

The detection of clinically relevant contact allergens with a standard screening tray of 28 allergens

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Summary

Background. A standard method for diagnosing allergic contact dermatitis in the United States is the Thin-layer Rapid Use Epicutaneous (TRUE) test (TRUE Test™), which consists of three panels containing 20 individual allergens and eight allergen mixes. Previous studies had raised concern regarding the adequacy of the initial two-panel TRUE Test™ system (16 individual allergens and seven allergen mixes) in fully assessing patients with possible allergic contact dermatitis.

Objectives. We sought to investigate the effectiveness of the current three-panel TRUE Test™ as the sole diagnostic tool for detecting allergic contact dermatitis.

Patients/materials/methods. This study was a retrospective analysis of 2088 patients who underwent patch testing between 1995 and 2010. Study groups were analysed to determine whether positive reactions were to allergens and/or mixes present in the TRUE Test™ panels.

Results. Of the 2088 patch-tested patients, 1385 had at least one positive reaction. Among these 1385 patients, 27.6% were fully evaluated by use of only the TRUE Test™ series, 49.9% were partially evaluated, and 22.5% did not have any of their allergens detected. On assessment for clinical relevance, similar percentages were observed.

Conclusion. In our study, the current TRUE Test™ series of 28 allergens would have completely identified allergens in only 27.6% of patients. Broadening the standard panel to include common allergens causing > 50% of allergic contact dermatitis cases in a given geographical location and aim testing allergens on the basis of the patient's history will increase the test's sensitivity.

Key words: allergic contact dermatitis; clinically relevant allergens; patch test; TRUE Test™.

Contact dermatitis is one of the most common reasons for patients visiting a dermatology clinic (1). Patch testing is the gold standard for evaluating patients with suspected allergic contact dermatitis (2, 3). This test

allows physicians to find causative allergens quickly, which has been shown to lead to early resolution of symptoms and improved quality of life (4, 5). Kadyk et al. (6) found that patients diagnosed by patch testing more than 36 months after disease onset had worse quality of life scores than those diagnosed earlier in the natural history of the disease. Delay in patch testing, and thus diagnosis, has been linked to progression to a chronic disease state, decreased response to treatment, and poorer prognosis (4, 5, 7, 8).

Several studies have analysed the reliability of a standard series (referred to as a 'baseline' series in

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Europe) alone in fully evaluating allergic contact dermatitis (9–12). These studies have shown that any one standard series may be insufficient for complete and correct diagnosis. To increase the diagnostic accuracy of patch testing, physicians must use allergens beyond those present in a standard series. A detailed medical, environmental and occupational history, coupled with knowledge of the allergens being tested on the standard series, allows the physician to determine which supplemental patch test allergens should be added to the standard series (9, 13). In the current study, we looked at the ability of the Thin-layer Rapid Use Epicutaneous (TRUE) test (TRUE Test™) allergens and/or mixes to detect all relevant allergic reactions in patients evaluated at the University of Kansas Section on Occupational and Contact Dermatitis in Kansas City, Kansas, and at American Dermatology Associates in Shawnee, Kansas.

Patients and Methods

All patients who were patch tested for allergic contact dermatitis at American Dermatology Associates in Shawnee, Kansas, between 1 July 2005 and 30 September 2010, and patients tested between 1 January 1995 and 30 June 2005 at the Section of Occupational and Contact Dermatitis, University of Kansas Medical Center in Kansas City, Kansas, were included in this study. Patients seen during this time had a broad assortment of occupational and contact dermatides; however, only those who underwent patch testing with at least the currently available, Food and Drug Administration (FDA)-approved, TRUE Test™ allergens and/or mixes, excluding quinoline mix, were included in this study. Quinoline mix was not included, because it has never been part of the standard series of the North American Contact Dermatitis Group (NACDG) and is not a commonly used medication in the United States. However, patients in this study who gave a history of using clioquinol were tested with this allergen.

Before patch testing, all patients answered the NACDG questionnaire composed of occupational, demographic and medical queries. During this 15-year time period, 2088 patients were patch tested with 27 of the 28 allergens and/or mixes similar to those present in the TRUE Test™ panels. These allergens (except quinoline mix) were contained in the more extensive NACDG standard series [Chemotechnique, Vellinge, Sweden (1 January 1995 to 31 December 2008) and allergEAZE, Calgary, AB, Canada (1 January 2009 to the present)]. Patients were tested with supplementary allergens in addition to the NACDG's standard series, on the basis of history, examination, and clinical opinion. These additional allergens included pure chemicals obtained

from commercial sources and personal/work-related products that were tested at appropriate dilutions. The vast majority of patients had not been previously patch tested. In the < 1% of patients who had had prior testing, these results did not influence which allergens were selected for testing.

