

Review Article

Evidence-based diagnosis in patch testing

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Evidence-based medicine (EBM) is defined as the integration of the best research evidence with clinical expertise and patient values. Based on the principles of EBM, we can conclude that patch testing is cost-effective only if patients are selected on the basis of a clear-cut clinical suspicion of contact allergy and only if patients are tested with chemicals relevant to the problem (high pretest probability). Random patch testing (low pretest probability) should be discouraged. Proper pretest probability assessment can only be done in expert centres, because problem-based testing requires both a thorough knowledge of the patch-test procedure and knowledge about potential sensitizers in a specific environment.

Key words: evidence-based medicine; patch testing; pretest probability; post-test probability.

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Evidence-Based Diagnosis

Evidence-based medicine (EBM) was introduced in clinical practice to fulfil the daily need for valid, up-to-date information. The EBM approach has, however, been the subject of discussion since its introduction. In the 1980s, the evidence-based approach was founded on the best available research data coming from randomized, controlled trials. The conflict between the results of studies and the individual case became, however, apparent. Nowadays, EBM is defined as the integration of the best research evidence with clinical expertise and patient values. The best evidence, as coming from well-designed studies, should be matched with the individual case (1).

Evidence-based medicine can (and should) not only be applied to therapeutic intervention but also to diagnostic procedures. Evidence-based medicine can help us assess the validity, accuracy and potential harm of a diagnostic procedure in relation to its costs. Evidence-based medicine applied to diagnosis and screening can be referred to as evidence-based diagnosis (EBD).

Patch Testing

Patch testing is a bioassay to investigate contact sensitization. It is a relatively cheap and safe procedure to determine a causal link between sensitization to a specific agent and allergic contact

dermatitis. It has, however, several pitfalls (2). Although patch testing is the gold standard in diagnosing contact allergy, a positive reaction as read by international guidelines cannot automatically be assumed as proof of sensitization (2, 3). In patch-test clinics, agents are often tested in standard and screening series. Sensitization not suspected by history and/or clinical examination can be detected in this way. Requirements to include a chemical in a standard series have been formulated by Bruze et al. (3). In addition, ready-to-use materials relevant to the specific leisure activities and working conditions can also be selected for patch testing.

In series, chemicals are tested in well-defined concentrations in order to reduce the chance of false-positive and false-negative reactions. However, in series, many substances are tested simultaneously, which may, because of multiple testing, give rise either to false-positives or to reactions not relevant to the specific situation. If only a small panel of chemicals are tested, selected on the basis of history of exposure, relevant allergies may be missed.

In this paper, we discuss the validity of a patch test in the context of the principles of EBD in relation to the patch-testing procedure. We will demonstrate the differences in post-patch-test probability if an agent is tested either randomly (standard series) or selectively chosen (problem based).

We also discuss the considerations relevant to the decision to test in a specific patient. Based on the application of EBD, we propose a problem-oriented, individualized approach carried out in centres with dermatological and occupational (environmental) expertise. This approach must guarantee a safe and cost-effective policy of patch testing.

According to Sackett et al., we have to answer 3 questions about patch testing if we apply EBD (1):

- (1) What is the validity of the patch-test procedure?
- (2) What is the importance (accuracy) of the patch-test procedure?
- (3) Can I apply the test in this specific situation?

What is the validity of the patch-test procedure? Is patch testing the gold standard?

Validity is the ability of a test to detect or measure the aimed biological phenomenon (1). In the case of patch testing, does a patch test predict contact sensitization (type IV hypersensitivity) or another biological phenomenon like contact irritancy? It is more than 100 years since Jadassohn carried out the first epicutaneous tests, and the method of patch testing is still the first choice in diagnosing contact allergy (4). A patch test is a bioassay where contact with a relevant allergen under controlled conditions is supposed to reproduce a delayed type of hypersensitivity. However, patch testing is influenced by many variables and, although substances are tested under controlled conditions, the allergic nature of the patch-test reaction cannot be assumed beyond all doubt. For most allergens, however, positive patch-test reactions, if performed and read according to international guidelines, are predictive for contact sensitization (5, 6). The validity of patch testing may, therefore, be considered as good for many chemicals, if tested under controlled conditions and in the proper concentration, but may be considered as poor for substances which are tested at a concentration eliciting an irritant reaction or with substances with unknown skin irritant potential.

What is the importance of the patch-test procedure? Does patch testing discriminate?

