

Practical Advice to Correctly Perform Patch Test

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Abstract

Purpose of review Allergic contact dermatitis corresponds to an inflammatory reaction caused by contact with an external agent. It is a reaction mediated by a type IV hypersensitivity mechanism or delayed, and requires prior sensitization of the individual. Patch testing is the gold standard method for the diagnosis of allergic contact dermatitis. It is the in vivo proof of the effect caused by contact with the allergen, and evokes on a small scale the elicitation phase of a delayed hypersensitivity reaction. The patch test is not a complex procedure; however, its success depends on different factors that include an appropriate assessment of the patient considering the different sources of exposure to possible allergens, the correct technique of placement of the patches, and the necessary knowledge to properly interpret the results and determine their relevance. The objective of this review is to provide a series of general recommendations to adequately perform this test, and so the results are reliable and allow proper management of the patient.

Recent findings Although used for more than 120 years, the patch test procedure is performed with variability around the world. Although the procedure is broadly similar to the original method, it is not uncommon to observe differences in the results reported by the different observers. This may be influenced, among other factors, for differences in the methodology used by the physician who perform it.

Summary There are numerous potential points for error that the physician must keep in mind. Although during the last decades great efforts have been devoted to the optimization and standardization of the materials and the methodology, physicians' knowledge and experience are fundamental for the reliability of the results and the benefits from this test.

Introduction

Allergic contact dermatitis is a frequent pathology and represents a common reason for consultation in dermatological practice. Predicting correctly the allergens that cause this pathology exclusively by history and clinical exploration can be complex, being more likely for frequent allergens such as nickel (50–80%) and less likely for rare allergens (< 10%) [1, 2]. An erroneous diagnosis, and therefore an inappropriate management of the pathology, leads to a torpid and often incapacitating evolution both in work activities and in daily life, which negatively affects the quality of life of the patient and

increases health expenditures. On the other hand, there is a generalized tendency in the population to attribute an allergic cause to various dermatoses produced by a different physiopathological mechanism, which can lead to adopting unnecessary restrictive measures. For this reason, it is necessary to make an appropriate study of this pathology, for which the parch test is indispensable. In this article, we summarize the most relevant characteristics of this test, emphasizing practical aspects that facilitate the execution and interpretation of the physician who performs them.

Pathogenesis

Allergic contact dermatitis is caused by small molecules of low molecular weight, known as haptens. These molecules have to penetrate the skin to bind proteins forming hapten-protein complexes, which are responsible for triggering the immune response. In the development of this reaction, we can identify two phases. The first phase, or sensitization phase, comprises the period from when the first contact with the sensitizing substance occurs until the subject acquires immunological memory, that is, it is sensitized. Its duration varies between 10 and 14 days to even weeks after exposure and usually evolves asymptotically. In this phase, the hapten-protein complexes induce an inflammatory response initially mediated by innate immunity with the release by the keratinocyte of $\text{TNF-}\alpha$, $\text{IL-1-}\beta$, $\text{IL-1-}\alpha$, IL-8 , IL-18 , and granulocyte-macrophage colony stimulating factor. This reaction activates the antigen-presenting cells, including the Langerhans cells in the epidermis and the dermal dendritic cells that process the “hapten-protein” to express it on its surface through the major histocompatibility complex molecules. Subsequently, they migrate to the paracortical zone of the regional lymph nodes, where they present the antigenic peptides to naive T lymphocytes (LT) specific for the antigen. This interaction produces a series of modifications with the activation and proliferation of the naive LT, which results in a large number of LT effectors, mainly of the Th1 class, and memory LT. However, a differentiation of Th2 class, Th17, and T regulators also occurs. Days later, clones of these lymphocytes leave the lymph node through the bloodstream to circulate in different tissues and secondary lymphoid organs until a new encounter with the sensitizing agent. The second phase, or elicitation phase, comprises the period from the re-exposure to the hapten to the inflammatory reaction and is the part of the immune response that reproduces the parch test. It occurs at 24–48 h after the new contact and unlike the previous phase, presents a clear clinical expression. After the hapten diffuses through the skin, it induces the production of proinflammatory cytokines that cause the first signal for the recruitment of LT CLA +, which correspond to a subpopulation of epidermotropic memory LT, and other specific LTs from the blood to the skin. CD8 + LTs comprise most of these cells and are mainly responsible for cellular

damage with the appearance of erythema, edema, vesiculation, and itching limited to the area of contact. Importantly, this ability to develop an immune response to certain haptens differs according to individual susceptibility, while some people may develop an allergy at the first exposure or subsequent exposures, others may maintain a continuous exposure without sensitization. The reason for this difference still remains unknown.

Clinical features

Allergic contact dermatitis (ACD) presents with erythema, edema, vesicles, oozing, and pruritus. In cases of long evolution, hyperkeratosis, lichenification, and cutaneous dryness can be observed. The lesions are not usually well defined and predominate in the contact area (Fig. 1), although they can be widely extended to other areas. Even, sometimes contact dermatitis can be generalized. The pathogenic mechanism by which it occurs still remains unclear. Exposure to high doses of allergens, dissemination through blood vessels, or generalized activation of immune effector cells has been suggested as potential explanations. In addition, contact dermatitis can occur atypically, with non-eczematous lesions [3] that correspond to:

- The erythema multiforme-like form, in which the lesions become edematous, forming well-defined, pruritic urticarial plaques with satellite lesions. It has been described in relation to epoxy resins, topical corticosteroids, metals such as cobalt and IPPD, among others.