All patients were tested in a standard manner with the Finn Chambers® technique (Epitest Ltd, Oy, Tuusula, Finland) on Scanpor® tape (Alpharma AS, Norgesplaster, Vennesla, Norway). The patch panels were placed on areas of the back that were clean and free of oils, lotions, and ointments. The test areas were regions without scars, active dermatitis, skin eruptions, or other conditions that could interfere with the interpretation of the test. The tests were interpreted on day 2, and patients were recalled on day 4 for a second, final reading. The patch tests were scored on a scale of 1–6 on the basis of the morphology of the reaction (14). Reactions were considered to be positive if they were scored as 1, 2 or 3 with the NACDG scoring system (14).

Relevance, exposure, and dermatitis site and type were recorded. The relevance of a positive patch test reaction was characterized as follows: 1, definite (the patient was tested with a product to which he or she had been exposed and that contained the allergen to which he or she reacted); 2, probable (the patient had a known cutaneous exposure to a product containing the allergen to which he or she reacted); 3, possible (the patient probably had a cutaneous exposure to a product known or suspected to contain the allergen to which he or she reacted); 4, past (the patient had prior episodes of allergic contact dermatitis after being exposed to the allergen to which he or she reacted); or 5, unknown (the allergen's relevance could not be determined) (15). Health Insurance Portability and Accountability Act 1996-compliant, de-identified data obtained for each patient were entered into a computer database (Access™; Microsoft Corp., Seattle, WA, USA), and appropriate queries were run.

Patients with at least one positive allergic response were then divided into three groups: (i) reactions only to allergens and/or mixes present in the TRUE Test™ panels; (ii) reactions only to allergens and/or mixes not present in the TRUE Test™ panels; and (iii) reactions to allergens and/or mixes contained in the TRUE Test™ series and to additional allergens. All positive reactions were scored for relevance, as defined above (14, 15). All procedures were performed in accordance with the Helsinki Declaration of 1975.

Results

Of the 2088 patients who were patch tested, 1385 (66.3%) had at least one positive allergic reaction (Table 1).

Table 1. Positive allergic reactions to TRUE Test™ allergens and their clinical relevance

	Positive to TRUE Test™ allergens and additional allergens	Positive to TRUE Test™ allergens only	Negative to TRUE Test™ allergens and positive to additional allergens
Positive allergic reactions (%)	691 (49.9)	382 (27.6)	312 (22.5)
Clinically relevant allergic reactions (%)	553 (45.9)	344 (28.5)	309 (25.6)

Table 2. Positive allergic reactions to the North American Contact Dermatitis Group top 50 allergens and their clinical relevance

	Positive to a top 50 allergen(s) and additional allergen(s)	Positive to a top 50 allergen(s) only	Negative to a top 50 allergen(s) and positive to additional allergen(s)
Positive allergic reactions (%)	589 (42.5)	624 (45.1)	172 (12.4)
Clinically relevant allergic reactions (%)	478 (39.6)	559 (46.4)	169 (14.0)

Among these 1385 patients, 27.6% would have had all of their known allergic reactions detected with the TRUE Test™ panels only. If only the TRUE Test™ allergens and/or mixes had been tested, 22.5% would not have had any of their allergens detected, and 49.9% would have been aware of only a partial list of their allergens. When relevance was used to identify those individuals with allergic contact dermatitis, these percentages did not materially change (Table 1).

Expanding the panel of standard allergens to include the top 50 allergens and/or mixes that we found in the current study increased the yield of positive reactions. However, even assuming a standard panel of the top regional 50 allergens and/or mixes, < 50% of our patients would have been correctly and completely diagnosed (Table 2). Among the 1385 patients with one or more positive reactions, 45.1% reacted only to these top allergens and/or mixes, 42.5% reacted to an allergen and/or mixture on this 'top 50' panel and to an additional allergen, and 12.4% reacted only to a supplemental allergen. When relevance was used as a criterion, these percentages did not dramatically change. The top 25 allergens and/or mixes, not contained in the TRUE Test™ series, that elicited positive reactions in our patient population are listed in Table 3.

