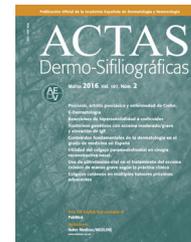




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OPINIO ARTICLE

The Spanish Standard Patch Test Series[☆]



La serie estándar en las pruebas alérgicas de contacto

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At a meeting held in Madrid on 23 and 24 October last, the members of the Spanish Contact Dermatitis and Skin Allergy Research Group (GEIDAC) approved the new composition of the Spanish standard patch test series, which is described in a consensus document published in this issue of ACTAS DERMOSIFILIOGRÁFICAS.¹

For any dermatologist using patch testing, this series is the starting point of the study of patients with dermatitis and is, therefore, considered to be the reference series, not only by us but also by dermatologists in other countries and allergists specializing in contact dermatitis.

What is a Standard Series?

A clinical history and physical examination of the patient provide clues about possible sensitizations and should guide the choice of patch tests. Unfortunately, it is rarely sufficient to test only suspected allergens because skin conditions are often found to be due to an unexpected allergen. An experienced dermatologist will sometimes be able to correctly predict the contact allergens involved in some cases based only on the history and clinical features of the lesion, but they will not be correct in all cases. The guess is more

likely to be correct when the patient is allergic to one of the more common allergens—such as nickel or isothiazolinones (50%–80%)—and much less likely to be correct in the case of less common allergens (< 10%).²

Since it is impossible to correctly identify the causative allergen without testing, whenever contact dermatitis is suspected the patient should be patch tested using a baseline or standard series. The standard series should ideally include all of the allergens that frequently cause reactions in the specific geographical area, the allergens found frequently in the patients' everyday environment, and some that are found less frequently but are of particular clinical relevance.³ In a study carried out by the European Environmental and Contact Dermatitis Research Group (EECDRG), the standard series alone detected from 37% to 73% of all the allergies diagnosed depending on the center where testing was carried out. In that study, the differences between centers were attributed to variations in the composition of the standard series and methodologies used and differences in the criteria used to select patients for testing.⁴ In the experience of the present authors, the standard series diagnoses about two-thirds of the patients who undergo skin allergy testing, and this proportion increases when products used by the patient are tested in addition to the standard series.

From the history of our specialty we learn that the dermatologists now considered the fathers of patch testing—Josef Jadassohn and, particularly, Bruno Bloch⁵—first developed the idea of testing patients using a predefined series of contact allergens (the ones they considered to be most important) in a standardized way, using the same procedure and the same preparations and concentrations for all

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patients. The method they developed is still used today. In recent years, there has been a growing interest among specialists in systematizing or standardizing the methodological aspects of epicutaneous testing as well. The new guideline for diagnostic patch testing published recently by the European Society of Contact Dermatitis (ESCD)⁶ is an invaluable guide for anyone who wishes to learn how to perform these tests reliably.

There is still some debate among experts about what a standard series should be. One proposal, made by many authors, is that it should only include a small number of molecules and serve as an initial study, which can then be expanded depending on the needs of each case. Other authors, particularly those of the north American school, defend the concept of an extensive battery of 65 or more haptens, a comprehensive baseline series that would cast a broad net and detect more sensitivities of potential clinical relevance; the results of some studies support this position.^{7,8} However, most European experts disagree with this concept and argue that a tool that screens for such a broad range of allergens—specially if the selection is not guided by the particularities of the case—would only serve to increase the cost of testing without offering a better guarantee of finding the cause of the condition. Moreover, the application of a larger number of allergens can often lead to unexpected positive reactions that are difficult to explain and may be totally unrelated to the patient's condition, and these reactions could pose more of a problem than a solution in the process of establishing a diagnosis.^{3,4}

Nevertheless, there is unanimous agreement that the precise composition of the standard series is less important than taking all the necessary information into account, thinking the case through logically, and work with the sincere desire to resolve the patient's problem while avoiding overdiagnosis of allergies that will not lead to clinical improvement of the lesions. For the clinical dermatologist, the key is not the number of patches we use but rather the ability to marshal all the information on the clinical course and features of the lesion, the past history, the results of physical examination and patch testing, and to reach the diagnosis that most reasonably explains the patient's condition. And this diagnosis may, at times, involve setting aside the sensitivities detected by tests because the physician considers them to be secondary or not relevant to the case. This brings us to the simple concept of the *current relevance* of the results of patch tests: an allergic sensitization is relevant if it explains the patient's current condition, the condition that was the reason for performing the test. If the sensitization does not explain the condition, then the allergy is not relevant.⁹

Indications for Epicutaneous Patch Testing

Patch testing should be performed in all cases of eczematous dermatitis when a contact allergy is suspected, irrespective of the site of the lesion or the age of the patient. Occasionally, noneczematous dermatitis—characterized by lesions similar to those of erythema multiforme, lichen planus, or psoriasis, or taking the form of granulomatous or lymphomatoid reactions—can be clinical presentations of a contact

allergy. Lesions with sharp borders outlining a specific shape suggestive of an area of contact are particularly indicative of a contact allergy. Another indicative feature is improvement of the condition when the patient avoids the suspected contact allergen.