Fig. 1. **a** and **b** Acute ACD to hair dye, extending to the cheeks and neck. The PPD patch test was positive. **c** Chronic ACD of the hands C in a patient who worked in construction. The chromium patch test was positive. **d** Erythema, vesicles, and crusting over the area of a temporary henna tattoo on a 7-year-old girl. The PPD patch test was positive.

- Lichen planus-like and lichenoid contact reactions. It is most frequently seen in the oral mucosa. The main allergens that produce this type of reactions are gold, nickel [4], mercury, palladium, cobalt, and acrylate, present in materials for dental use [5].
- The lymphomatoid form. This variant cannot be defined as a clinical distinctive entity [6]; it is based only on histopathologic criteria that they are superimposable with mycosis fungoides [7] but with less atypia. In addition, very few cases of allergen-induced B cell cutaneous lymphoid hyperplasias have been described. They have been reported in relation with gold [8, 9], zinc [10], and IPPD [11].
- Other: ACD type dyshidrotic or pompholyx (nickel), pigmented purpura (textile dyes, anti-inflammatory non-steroidal topical drugs, etc.), pustular reactions (fragrances, black rubber, topical nitrofurazone, isoconazole nitrate) [12], granulomatous reactions (nickel, palladium, mercury, chromium) [13], scleroderma-like lesions (due to organic solvents), and resembling a Sweet's syndrome (p-phenylenediamine) [14].

Variants of allergic contact dermatitis

In addition to the classic ACD form, other less frequent variants can be differentiated.

Systemic contact dermatitis

Systemic contact dermatitis is a generalized inflammatory disease that appears in individuals sensitized by contact to an allergen, when this allergen is exposed by non-cutaneous route (ingestion, parenteral, suppository, implanted, and inhaled). Dermatitis can manifest as oral, anogenital, flexural, fixed, reactivation of a previous positive patch test site or flare of previous dermatitis, vasculitic lesions, vesicular hand dermatitis, or a widespread dermatitis [15, 16]. There is a wide variety of metals capable of causing it (nickel, mercury, cobalt, copper, gold). It has also been described with plants, medications (including antibiotics, corticosteroids, antifungals, and antiepileptics), and other compounds such as the balsam of Peru.

Airborne contact dermatitis

Sometimes the substances that cause contact dermatitis are in the air in the form of vapors, drops, or solid particles that are deposited on the skin and, in some cases, also produce respiratory disorders such as asthma and rhinitis or ophthalmologists such as conjunctivitis. It mainly affects the face, the arms, and the back of the hands, and the fact of affecting the areas not exposed to the photo (such as the auricular folds or the submental area) serves to distinguish it from photo-induced eczema.

Photoallergic contact dermatitis

It is a type of ACD caused by the contact of a photosensitizing substance and subsequent exposure to light radiation. The most commonly

responsible agents are topical non-steroidal anti-inflammatories and chemical photoprotectants.

Indication for patch testing

Patch testing should be considered in all patients with a clinical history suggestive of ACD. Some common indications include eczemas located in areas highly suggestive of ACD, such as hands, feet and eyelids, as well as unilateral presentations; patients with high risk of occupational dermatitis, for example hairdressers, cosmetologists, and health care workers; and important dermatitis eczematosa that does not improve or worsens with the treatment. Also, the performance of this test should be considered under conditions that may represent a ACD such erythema multiforme-like lesions, lymphomatoid or granulomatous reactions, some lichenoid lesions on oral mucosae and although not discussed in this article, could also be indicated to investigate certain reactions to drugs that result from a mechanism of delayed hypersensitivity such as the maculopapular rash and the fixed eruption to medications.

Testing procedure

Materials

To perform this test, in addition to allergens, it is necessary to have panels with application cameras, markers, hypoallergenic adhesive tape, reading maps, and a refrigerator for the storage of allergens.

Application chambers

Application chambers correspond to the device where the substances to be tested are placed. They are designed to avoid sensitization due to their composition. They exist in aluminum or plastic (e.g., polyethylene or polypropylene). They are also found in different shapes, circular and square (Fig. 2a). The latter, according to the supplier, have been designed to facilitate the differentiation between an allergic and irritative reaction. The T.R.U.E test® corresponds to a special system in which allergens are incorporated in standardized doses. While it has the advantage of faster test execution, it has the disadvantage of being available only for some allergens and does not fully cover the standard series of some countries. There is no evidence to show that one test system is better than another. However, depending on the antigen tested, the T.R.U.E. test® has shown a concordance (62 to 63%) with the individual charging system in the cameras (ex. Finn chamber system®) [17•]. Therefore, sometimes there are discrepancies in the results depending on the system, which is why specific training in this technique is necessary. Table 1 summarizes the characteristics of some of the most commonly used allergen application systems.

