the allergen is not relevant, (2) the patient did not avoid the allergen, or (3) the patient does not have ACD or has an additional condition that is not being recognized or adequately treated. A confounding factor is present when patients have reacted to multiple allergens and multiple allergens are felt to be relevant.

True relevance is more accurately determined after patients have had more time to decide which allergens they need to avoid to remain free of dermatitis. Follow-up after

Table 6. Ratings of Reactions to Fragrance Mix and Related Products

<i>Patient Rating</i>	<i>Physician Rating</i>	
	<i>Relevant</i>	<i>Irrelevant</i>
Relevant	21	3
Irrelevant	10	3

patch testing provides an additional outcome measure that can be used by the physician to gauge which allergens are truly relevant.⁵

Formaldehyde-releasing preservatives (such as quaternium-15, imidazolidinylurea, and bronopol) that are specifically labeled on personal care products had the highest percent agreement between patient and physician assessments of relevance. Formaldehyde-releasing preservatives were tested separately but were grouped together for the purposes of this study due to low numbers, which may limit interpretation. Formaldehyde is a marginal irritant that is difficult to patch test.⁶ In the United States, formaldehyde is often not labeled on industrial products such as coolants, and formaldehyde-related textile resins are not declared in fabrics. These factors would be expected to decrease percent agreement.

Neomycin is specifically labeled on topical antimicrobial products, it is used in a limited number of products, and it is most often applied only to a small area of the skin's surface. This makes physician assessment of neomycin-associated ACD relevance fairly straightforward, and we would expect a relatively higher percent agreement.

Nickel sulfate hexahydrate carried the median percent agreement among the allergens. Patients are taught to test metal with dimethylglyoxime to determine whether nickel is present, and reaction patterns and avoidance strategies are also fairly straightforward.

Fragrance mix and gold sodium thiosulfate had lower percent agreement rates between physician and long-term patient assessments of relevance. Screening for fragrance allergy is frequently performed by using a fragrance mix that screens for sensitization to any of its components. The

Table 5. Ratings of Reactions to Nickel Sulfate Hexahydrate

<i>Patient Rating</i>	<i>Physician Rating</i>	
	<i>Relevant</i>	<i>Irrelevant</i>
Relevant	13	3
Irrelevant	3	2

Table 7. Ratings of Reactions to Gold Sodium Thiosulfate

<i>Patient Rating</i>	<i>Physician Rating</i>	
	<i>Relevant</i>	<i>Irrelevant</i>
Relevant	7	5
Irrelevant	2	2

Table 8. Physician-Patient Percentage Agreement on Allergen Relevance

Allergen	Percent Agreement
Formaldehyde and formaldehyde-releasing preservatives	88%
Neomycin sulfate	78%
Nickel sulfate hexahydrate	71%
Fragrance mix and related products	65%
Gold sodium thiosulfate	56%

North American Contact Dermatitis Group standard tray includes a “fragrance mix I,” which includes cinnamic alcohol, cinnamic aldehyde, eugenol, hydroxycitronellal, isoeugenol, geraniol, oak moss absolute, and alpha-amyl cinnamic aldehyde. *Myroxilon pereirae* (balsam of Peru) resin is also used to screen for fragrance allergy. Not all fragrance mix constituents are listed on product labeling, and products that list “fragrance” may include different chemicals.⁷ In addition, products that are labeled as “unscented” may still contain certain fragrances.⁸ Patients may tolerate some fragrance mix constituents but not others. Given the inconsistency in product labeling and variability in tolerability, lower percent agreement is not surprising.

Gold-containing objects vary in their release of gold,⁹ which may depend on environmental factors such as the presence of titanium dioxide particles, perspiration, and friction on exposed skin. Variation in bioavailability would allow many gold sodium thiosulfate patch test-positive patients to tolerate gold-containing jewelry and lowers patient relevance measures as compared to conservative physician estimates. Additionally, the prevalence of positive patch-test reactions to gold sodium thiosulfate is similar between patients and the background population,¹⁰ supporting the notion that a positive patch-test reaction to gold sodium thiosulfate may have limited clinical value.