Table 3. Top 25 allergens not contained in the TRUE Test™ in decreasing order of frequency^a

Allergens	Percentage of patients with positive reactions (1, 2, or 3+)	Percentage of positive patients whose reactions were relevant (1, 2, or 3)
Fragrance mix II (n = 413) ^b	6.3	80.8
Bacitracin ^c	5.8	43.0
Sodium gold thiosulfate (n = 1283) ^d	5.3	13.2
Methyldibromo glutaronitrile/phenoxyethanol ^c	4.0	61.4
Melamine formaldehyde (n = 1029) ^e	3.3	73.1
Benzalkonium chloride (n = 1524) ^e	2.6	41.0
DMDM hydantoin ^c	2.6	89.0
Ethyleneurea melamine/formaldehyde (n = 1884) ^f	2.6	71.4
Urea formaldehyde (n = 1029) ^e	2.5	73.1
2-Bromo-2-nitropropane-1,3-diol ^c	2.3	20.4
Iodopropynyl butylcarbamate (n = 1091) ^g	2.2	75.0
Cocamidopropyl betaine (n = 1831) ^h	1.9	91.4
Tetramethylol acetylene diurea (n = 1029) ^e	1.8	89.5
Benzophenone-4 (n = 1524) ^e	1.7	41.0
Disperse Blue 106 (n = 1408) ^h	1.7	66.7
Propylene glycol ^c	1.7	47.1
Benzoyl peroxide (n = 1524) ^e	1.6	87.5
Glyceryl thioglycolate ^c	1.4	31.0
Oleamidopropyl dimethylamine (n = 1571) ^e	1.4	72.7
Ethyl acrylate ^c	1.3	70.4
Methyl methacrylate ^c	1.3	70.4
Glutaraldehyde ^c	1.1	52.2
Tosylamide/formaldehyde resin ^c	1.1	81.8
Compositae mix (n = 1831) ^h	1.0	72.2
Mixed dialkylthiureas ^c	1.0	71.4

^aThe remaining top allergens not listed are the allergens and/or mixes, excluding thimerosal, ethylenediamine dihydrochloride, and quinoline mix, present in the TRUE Test™ panels. n = 2088 except where indicated after the specific allergen.

^bNorth American Contact Dermatitis Group (NACDG) standard series, 2007–2010; aim tested prior to 2007.

^cNACDG standard series, 1995–2010.

^dNACDG standard series, 1996–2004; aim tested prior to 1996 and from 2005 to 2010.

^eAim tested only, 1995–2010; never in NACDG standard series.

^fNACDG standard series, 1995–2006; aim tested, 2007 to present.

^gNACDG standard series, 1998–2010; not previously tested prior to 1998.

^hNACDG standard series, 2001 to present; aim tested prior to 2001.

Had only the NACDG standard 65-allergen series from 2005 to 2006 been tested (Table 4), 43.0% of our patient population would have had all of their potential allergic reactions detected, 43.9% would have been partially

Table 4. Positive allergic reactions to North American Contact Dermatitis Group (NACDG) 2005–2006 standard series allergens and their clinical relevance

	Positive to NACDG standard allergens 2005–2006 and additional allergens	Positive to NACDG standard allergens 2005–2006 only	Negative to NACDG standard allergens 2005–2006 and positive to additional allergens
Positive allergic reactions (%)	608 (43.9)	595 (43.0)	182 (13.1)
Clinically relevant allergic reactions (%)	485 (40.2)	544 (45.1)	177 (14.7)

evaluated, and 13.1% would not have been aware of any of their allergens. When relevance was used, these percentages did not materially change. The percentage of patients fully evaluated with only the NACDG standard series did not markedly differ from the percentage of patients fully evaluated with only our top 50 allergens and/or mixes (45.1%). Not surprisingly, our top allergens and/or mixes standard panel fully evaluated more patients than did the NACDG standard series alone.