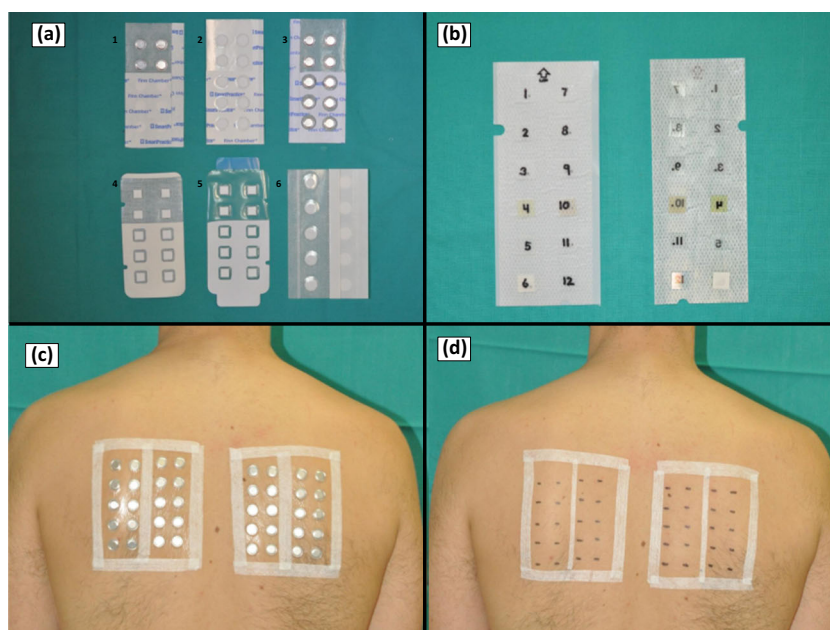


Fig. 2. **a** Examples of chambers: (1) Finn chambers on Scanpor, (2) Finn chambers open, (3) Finn chambers aqua, (4) AllerGEAZE, (5) AllerGEAZE Clear, (6) Curastet F. **b** (1) Order of the cameras when loading. (2) After placing the cameras, the order is reversed. **c** Generally, the back is the site of choice for placement of the patches. The area of the spine should be avoided because of the increased risk of detachment. **d** After removing the patches, it is advisable to mark the place where the cameras were attached.

Commercial allergens

More than 4000 allergens have been identified [18]; however, only a limited number of them are commercialized. There are several companies that supply them (e.g., AllergEAZE®, Chemotechnique Diagnostics®, SmartPractice®). Different allergen batteries are also available depending on professions or specific activities. The concentrations and vehicles used in its formulation have been tested to optimize the results of the test, avoiding irritative reactions or absence of response. The most commonly used vehicle is petrolatum, since it is economical, rarely sensitizing, and allows adequate preservation of the allergen. In cases of hydrophilic substances, other vehicles such as water, acetone, or alcohol should be used. The concentration differs according to the characteristics, especially irritative, of the allergen. The different compounds are stored in labeled syringes where the name, concentration, vehicle, and expiration date are indicated. They should remain protected from light and in a refrigerator at a temperature of 4 °C. It has been recommended that potentially unstable allergens, such as isocyanates and acrylates, be stored in the freezer at – 18 °C (– 0.4 °F) to slow degradation [19••, 20]. These allergens will also typically require more frequent renewal.

Indications to the patient

To avoid problems of interpretation or reading, the patient should be given some indications before and during the test. Prior to the application of the patches:

Table 1. Main application chambers and their characteristics

Finn Chambers® (SmartPractice, Finland)	<i>On Scanpor</i>: Circular chambers of 8-mm diameter composed of aluminum (also available 12 and 18 mm). It provides an area of 50 mm². It requires a volume of 20 µL of the allergen. Does not incorporate the filter paper for liquids. Available in panels of 10 chambers on an adhesive tape based on acrylate. Incompatible with aqueous solutions of mercury. It is not resistant to water. <i>On Scanpor open</i>: Unlike the previous chamber, it is perforated to allow allergens to be applied without first releasing the patch. <i>AQUA</i>: Unlike the previous camera, it incorporates the filter paper which allows the direct application of liquid allergens. It is also resistant to water/sweat by allowing the shower. Available in panels of 10 cameras mounted on flexible polyurethane.
IQ® (Chemotechnique Diagnostics, Canada)	<i>Ultra</i>: Square chambers composed of polyethylene foam. Internal area of 64 mm². Volume of 32 µL. The filter paper is incorporated. They are mounted in series of 10 cameras on a hypoallergenic adhesive tape. The cameras are covered by a rigid plastic sheet with 10 compartments to protect the allergens in case of pre-filling. It is not resistant to water. <i>Ultimate</i>: It differs from the previous chamber where it is resistant to water.
AllerGEAZE® (SmartPractice, Canada)	Square chambers of 8 × 8 mm² of polyethylene terephthalate. Internal area of 64 mm². Maximum volume of 40 µL but requires 20 µL of allergen. The filter paper is incorporated. Available in panels of 10 cameras mounted on non-woven polyester. It is not resistant to water. <i>Clear</i>: It differs from the previous camera by the water/sweat resistance so it allows the shower. Available in panels of 10 cameras mounted on polyurethane coated on one side with acrylic adhesive. Perforated chamber.
Van der Bend® (Van der Bend B. V, Netherlands)	Square chambers 8 × 8 mm ² composed of polypropylene. Internal area of 64 mm ² . Maximum volume 40 µL. Whatman filter paper fixed in each chamber. Available in panels with 10 cameras. It is not resistant to water.
Haye's Test® (HAL Allergenen Lab.B.V, Netherlands)	Square cameras 8 × 8 mm ² composed of non-woven polyester. Internal area of 64 mm ² and volume of 40 µL. Whatman filter paper fixed in each chamber. They are mounted on panels of 10 cameras on a tape of acrylic adhesive.
Curatest F® (Lohmann-Rauscher, Germany)	Round filter paper chambers on a non-woven polypropylene strip adhesive tape and hypoallergenic polyacrylate adhesive. They are mounted on panels of 10 cameras labeled laterally to facilitate identification of the allergen. It is not resistant to water. It has the disadvantage that the allergens migrate and the results of the reactions are not localized.
T.R.U.E Test® (SmartPractice, USA)	Allergen incorporated into a thin layer of the hydrophilic gel printed in turn in a polyester patch which is incorporated along with other allergens in cellulose strips with acrylic adhesive. It includes 35 substances plus a control distributed in 3 panels. Inconvenient of being available only for some allergens.