Under ideal conditions, a diagnostic test predicts with 100% certainty the presence or absence of a disease. Most tests, including patch tests, are, however, not capable of predicting the truth beyond any doubt. The ability of a valid test to distinguish between patients who have a disease or not (the importance or accuracy of the test) is dependent on the sensitivity and specificity of the diagnostic procedure and the prevalence of the disease. Sensitivity is defined as the proportion of the people with the target disorder with a positive test and specificity as the proportion of people without the target disorder with a negative test. In the case of patch testing, sensitivity indicates the number of sensitized patients with a positive test and specificity the number of patients not sensitized to an allergen with a negative test for the specific allergen. Data on the sensitivity and specificity of positive patch-test results are scarce. Nethercott reported that sensitivity and specificity of patch testing approximate to 70% (7). Although the concepts of sensitivity and specificity are needed to determine the accuracy, they are in themselves not very useful. The clinician is more interested in the odds that a person has the disease or not, and to what extent a diagnostic test can help estimate the probability of disease after testing. For that purpose, we have to delineate the concepts of likelihood ratio, pre-test and post-test odds and pretest and post-test probability (Table 1).

Without any additional information, pretest probability equals the prevalence of a disorder. If more information becomes available from history taking, clinical investigations and diagnostic tests, then the probability of having or not having a disease may come close to 100%. Post-test probability is calculated from the post-test odds [post-test odds/(post-test odds + 1)], and post-test odds is defined as the pretest odds multiplied by the likelihood ratio of a test. To calculate the post-test odds, we need the well-known concepts

Table 1. Concepts of likelihood ratio, pretest and post-test odds and pretest and post-test probability

Diagnostic test result (patch test)	Target disorder (allergic contact dermatitis)		Totals
	Present	Absent	
Positive	<i>a</i>	<i>b</i>	<i>a + b</i>
Negative	<i>c</i>	<i>d</i>	<i>c + d</i>
Totals	<i>a + c</i>	<i>b + d</i>	<i>a + b + c + d</i>

Sensitivity = $a/(a + c) = 0.7$; specificity = $d/(b + d) = 0.7$; positive likelihood ratio (LR+) = sensitivity/(1 - specificity) = $0.7/(1 - 0.7) = 2.33$; negative likelihood ratio (LR-) = (1 - sensitivity)/specificity = $(1 - 0.7)/0.7 = 0.43$ (all according to Nethercott (7)); positive predictive value = $a/(a + b)$; negative predictive value = $d/(c + d)$; prevalence = $(a + c)/(a + b + c + d)$; pretest odds = prevalence/(1 - prevalence); post-test odds = pretest odds $\times$ likelihood ratio; post-test probability = post-test odds/(post-test odds + 1).

of sensitivity and specificity. The positive likelihood ratio is defined as: sensitivity/(1 – specificity). It is, in fact, the ratio of the chance of a positive test result in a person with the disease versus the chance of a positive test result in a person without the disease (a ‘good’ test has a high likelihood ratio). If, for the purpose of clarification, we follow the estimate of sensitivity and specificity of patch testing of Nethercott in general, this ratio will be $0.7/(1 - 0.7) = 2.33$.

Thus, the post-test odds is the ratio between the probability that contact allergy is present after a positive patch test versus the probability that allergy is absent. The post-test probability is the probability that contact allergy is present after a positive patch test. We will show how disappointing the post-patch-test probability is with the presumed sensitivity and specificity, as estimated by Nethercott.

Pre-patch-test probability of contact allergy. The prevalence of contact sensitivity to allergens is difficult to determine. In the general population, it is not known because hardly any epidemiological data are available (8). In subgroups of patients with dermatitis, the prevalence can be estimated using clinical and scientific data (9–12). The prevalence of contact sensitization will, however, vary significantly, depending on the specific characteristics of the subgroup.

In order to estimate the value of patch testing, we can assess pretest odds and probability and post-test odds and probability, in patients with or without clinical suspicion of contact dermatitis.

In the first situation, we can use the prevalence data obtained by patch testing with the European standard series. These data, although overestimating prevalence by patient selection, come closest to the prevalence of contact allergy in the general population. In this situation, patch testing is performed in a patient population without any specific suspicion of contact allergy (routine testing). For our calculations, we used the patch-test results of the patients who visited our department of occupational dermatology from 1995 to 2000 for patch testing (Table 2). In the second situation, we have, based on clinical and epidemiological grounds, a clinical suspicion of contact allergy. To demonstrate the importance of a test with a particular sensitivity and specificity, we have to estimate pre-patch-test probability. We select a pretest probability of 50% for explanatory reasons. However, any other percentage can be used instead, because this probability depends on the specific additional information in the individual patient.