Characteristics specific to individual allergens (such as the ease of determining an allergen’s presence in a product and variation in bioavailability) help explain the variation in agreement between physician assessment of relevance at the time of final reading and patient-reported relevance months later.

Study Limitations

Our questionnaire was not formally validated prior to being sent to patients. Also, patients who saw significant

improvement in their ACD may have been more likely to return the questionnaire. Our clinical practice is to counsel patients on the avoidance of allergens that yield a “lost” (ie, positive early but negative at late reading) result only if the clinician believes there is a high likelihood of relevance; the only allergens in this study that were “lost” and about which we queried patients about relevance were *Myroxilon pereirae* resin (balsam of Peru), carba mix, and thiuram mix. This practice may inflate the correlation of relevance observed in this study for *Myroxilon pereirae* resin.

Conclusion

The physician’s assessment of relevance at the time of final reading is not the “gold standard” for determining which allergens are truly responsible for a patient’s allergic contact dermatitis but should be viewed as a tentative guide for the patient to follow when avoiding allergens. As seen in this study, the true relevance of allergens such as fragrance mix and gold sodium thiosulfate is not always straightforward, likely owing in part to incomplete labeling (as in the former case) or variations in bioavailability (as in the latter case). Patients’ reporting of relevance some months after being educated about allergens, alternative products, and avoidance may aid in the determination of which allergens are truly relevant.

Thus, we recommend (1) continuing to assess significance or relevance at the time of final reading to provide the patient with a list of allergens to avoid and (2) contacting patients 3 to 6 months after patch testing to assess whether the dermatitis has improved and which allergens have been avoided. Telephone contact is a reasonable way to accomplish this. If the patient’s dermatitis has not resolved, a follow-up visit is indicated for reevaluation. This practice provides more continuity of care and provides the physician with more feedback regarding patients’ practices in allergen avoidance.

We recommend that future research in patch testing focus on patch-test outcomes—specifically, whether or not patients improved and maintained improvement following patch testing. Such research would shed light on the optimum time at which true relevance may be assessed.

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References

1. Cheng LS, Alikhan A, Maibach HI. Compilation of international standards for patch testing methodology and allergens. *Dermatitis* 2009;20:257–60.
2. Warshaw EM, Nelson D. Prevalence of patch testing and methodology of dermatologists in the US: results of a cross-sectional survey. *Am J Contact Dermat* 2002;13:53–8.
3. Warshaw EM, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 2003–2004 study period. *Dermatitis* 2008;19:129–36.
4. Carlson S, Gipson K, Nedorost S. Relevance of doubtful (“equivocal”) late patch-test readings. *Dermatitis* 2010;21:102–8.
5. Gallo R, Baldaril M, Fausti V, et al. Measurement of a possible patch-testing outcome indicator. *Contact Dermatitis* 2010;62:150–6.
6. de Groot AC, Flyvholm MA, Lensen G, et al. Formaldehyde-releasers: relationship to formaldehyde contact allergy. Contact allergy to formaldehyde and inventory of formaldehyde-releasers. *Contact Dermatitis* 2009;61:63–85.
7. Scheman A, Jacob S, Zirwas M, et al. Contact allergy: alternatives for the 2007 North American Contact Dermatitis Group (NACDG) standard screening tray. *Dis Mon* 2008;54:7–156.
8. Nelson SA, Yiannias JA. Relevance and avoidance of skin-care product allergens: pearls and pitfalls. *Dermatol Clin* 2009;27:329–36, vii.
9. Liden C, Nordenadler M, Skare L. Metal release from gold-containing jewelry materials: no gold release detected. *Contact Dermatitis* 1998;39:281–5.
10. Fleming C, Lucke T, Forsyth A, et al. A controlled study of gold contact hypersensitivity. *Contact Dermatitis* 1998;38:137–9.