- Avoid the administration of oral corticosteroids at least in the previous 3 weeks.
- Do not apply corticosteroids or topical calcineurin inhibitors in the area of application of the patches in the previous 7 days.
- Avoid sun exposure the previous 2 weeks, due to its anti-inflammatory effect that can reduce the ability to respond.
- Although there are no current recommendations for patients who are pregnant or breastfeeding, it is prudent not to do epicutaneous tests at that time.

- Antihistamines and disodium cromoglycate do not need to be suspended, as they do not interfere with this test.

After the application of the patches:

- The application area of the patches should remain dry, so the patient cannot take a shower until the end of the test. However, there are some patches that allow the shower to be waterproof.
- Avoid exercise or physical efforts that cause sweating.
- If the patch starts to come off, it should be reinforced with hypoallergenic tape.

Selection of allergens

The selection of allergens depends on the patient's clinic. The history and physical examination provide clues about potential sensitizers and should guide the choice of epicutaneous tests to be performed in their study. Unfortunately, it is seldom enough to just patch the suspected allergens, since often unsuspected allergens turn out to be the cause. An experienced doctor will be able to correctly predict the allergens involved in the allergy only in some cases, being most likely for common allergens. For this reason, all patients with suspected allergic contact dermatitis should be studied with a baseline series. Recommendably, this series should include the most common allergens in the patient's environment, which differs in different geographical areas. At present, there are several work groups that have developed their own standard series according to the data recorded in their units, which has allowed to increase the profitability of this test. It is accepted that the standard battery serves as a screening in 70% of cases of suspected allergic contact dermatitis. However, its true value is unknown. In a third of the cases, especially at the professional level, it is necessary to carry out complementary series. In the market, there is a wide variety of batteries that allow the study of possible ACD for the compounds that trigger them most frequently.

Dosage and loading of allergens

For an adequate interpretation of the test, it is necessary that the allergen dose per skin area is correct. There may be small variations depending on the chamber used, but as a general concept the allergen should completely cover the chamber without spreading out of it. In the case of liquid allergens, remember to place filter paper if necessary and, to avoid differences in the amounts charged, it is preferable to use pipettes for its application. Ideally, allergens should be loaded into the chambers at the time of application of the patches. However, if they are incorporated in petrolatum, they can be prepared 24–48 h before application. It is different in the case of liquid or volatile allergens, for which an early preparation can lead to the evaporation or alteration of the product modifying its characteristics. It must be taken into account that when placing the patches, the order of the chambers will be reversed, so we must load the first antigen in the first row on the right (Fig. 2b).

Anatomical place of application

The site of choice is the upper part of the back that provides a large, comfortable surface and can easily be protected from environmental exposure. In addition, it

is the site where the concentrations of commercialized allergens have been determined. They should be applied leaving the central area of the back free, since if they adhere on the spine, they often break off (Fig. 2c). In the event that the back is insufficient, or that for other reasons it is not possible to apply the patches in this area, the anterior part of the forearms or the lateral sides of the arms are other suitable sites.

Placement and removal of patches

The skin where the patches will be applied should be dry, clean, and free of hair. The patches should be applied by pressing evenly to ensure good adhesion. They can be reinforced with hypoallergenic adhesive tape adhered to the margins or covering the total surface. At the time of removal, it is advisable to mark with a marker next to each camera and on the edges where the panels were attached, in order to facilitate later reading (Fig. 2d). Always remember to give the pertinent indications to the patient.

Reading times

After 48 h of contact with the skin, the patches should be removed. A time of 15–30 min should be allowed before beginning the reading, to avoid confusion due to the erythema that causes the occlusion or detachment of the patches. Ideally, three readings should be made, which may vary fundamentally for health organization reasons or for the sensitizer studied. Table 2 summarizes the possible times of readings. In most cases, two readings are performed, the first at 48 h, minutes after removing the patches, and a second at 96 h, a third reading being necessary around the seventh day in case of suspicion of some sensitizers that most often cause delayed reactions, such as metals (nickel sulfate, gold sodium thiosulfate, palladium chloride, potassium dichromate, cobalt chloride), paraphenylenediamine (PPD), topical corticosteroids, and neomycin. It has been reported that if a delayed reading is not taken in some, these allergens 7–30% of positive reactions will be missed [21–23].

Reading

The International Contact Dermatitis Research Group has established patch test reading criteria based on morphology [24] (Table 3) which have been adopted by multiple working groups. Usually, the positive reaction is maintained for a period of up to 2 weeks. An exceptional positive response is the so-called ring effect, in which the positive reaction manifests from the edges of the patch. It is usually seen in sensitizers with liquid vehicles due to the displacement of the solution towards the edge of the patch, although it has also been described in association with the study of allergy to topical corticosteroids due to its anti-inflammatory effect on the exposed skin.

It is essential, after 3 or 7 days, to differentiate an allergic reaction from an irritative reaction. There is no characteristic in itself that can distinguish them; however, there are some particularities that can guide one or another etiology (Table 4). Less frequent irritative manifestations include purpuric reactions caused by metallic salts, such as cobalt chloride, and pustular reactions with

Table 2. Reading times of the patch test

	48 h	72–96 h	7th day (5th–10th day)	Commentary
Optimum	1st reading	2nd reading	3rd reading	• It allows to observe the evolution of the reactions, facilitating the differentiation between an allergic and irritative response. • It is the one that greater number of reactions detects.
Valid alternative		1st reading	2nd reading	• It can be especially useful if a sensitizer is studied with a predisposition to late reactions. • The ability to verify the adherence of the patches at 48 h and other minor reactions is lost.
Acceptable	1st reading	2nd reading		• Optimizes the time, when performing the detachment of patches and 1st reading in the same visit. • Part of late reactions may be lost.
Not recommended routine		1st reading		• In special circumstances in which only 1 visit is available, the patient or relatives remove the patches at 48 h and at 96 h it is read by the attending physician.

metals such as chromium, cobalt, and nickel. Finally, it is important to remember that, although in most cases a negative result excludes a contact dermatitis, in case of a high suspicion of sensitization, the possibility of a false negative result should be considered. Figure 3 summarizes the different causes according to the result of a patch test.