Post-patch-test probability of contact allergy. Table 3 summarizes the post-patch-test probability data using the likelihood ratio corresponding to a sensitivity of 70% and a specificity of 70%, as estimated by Nethercott (7). These results make clear that post-patch-test probabilities do not justify random testing, as suggested by Bruze et al. (3). In Table 3, the post-patch-test probabilities are also summarized if an allergen is tested in a patient with a clinical suspicion of 50% of having a specific sensitization. Although the probability

Table 2. Percentage of positive patch-test results, European standard series 1995–2000, Nijmegen ($n = 1701$)

1	Potassium dichromate	5.70
2	4-Phenylenediamine-free base	2.87
3	Thiuram mix	2.50
4	Neomycin sulfate	1.38
5	Cobalt chloride	7.06
6	Benzocaine	0.75
7	Nickel sulfate	14.73
8	Quinoline mix	0.48
9	Colophonium	3.52
10	Paraben mix	0.64
11	<i>N</i> -Isopropyl- <i>N</i> -phenyl-4-phenylenediamine	1.01
12	Lanolin alcohol	4.16
13	Myroxylon Pereirae resin (balsam of Peru)	7.38
14	Epoxy resin	0.96
15	Mercapto mix	2.14
16	4- <i>tert</i> -Butyl phenolo formaldehyde resin	2.29
17	Quaternium-15	1.01
18	Primin	0.37
19	Fragrance mix	18.10
20	2-Mercaptobenzothiazole	1.60
21	Sesquiterpene lactone mix	0.85
22	Formaldehyde	2.18
23	Methylchloroisothiazolinone + methylisothiazolinone (Kathon [®] CG)	2.35

Table 3. Post-patch-test probabilities

		Post-patch-test probability (%)	
		If pretest probability equals prevalence in patch-test clinic	If pretest probability equals 50%
1	Potassium dichromate	12.3	70.0
2	4-Phenylenediamine-free base	6.4	70.0
3	Thiuram mix	3.2	70.0
4	Neomycin sulfate	15.0	70.0
5	Cobalt chloride	1.7	70.0
6	Benzocaine	28.7	70.0
8	Quinoline mix	1.1	70.0
9	Colophonium	7.8	70.0
10	Paraben mix	1.58	70.0
11	<i>N</i> -Isopropyl- <i>N</i> -phenyl-4-phenylenediamine	2.3	70.0
12	Lanolin alcohol	9.2	70.0
13	Myroxylon Pereirae resin (balsam of Peru)	15.7	70.0
14	Epoxy resin	2.2	70.0
15	Mercapto mix	4.8	70.0
16	4- <i>tert</i> -Butyl phenol formaldehyde resin	5.2	70.0
17	Quaternium-15	2.3	70.0
18	Primin	0.9	70.0
19	Fragrance mix	34.0	70.0
20	2-Mercaptobenzothiazole	3.6	70.0
21	Sesquiterpene lactone mix	2.0	70.0
22	Formaldehyde	4.9	70.0
23	Methylchloroisothiazolinone + methylisothiazolinone (Kathon [®] CG)	5.3	70.0

does not come close to 100%, the patch test is much more informative in this case, as is summarized in the table. It should, however, be realized that sensitivity and specificity data of patch testing may be allergen specific and may vary with the severity of the patch-test reaction. This means that the importance of the test may be higher in one allergen than in another, and also, higher in ++ and +++ reactions versus + reactions.

Moreover, we can increase the post-test probability if we perform more diagnostic tests (multilevel testing). After each test, the pretest probability for the subsequent test increases. Repeated patch testing or testing with (chemically) related substances may, in this way, increase post-test probabilities (1, 13).

Relevance of a contact allergy. If contact allergy is suspected with reasonable certainty, the next step is to judge the relevance of the sensitization for the patient's dermatitis. It is not possible to provide absolute rules for the determination of relevance. Based on the presence of a putative chemical in materials which come into contact with the skin either occupationally or during leisure activities, the distribution of the skin lesions and the effect of elicitation by exposure and healing of the dermatitis by avoidance, positive patch-test results are judged as possible, probable or certainly relevant. Sensitization may have taken place in the past and may be irrelevant

to the present dermatitis. Recently, we estimated the relevance of positive patch-test reactions in otitis externa as 10% for the current dermatitis (14).

Can I apply the test in this specific situation? Is patch testing cost-effective and safe in this specific patient?

The patch-test procedure must be cost-effective and safe enough to justify application in an individual patient. As we have shown, cost-effectiveness depends heavily on the clinical suspicion of contact allergy. To answer that question, we have to judge the pretest probability. Moreover, we have to estimate the risk of side effects from the procedure (active sensitization, excited skin, severe patch-test reactions and any mutagenic and teratogenic risks). Finally, the procedure must satisfy patient values. The discomfort of the procedure must be accepted by the patient and must be compensated for by the possible advantages, as judged by the patient (1).

Conclusion

Patch testing is safe and cost-effective if patients are selected properly. Random patch testing should be discouraged because randomly performed tests are hardly informative. If positive results from random tests are at hand, these results should only be considered as relevant

after careful history taking and physical examination. If any doubt persists, testing with chemically related substances or repeated testing may be of help (multilevel testing).

A problem-based approach can only be implemented in expert centres, as problem-based testing requires both a thorough knowledge of the patch-test procedure and its pitfalls, and knowledge about potential sensitizers in a specific environment. Only in these centres, staffed by dermatologists experienced in both clinical and diagnostic aspects of contact allergy, can a sufficient likelihood ratio and post-test probability be obtained.

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