Occasionally there is no clinical suspicion of a contact allergy, but patch testing is indicated because the patient presents a dermatitis (seborrheic, atopic, nummular, etc.) that fails to improve or even worsens with appropriate treatment. Patch testing is also indicated in patients with chronic hand eczema (persisting for more than 3 months).

Some skin reactions to drugs are also indications for patch testing when a delayed hypersensitivity reaction is suspected; these include exanthemas, exanthematous pustulosis, fixed drug eruption, drug rash with eosinophilia and systemic symptoms (DRESS), mucosal reactions (stomatitis, conjunctivitis, vulvitis), and, occasionally, the presence of metal implants (prostheses or stents).

Patch testing is contraindicated in the presence of severe active dermatitis and when the condition affects the proposed study area. Its usefulness should be carefully considered in patients receiving treatment with immunosuppressants, principally corticosteroids at a dose equivalent to 20 mg or more of prednisone daily. However, immunosuppressive treatment is a relative contraindication because performing patch testing during such treatment may sometimes be the only option; nevertheless, in such cases the results should always be interpreted with caution. Recent exposure of the test area (the back) to UV radiation is also a contraindication because of the risk of false negatives. Although there is no evidence that patch testing during pregnancy or breastfeeding is harmful, most experts prefer to postpone the testing as a precaution.⁶

Various methods are used to apply and occlude the allergens. Usually, test substances are applied by way of paper strips and a hypoallergenic acrylic-based adhesive. Each strip is loaded with 5 or 10 aluminium or plastic chambers containing the different allergens dispersed in petrolatum or water.¹⁰ Another option is the TRUE-test (Thin-layer Rapid Use Epicutaneous Patch Test, Smartpractice, USA), a pre-packaged product containing allergens homogeneously dispersed in a cellulose- or povidone-based hydrophilic gel.

The advantage of TRUE-test is that it saves time and prevents errors in the preparation of the test solutions. The disadvantage is that the allergens included do not completely cover the standard Spanish series. In the absence of any evidence supporting one system over the other, the choice should be based on the personal criteria and experience of each dermatologist.

What Should a Standard Series Contain?

The standard series should represent a common denominator, that is, a minimum set of allergens necessary for testing any patient suspected of having contact dermatitis. Ideally, it should be complete but manageable, allowing a reasonable certainty of exposing the patient's skin to the main set of haptens present in the usual environment of most individuals, without involving a disproportionate expenditure of time, effort, or resources.

Based on this philosophy—which is neither minimalist nor comprehensive—and for practical reasons, a baseline series should contain around 30 allergens.

The following criteria are taken into account in the selection of the allergens to be included in the standard series:

1. The frequency and relevance of the allergen in the environment: the hapten should cause a positive reaction in at least 0.5% to 1% of patients tested if it is to be included in the standard series.³ While this is an unwritten rule, it is also a good guideline to follow when trying to identify the haptens often encountered in clinical practice and those that are uncommon. Paraphenylenediamine, for example, causes positive reactions in 4% to 5% of patients tested and the reactions are usually relevant, making it an essential element in the standard series.
2. Diagnostic significance: the frequency of a positive reaction is not always the factor with most weight in the decision to include an allergen in the standard series. Certain rare allergens play a very important role in the series because of their clinical importance or because they do not usually give rise to clinical suspicion and are, therefore, only detected through testing. These include, for example, epoxy resins and corticosteroids.
3. Tradition: allergens that were very prevalent in the past and often continue to be ubiquitous in the environment are included even though the conditions of exposure may have changed and reactions have become more uncommon. This is the case of parabens, methylidibromoglutaronitrile, and certain rubber additives.
4. Need for epidemiological surveillance: this criteria relates to emerging allergens, such as new perfumes, and also to cases in which circumstances cause a resurgence in reactions to an older allergen because of variations in the frequency or manner of exposure. This is the case of formaldehyde.

We should note that some emerging allergens are systematically studied and patch tested by GEIDAC for years before their inclusion in the standard series is considered (candidate allergens). This was the case with methylisothiazolinone.

The standard series changes and is subject to continuous assessment and occasional modification. In this respect it reflects life itself, and the changes will depend on variations in the prevalence of regional and individual sensitization. Some dermatologists complement the standard series with a small set of allergens of local importance.