Interpretation and relevance

A positive patch test indicates only sensitization to an allergen, but not necessarily that the allergen is the cause of the pathology being investigated. This is why, to determine if this result is related to the clinic presented by the patient, we must analyze what is its relevance, which is defined by:

- History of exposure to the sensitizer with positive patch test
- Clinical presentation that correlates anatomically with the area of contact with the allergen
- Improvement with avoidance and recourse with re-exposure

The relevance can be current if it is related to the present history of the patient, and is therefore the cause of the disease, or passed when the positivity is not related to the current clinic but history can find history of such reaction. Therefore, the diagnosis of an allergic contact dermatitis requires that the

Table 3. Scoring of patch test reactions according to International Contact Dermatitis Research Group recommendations

Symbol	Morphology	Interpretation
–	No reaction	Negative
?/+	Erythema only, no infiltration	Doubtful reaction
+	Erythema, infiltration, possibly discrete papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction
+++	Erythema, infiltration, papules, confluent vesicles	Extreme positive reaction
IR	Different types of reactions (soap effect, vesicles, blister, necrosis)	Irritant reaction

positive patch test be clinically relevant to the dermatitis experienced by the patient. On the other hand, when faced with a positive result, we do not find a relationship—because of the absence of exposure or anatomical discordance with dermatosis—we say that the relevance is unknown. At present, it is preferable not to use the term “without clinical relevance,” since there are multiple reasons why the relevance may not be detected.

Once the patch testing procedure is completed and the allergens are identified and relevance has been established, the education is critical. We must explain to the patient the need to avoid possible sources of exposure to the allergen, also providing handouts with synonyms and common uses is often helpful [25•, 26–29].

Variations of the patch test

If no plausible result is achieved using a conventional patch test despite suspected contact allergy, modifications of the patch test can be considered.

ROAT

Repeated open application test (ROAT) corresponds to the standardized variant of the use test, where it is tried to reproduce the usual situation of application of a formulated product, mainly cosmetics, personal hygiene products with and without rinsing or topical medicines. Applications should be maintained until the reaction occurs with a maximum of 2 to 4 weeks. There is a specific scale for reading your results [30].

Table 4. Differences between an irritative and allergic reaction

Irritating reaction	Allergic reaction
Limited to the patch	Exceeds the patch
Early onset, before 48 h	Late appearance, at 48–96 h and even at 7 days
Erythema, without infiltration, blister	Eczematous lesions, infiltration, pruritus, Koebner's phenomenon
Rapid disappearance, negative at 96 h	The reaction is maintained for days

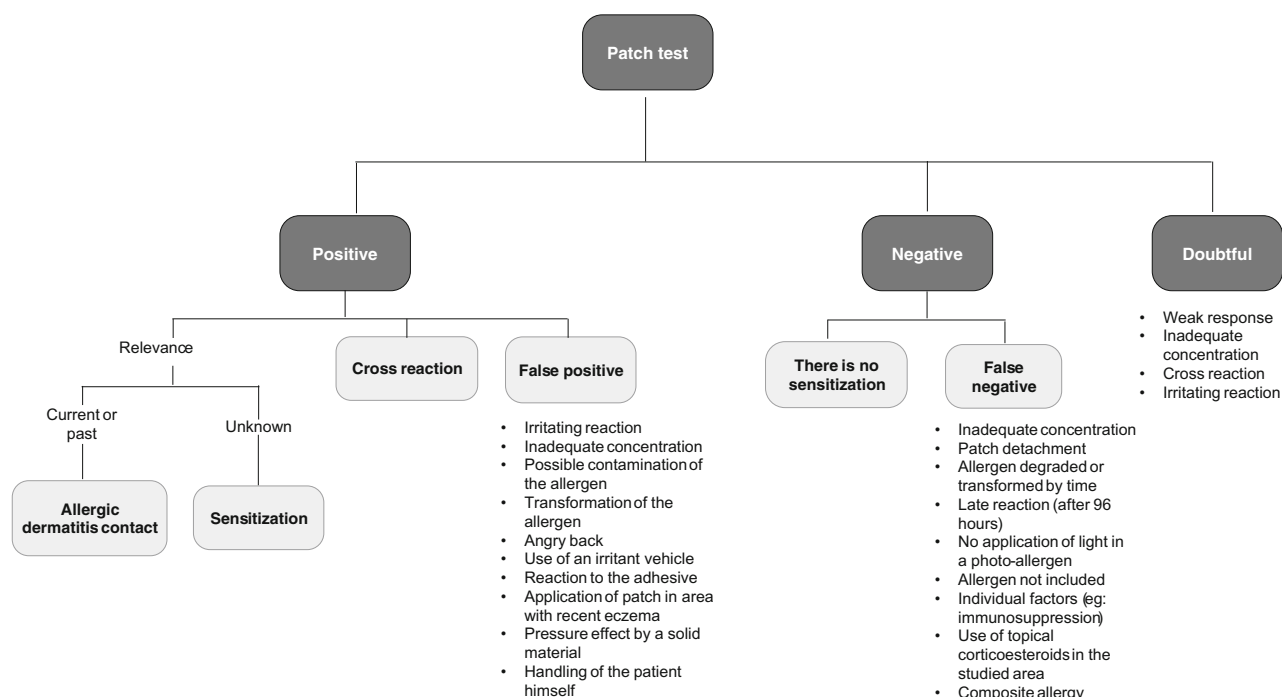


Fig. 3. Possible results of the patch test.