Discussion

Patch testing is the standard method for detecting allergens responsible for eliciting allergic contact dermatitis (2, 3). The current FDA-approved standard for diagnosing allergic contact dermatitis in the United States is the TRUE Test™, which consists of three panels containing 20 individual allergens and eight allergen mixes. Although any standard series will be limited, in that it is not tailored to a patient's possible exposures (11), our results show that the current TRUE Test™ allergens and/or mixes correctly diagnosed < 30% of the patients in this study. However, when put into the perspective that there are over 3700 allergens identified in the literature (16), the TRUE Test™ system performs well, given its relatively small number of allergens.

A previous study had raised concern regarding the adequacy of the initial two-panel TRUE Test™ for full evaluation of patients with possible allergic contact dermatitis. In their study of 898 patients, Saripalli et al. (10) found that only 28% of patients with clinically relevant reactions would have been given a complete diagnosis had the 23 allergens and/or mixes present in the initial TRUE Test™ been used. In addition, 47% of patients would have been only partially evaluated, and 25% of patients would not have had any of their potential

allergens identified (9). The addition of the third panel to the TRUE Test™ has not enhanced the efficacy of the test.

In our study, only 28.5% of patients with clinically relevant reactions would have been fully evaluated had only the TRUE Test™ allergens and/or mixes been tested, 25.6% of patients would not have had any of their clinically relevant allergens detected, and 45.9% of patients would have been aware of only a partial list of their potential allergens. Even after expansion of the initial TRUE Test™ to include a third panel, the test still failed to give a complete and correct diagnosis in the majority of patients. However, it must be noted that it is difficult to gauge exactly how well any given standard series performs, as the results will be affected by the number of non-standard allergens tested. In a multicentre European study assessing the efficacy of the European baseline series in diagnosing allergic contact dermatitis, the percentage of patients reacting to only the baseline allergens ranged from 37% to 73% (12). This phenomenon was clearly observed in our study as well. As shown in Table 3, the percentage of positive patch test reactions to those allergens that were 'aim tested' are almost certainly higher than would have been observed had they been tested with the baseline series, as reflected by the overall high relevance of the 'aim tested' allergens.

Several authors have stated that larger standard series more accurately identify clinically relevant allergens in patients with suspected allergic contact dermatitis (9–11). If we had used a standard panel of the top 50 allergens and/or mixes detected in the current study, the percentage of patients who had positive relevant reactions would have dramatically increased. However, even using a panel of our 50 top allergens, as shown in Table 3, we would have failed to fully diagnose the majority of our patients (Table 2). Cohen et al. (9) studied 794 patients, and found that if only the 65 allergens and/or mixes present in the NACDG standard series had been tested, 34.2% of patients would have had at least one allergen missed during the course of their disease. Our study showed that 54.9% of patients with clinically relevant reactions would have had one or more allergens missed if only the NACDG standard series had been used.

Although larger standard series increase the sensitivity of the patch test, the use of any standard series alone may be inadequate for accurate evaluation, as no standard series can accurately include allergens encountered in the environments of all individual patients (17). Wetter et al. (18) showed the importance of patch testing with supplemental allergens. In their study of 945 patients, use of only the three-panel TRUE Test™ series would have missed 22.5% of patients with preservative allergy,

11.3% with fragrance/plant allergy, and 17.3% with vehicle allergy. Militello et al. (19) studied 183 patients, and found that the TRUE Test™ series would have missed 22.2%, 25% and 33.3% of patients with suspected hand, facial and periorbital dermatitis, respectively. A detailed history of occupational, personal, medicinal and environmental exposures allows the physician to determine which supplemental patch test allergens should be added to the standard series (13). With access to various allergens and knowledge of which allergens are being tested, physicians should be able to properly diagnose and treat allergic contact dermatitis (13, 17). Avoidance of the offending chemicals and products should relieve the symptoms associated with allergic contact dermatitis (20), and will improve prognosis in many patients (4–7, 11, 20). In general, each patient's patch tests should include allergens commonly used in personal care and work

products, in addition to allergens that commonly cause reactions.

Conclusion

The available, FDA-approved, 28-allergen TRUE Test™ panels are not effective in fully diagnosing relevant allergic contact dermatitis. In many regions of the United States, some insurance providers restrict patch testing to ≤ 30 allergens per patient (17). This restricts physicians to testing with an extremely limited number of allergens. The results are damage and harm to the patient (10, 20). Patch testing is the gold standard for diagnosing individuals with allergic contact dermatitis, and arbitrarily limiting the number of allergens that are allowed to be tested is contrary to the delivery of proper and cost-effective medical care.

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