Clinical Suspicion: the Key to the Diagnosis of Contact Dermatitis

Despite their simplicity, patch tests are reliable diagnostic tests, which, when performed correctly, can clearly show whether or not the patient is sensitized to a particular allergen. Nevertheless, the fact that a patient is sensitized to a particular allergen does not necessarily imply that their skin condition is completely or exclusively the result of that allergy. The task of the clinician is to assess the relative importance of the test results, and we should always remember that patch tests are just that—tests—and that

to establish a diagnosis the results must be correlated with all the other clinical information. In patients suspected of having contact dermatitis, the clinical course and medical history can often carry as much or more weight than positive test results; the art of the good detective lies in being able to interpret the clues correctly.

The following are three common misconceptions of physicians when they first use patch tests.

1. “Positive patch test reactions always explain the patient’s skin disorder.” This is not the case, and it is unusual that the allergy detected is the only factor responsible for the problem (current or demonstrable relevance). A lack of improvement after avoidance measures have been taken often indicates that there is more than one cause.
2. “If the patch test results are negative, the origin of the condition is not allergic.” By rapid deduction the clinician also comes to the conclusion that the patient has an irritant dermatitis. This is a double fallacy. Negative patch test results only allow us to affirm that the patient is not sensitized to the allergens to which he or she has been exposed. The patient could be allergic to other substances or the tests performed may have yielded false negatives, and we should continue to investigate the possibility of an allergic condition. Irritant dermatitis is not automatically the default diagnosis in the case of negative patch test results.
3. “Once allergic contact dermatitis has been diagnosed, most patients are cured.” Often the patient is not cured. We frequently encounter a contact allergy that is relevant to the patient’s condition but plays an exacerbating or triggering role in conjunction with another endogenous or exogenous condition. For example, it is not unusual to see a recalcitrant, adult-onset atopic dermatitis in association with sensitization to a certain component in a moisturizer or topical drug.

When no contact allergen has been identified after a careful clinical assessment, the most likely result is that patch testing will yield negative results. However, in such cases patch testing can be useful because of its negative predictive value, which can calm the patient’s anxiety about the possibility of allergic sensitization, or reestablish the patient’s loss of confidence and increase their adherence to treatment in chronic cases in which it may seem that the condition is never going to respond to treatment.

Negative patch test results can open the door to a wide range of diagnostic possibilities, and the dermatologist is the health professional in the best position to deal with the situation. This is the strongest argument in favor of our authority in the field of contact dermatitis: the dermatologist is the specialist best placed to assess the patient’s condition because very often the final diagnosis does not involve an allergy.

What Does Patch Testing Offer the Dermatologist

Even when the results are negative, patch testing offers many advantages. In the case of suspected contact

dermatitis, the testing process gives the dermatologist time to focus on the patient, ask questions, and reexamine the lesions; it allows the clinician to review the case, broaden their diagnostic horizons, and make decisions with greater confidence.

Cases of patients with a complicated and severe dermatitis who have negative or inconclusive results on patch testing are not uncommon in the subspecialty of contact dermatitis. In this difficult situation, despite appearances, the dermatologist is in a better position than any other physician to provide the patient with the best care: and the very methods used to perform the test ensure that the patient and physician spend valuable time together during scheduled visits, which enhances the patient-doctor relationship and the diagnostic process. In the course of this time spent together, they cement their relationship, they explore the factors that aggravate and alleviate the lesions, the patient can be helped to express fear or negative thoughts, and the dermatologist has the opportunity to examine the lesion on several occasions and see how it evolves over time.

In the experience of the present authors, this opportunity to reassess the case completely, with greater care and attention, is the aspect of patch testing that can offer the greatest advantage to the dermatologist.

Being mentally prepared and willing to engage with a case, no matter how difficult it may appear, are essential elements of successful health care; they are also characteristics typical of the good clinical dermatologist, the clinician who will not rest until the case is resolved.

As dermatologists, we are the leading specialists in the study of patients with dermatitis. The present authors, representing GEIDAC, encourage all of you to use this new standard series, an update on the last revision done in 2012.¹¹ We also reaffirm our dedication to increasing the body of knowledge in this exciting field and to sharing this knowledge with the wider community of dermatologists.

Patch testing is an art and allow us to suggest that the physicians who specialize in contact dermatitis are artists. We can learn a great deal from the masters, who we

acknowledge and remember in this article. And, as in any art, in addition to talent 3 other key elements are needed: technique, tools, and experience. The standard series is one of these tools; the other elements must be acquired with dedication, enthusiasm, and constancy.

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