Semi-open or semi-occlusive test

It is a variant where the tested product is not left under occlusion, but is covered with a hypoallergenic and permeable adhesive tape. It is mainly indicated in the study of potentially irritant products, which would increase under occlusion, such as some products provided by the patient, including detergents, shampoos, soap, antiseptics, industrial products, etc. An approximate amount of 15 ml of the product, usually diluted, is applied over an area of 1 × 1 cm and allowed to dry. It is usually applied on the ventral side of the forearm, upper back, or outer face of the arm. The first reading is done at 20–30 min to rule out a contact urticaria. Subsequently, it is covered with a permeable adhesive tape. For reading, the same times and criteria are used as in the conventional patch test.

Open test

In this test, the product is applied directly to the skin, without covering or occluding. It is recommended in cases of suspected immediate reactions (contact urticaria).

Considerations of some selected allergens

- 1.- *Nickel sulfate*: Most patients will have a history of eczema in the contact area similar to that of any other allergen. However, in patients with a very high sensitization level, contact eczema can appear systemically if there is

parenteral or digestive exposure [31]. The possible forms of presentation of these eczemas are symmetrical eczemas in flexures of limbs, inner side of thighs, perineum, axillae, lateral neck, and eyelids; dyshidrotic eczema on palms, soles, and fingers of the hands or feet; phenomenon recall, which is the reappearance of lesions where contact eczema has previously been presented by nickel or at the site where the patch test, was positive. In addition, as in other tests with metal salts, care must be taken with possible false positives. They usually present as follicular center pustules and are particularly frequent in patients with atopic dermatitis.

- 2.- *Neomycin sulfate*: Neomycin is an antibiotic widely used topically in various creams or ointments. It is the aminoglycoside with the greatest potential for contact sensitization, and may present cross-reactivity with other antibiotics in this group [32], such as tobramycin and gentamicin (the most commonly used topically, apart from neomycin). It is possible that oral neomycin or parenteral administration of other aminoglycosides may trigger a systemic contact dermatitis, although the actual frequency of these reactions in patients with a neomycin-positive patch is unknown. Clinical suspicion is not easy since it is not usually an acute eczema, but rather it is a worsening or no improvement of a preexisting dermatitis. It should also be taken into account that it is often marketed in association with topical corticosteroids, so that the anti-inflammatory effect of the latter could mask the allergy to neomycin.
- 3.- *Chromium and its salts*: They are the salts of chromium (chromates) and not the pure metallic chromium, those that trigger the contact allergy. That is why some compounds containing chromium will not cause problems for the patient. Sensitization to chromium is more frequent in men and is usually in most cases of professional origin. The most frequent sources of exposure are construction materials (wet cement causes up to 90%, bricks, concrete, etc.) [33] and leather products tanned with chrome (shoes, gloves, belts, etc.). However, there are multiple other sources of exposure. Like other metals, it can be ingested in food, but there is a discrepancy in the literature about the possibility of triggering systemic reactions or aggravating existing ones [34, 35]. Also, although the chromium of the prosthesis usually causes little sensitization, it should be avoided in already sensitized patients.
- 4.- *Mix of cains*: It usually contains three anesthetics for topical use. Two of them belong to the group of para-aminobenzoic acid (PABA) esters: tetracaine (amethocaine) and benzocaine. The third belongs to the amide group: cincoína (dibucaína). It is generally accepted that there is no cross-reactivity between the local anesthetics of the ester group and those of the amide group. Although the drugs included in the caine mixture are not usually used as an injectable local anesthetic, the possibility of cross-reactions with other molecules of the ester group must be taken into account. Although they are available, they are currently used very little, such as procaine (local anesthetic) and procainamide (antiarrhythmic). In addition, other possible cross-reactions with other PABA derivatives (paraphenylenediamine dye, sulfonamides, and some sunscreens) should be considered.

- 5.- *Fragrance mix*: Fragrances are a group of chemical substances present in multiple cosmetic products, for domestic use, industrial, topical medicines, and even foods so they are difficult to avoid. The components of this mixture can vary depending on the selected products (e.g., TRUE test contains eight components that may differ from those included in a certain standard series). When a positivity is found in the fragrance mixture, it is recommended to patch a specific series of fragrances to try to determine which fragrances are responsible for the positivity.
- 6.- *Colophony*: It is an oleoresin obtained from the trees of the family pinaceae (pine). Colophony is a very ubiquitous substance and has been described in more than 300 sources of exposure. More than 50% of the rosin produced in the world is used in the manufacture of glues, adhesives, and printing inks. Glue and adhesives have multiple uses including medical devices (tape, bandages), footwear, and other multiple applications in the industrial field. There are chemically modified forms of colophony (hydrogenated, esterified, etc.) which are relatively new potent allergens and which are not detected by the unmodified colophony tests [36–39]. When allergy to a modified form of colophony resin is suspected, it is recommended to apply the suspect product and the modified resins if the manufacturer collaborates with the study by providing the allergen or informing of the composition.
- 7.- *Epoxy resin*: The epoxy systems are glues that are used in a wide variety of activities. They are composed of epoxy resin, diluents, and hardeners. Epoxy resin is responsible for sensitization to epoxy systems in approximately 80% of cases and hardeners in 20%. Epoxy systems are used in many professional activities and their use outside these is rare, except in diy or home repairs. Once the glue is dry, it does not give allergic problems. It can only produce reactions in wet or viscous state. Clinically, it usually affects the back of the fingers of the hands, being frequent also the airborne distribution. Also written are lichenoid lesions and others reminiscent of erythema multiforme (erythema multiforme-like). The resin that most often is patched is bisphenol A (DGEBA); however, there are specific resins/epoxy systems that should be used when clinical suspicion is high.
- 8.- *Methylchloroisothiazolinone and methylisothiazolinone*: Methylchloroisothiazolinone and methylisothiazolinone are chemical compounds designed as preservatives or biocides. Its essential function is the prevention of contamination of a product (especially liquids) by infectious agents, especially bacteria and fungi. Methylisothiazolinone can be present alone or as part of the mixture known as Kathon-CG. The introduction of methylisothiazolinone in cosmetic products in 2005, as well as the excessive concentrations of it in cleaning products, originated an authentic epidemic of allergic contact dermatitis by these biocides. [40, 41]. However, in Europe, the concentration of methylchloroisothiazolinone and methylisothiazolinone in personal care products has decreased due to the current legislation that prohibits its presence in those products that are applied directly on the skin.
- 9.- *Balsam of Peru*: It corresponds to an aromatic resin extracted from the trunk of a Central and South American tree (*Myroxylon pereirae*). It is a

fragrance and a flavoring agent widely used in perfumes, cosmetics, and food. It is also found in medicines for its mild bactericidal action and in various dental products. In our environment, the ACD per balsam of Peru is most characteristic in patients with ulcers of the lower extremities in which scar dressings are applied (Linitul®). The balsam of Peru is usually interpreted as a marker of allergy to fragrances, so before a test of the positive patch to this allergen, it is advisable to complete the study with a battery of fragrances.

- 10.- *Cobalt chloride*: Cobalt is a ubiquitous and powerful allergen sensitizer. The most frequent source of exposure is the nickel-plated metal objects of daily use, which almost always contain cobalt that brightens the coating. Cobalt sensitization is often concomitant with nickel allergy. It is important to know that an object may contain cobalt but not release it on contact with the skin, so it will not produce allergic contact dermatitis clinic. Leather is also a source of exposure that has gained importance in recent years.
- 11.- *N-isopropyl-n-phenyl-p-phenylenediamine (IPPD)*: It is a substance that is added to the gum to reduce its deterioration. As it is frequent that it produces changes of coloration in the gums, usually they are only incorporated to the black- or dark-colored gums. Although it usually manifests as a dermatitis in the contact area, other clinical forms have been seen as lichenoid lesions or erythema multiforme-like [42]. The development of purpuric lesions within the so-called PPPP syndrome, characterized by pruritus, petechiae, purpura, and IPPD sensitization [43, 44], should be highlighted as a distinctive manifestation. There is cross-reactivity with PPD. The majority of patients with IPPD positivity are positive for p-phenylenediamine, but not the other way around.
- 12.- *Formaldehyde*: Formaldehyde is a colorless, flammable, and strong-smelling chemical that is used to make various materials. It is considered a ubiquitous substance, being possible to detect it in a wide variety of sources such as cosmetics, personal hygiene products such as domestic, topical medicines, clothing, footwear, etc. Sometimes some products do not contain formaldehyde but some substances called "formaldehyde releasers." These substances can undergo chemical reactions that, over time, lead to the formation of small concentrations of formaldehyde (the main ones are quaternium-15, diazolidinyl urea, DMDM hydantoin, imidazolidinyl urea, 2-bromo-2-nitropropane-1, 3-diol). Therefore, patients allergic to formaldehyde also need to be educated about formaldehyde releasers.
- 13.- *Parafenilendiamida (PPD)*: It is used primarily as a component of industrial compounds and polymers. It is also a common ingredient of hair dyes and sometimes it is used as an additive for henna. Most sensitization to PPD is produced by contact with hair dyes, both in hairdressing professionals and in users [45]. Henna tattoos are another remarkable source of sensitization [46], and this is probably due to the high concentration present in the mixture and the prolonged contact with the skin.

- 14.- *Corticosteroids*: Among the most used is budesonide and tixocortol pivalate, both belonging to group I in the corticosteroids (CS) classification. There are corticosteroid batteries that include CS of the three chemical groups. It is assumed that the cross-reactions will be more frequent within the CS of the same group; however, budesonide has an isomer that allows it to also detect those allergic to group II [47]. Corticosteroids ACD are rarely suspected because the history and morphology of dermatitis can be modified by the anti-inflammatory effect. Any patient with a long-term dermatitis treated with topical corticosteroids (such as stasis dermatitis, hand eczema) who experiences a poor response or worsening of eczema should be investigated for corticosteroids ACD. Occasionally, eczema may adopt an annular morphology due to the more potent anti-inflammatory effect in the central zone where there would be a greater concentration of the drug [48]. Other reactions reported include reactions erythema multiforme-like, angioedema with exudative eczematous reaction, and generalized rash. It is important to consider that a very high CS concentration can result in a negative test due to the anti-inflammatory effect. Another phenomenon is the "ring effect," which is a positive test reaction just outside the PT site and a negative reaction within the area of the patch chamber. For most allergens, the edge effect is interpreted as a result negative. However, in CS, the test will usually be positive on a later day (day 6 or 7), emphasizing the importance of late readings for CS. The allergic reaction may be suppressed in the first readings and be positive in subsequent readings. Once the anti-inflammatory effect, 30% of contact allergy cases to CS would have been lost if the last readings had not been made.
- 15.- *Quaternium-15*: It is a broad spectrum preservative with a high capacity to eliminate a great variety of microorganisms such as yeasts and bacteria, particularly *Pseudomonas aeruginosa*. It is found in a wide variety of products including cosmetics, soaps, glues, in the metallurgical industry as a component in cutting oil, etc. It belongs to the group of "formaldehyde liberators" and is the one that generates the highest amount of formaldehyde. In North America, it is the liberator most frequently involved in contact dermatitis. However, in Europe, the prevalence is lower and is mainly linked to exposure in the workplace.

Considerations in special situations

Pediatric patients

There is no minimum age for the application of the patch test. The preparation of allergens and the technique is the same as for adults. The only exception is applied in children with a history of contact allergy to henna tattoos; in these cases, the concentration of PPD should be reduced much below that currently used (1%) due to extreme reactions previously observed in these patients [49]. The main problem is the smaller test surface that may be insufficient to apply the full battery. In these cases, you can also apply patches in other areas, such as in the flexor area of the forearms. In the situation that due to the size of the child it is not possible to apply the complete battery, the most likely allergens should be selected according to

age and clinical history, for example, sensitizers found in toys and topical products. Those that have been most frequently detected as causing allergic contact dermatitis in children include nickel, balsam from Peru, fragrance mixture, neomycin, potassium dichromate, cobalt, mixture of thiuranes, lanolin, formaldehyde, formaldehyde releasers, and PPD [50].

Immunosuppressive treatment

In patients who cannot stop immunosuppressant medication, the patch test can be performed in the same way, but taking into account the higher probability of a false negative. The evidence is different between the different immunosuppressants:

Corticosteroids: a lower response to the test has been seen in a patient receiving doses of 20 mg/kg/day or more of prednisone. Other immunosuppressants: their interference is less clear.

However, in the literature, cases of positivity have been reported in patients receiving cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, tacrolimus, infliximab, adalimumab, etanercept, ustekinumab, and secukinumab [51]. It is recommended to perform late readings.

Immunosuppressive diseases

Patients with immunosuppressive diseases may have decreased ability to produce contact sensitization reactions. However, before suspicion is suggested to perform the patch test considering also the higher probability of false negatives. It is recommended to perform late readings.

Atopic dermatitis

In addition to the classic indications of the patch test, patients with refractory atopic dermatitis should undergo this test, because unlike what was previously thought, they can be sensitized as well as non-atopic patients.

Exposure to sunlight

The anti-inflammatory effect of UVB radiation can reduce the ability to elicit response in sensitized people. It has been reported that UVA does not have this effect, but there has been less reaction with UVA plus psoralens.

Adverse effects

Active sensitization

The induction of an allergic reaction is due to the patch test, it is an exceptional complication at the doses of allergens currently used. The exact rate is unknown, but it is felt to be rare and estimated to occur in 0.1% of patients tested [52, 53]. It is characterized by a positive reaction at the site of the patch that appears very late, after 15 to 21 days after the end of the test. Due to the difficulty in differentiating from a delayed response, the verification requires the repetition of the test. If the positive reaction occurs in 24-48 hours, it supports the diagnosis of active sensitization. The most frequently reported active sensitization has been that induced by p-phenylenediamine.

Irritative reactions

The most common adverse effect is irritation by the adhesive tape, although it is usually mild and self-limiting. Irritant reactions due to allergens are minimal using commercialized batteries.

Itching

Pruritus is very frequent due to the occlusion, which reaches its maximum intensity when taking off the patches. Itching is not considered an adverse effect located in a positive reaction since it is part of the normal response of the reaction.

Changes in pigmentation

Occasionally, a postinflammatory hyper/hypopigmentation can be observed in patients who have presented a positive result. They tend to be mild and transient.

Exacerbation of a preexisting eczematous dermatitis

It can be seen in cases of positive reactions in the patch test, which indicates that the allergen itself is responsible for eczematous dermatitis.

Persistent reactions

The reactions that remain for more than 30 days are considered persistent. The mechanism because some patients present this type of reactions is unknown. The most registered allergen is gold, in the form of gold chloride or sodium gold thiosulfate [54, 55]. Other reported causes include phenylephrine, methyl methacrylate, and textile dyes.

Scars

They are rare and can be seen in patients with an abnormal scarring tendency who have presented very intense irritative or allergic reactions.

Angry back syndrome

Clinically, it manifests as true positive reactions that induce false positive reactions due to inflammation and irritability of the adjacent skin. It should be suspected in patients with more than five reactions of close proximity to each other. It is extremely rare that they are all positive; in this case, a possible allergy to the vehicle or material of the test chambers should be considered. Its physiopathological mechanism is unclear. To address it, it is essential to investigate the relevance, in order to differentiate this syndrome from a patient with multiple relevant positive reactions. This reaction is not reproducible within the same patient [56], so it can be checked in a period of 2 to 3 months [57]. For this, it is advisable to carry out the test

sequentially with each allergen separately or simultaneously, but far more than the usual distance between the allergens.

Infections

Isolated after a positive reaction, in the place where the eczematous reaction is located, bacterial superinfection can occur, usually due to *Staphylococcus*. Exceptionally, a herpetic reactivation may occur. The case of a deep fungal infection has been reported after the patch test with a plant [58, 59].

Anaphylaxis

Reactions of anaphylaxis can rarely be triggered by the patch test. They are presented within the first 30 min of application of the test and, although potentially any allergen can produce it, among the most reported is the ammonium persulfate, which is used as a hair decolorizer. However, latex, formaldehyde, penicillin, and others also have been reported [60–63].

Koebnerization

It can be seen at the application site of patches in patients with some underlying dermatosis such as psoriasis or lichen planus.

Compliance with Ethical Standards

Conflict of Interest

Camila Cortés Pinto, Verónica Sanmartín Novell, and Ana María Giménez-Arnau declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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