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Contact Dermatitis (A Giménez-Arnau, Section Editor)

# Usefulness of Cutaneous Provocation Tests to Study Drugs Responsible for Cutaneous Adverse Drug Reactions

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## Abstract

*Purpose of Review* Cutaneous adverse drug reactions, particularly immune-mediated idiosyncratic reactions, are a very challenging area of Dermatology. For confirming the culprit drug, after a complete history of drug exposure with its chronologic relation with the eruption and characterization of the pattern of the drug eruption, skin provocation tests can be performed after resolution of the acute phase.
*Recent Findings* Patch tests are indicated in the study of non-immediate T cell–mediated drug eruptions (maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis, fixed drug eruption, and drug photoallergy). It is recommended to test with pure drugs usually at 10% pet commercialized as patch test allergens, but in most cases, drugs have to be prepared in house, whenever possible in a final dilution at 10% pet. Methods are similar to patch testing in allergic contact dermatitis except in fixed drug eruptions where duplicate tests are needed; one of them applied for 24 h on a residual lesion.
*Summary* Patch tests are safe and highly specific when performed according to the recommendations, but sensitivity is highest in exanthemas, DRESS, and fixed drug eruptions and particularly for abacavir, carbamazepine, aminopenicillins and other antibiotics, diltiazem, and tetrazepam. Allopurinol is never positive, and reactivity is low in SJS/TEN. Therefore, a negative patch test cannot exclude a possible culprit, but a positive patch test is almost always relevant. Patch tests with drugs are also useful for evaluating cross-reactions and studying effector mechanism involved in the cutaneous adverse reaction.

## Introduction

Cutaneous adverse drug reactions (CADR) represent a frequent and very challenging area of Dermatology. Many CADR represent an exaggerated or aberrant pharmacologic activity of the drug, but the most challenging reactions are immune-mediated idiosyncratic drug eruptions. They involve complex hypersensitivity reactions, with immediate reactions mostly dependent on specific IgE (urticaria, angioedema, anaphylaxis), and delayed reactions involving different phenotypes of drug specific effector T cells, often in an interplay with viral infectious and a particular genetic background (specific HLA haplotypes) [1, 2•]. Immune-mediated CADR present under many different clinical patterns, some very typical of a CADR, like toxic epidermal necrolysis (TEN), and fixed drug eruption (FDE); others less specific, like acute urticaria or maculopapular exanthema (MPE); and in some cases, overlapping features can occur [3]. Also, temporal relationship with the drug administration varies with each phenotype of non-immediate CADR.

Maculopapular exanthema (MPE) is the most frequent non-immediate generalized reaction that occurs 1 to 3 weeks after introduction of a new drug, or within 24–48 h if there is re-exposure in a sensitized individual, and it resolves within 1–2 weeks with no systemic symptoms. A maculopapular-like eruption can nevertheless be the very initial presentation of a more severe CADR, like one within the spectrum of exanthematous necrolysis (Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)), or drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS). DRESS, which is associated with potentially fatal systemic symptoms (toxic hepatitis, renal impairment), usually has a longer latency period (3–8 weeks) and tends to last longer (>3 weeks). "Baboon syndrome" or SDRIFE (symmetrical drug-related intertriginous and flexural exanthema), a possible manifestation of systemic contact type dermatitis, and acute generalized exanthematous pustulosis (AGEP) usually develop within 1–3 days after the introduction of a new drug. The more localized FDE usually reactivates within a few hours of drug re-exposure [1, 2•].

Due to its various clinical phenotypes and absence of a specific histopathologic feature, the definite diagnosis of a drug reaction, characterization of its phenotype and prognosis, identification of possible culprits, and confirmation of the offending drug among several culprits can sometimes be very demanding. A crucial step in the initial management of a CADR is the careful evaluation of the possible offending drugs, as an early drug withdrawal can revert an on-going CADR or improve its prognosis [2•, 4]. This is based on a good medical history, selection of drugs introduced within the usual latency period for each pattern of CADR, and identification of those usually associated with such a reaction pattern. Algorithms, like the one from French pharmacovigilance system or the Naranjo score, can be of help, but any drug can induce any type of CADR [2•].

A correct confirmation of causality is of outmost importance to forbid the relevant drug to prevent future adverse reactions, especially in severe CADR, or to advise safe alternative treatments. There is no universal in vivo or in vitro test for confirming a possible culprit, and safety, sensitivity, and specificity of the tests varies widely, and they are not routinely performed.

RAST (radioallergosorbent test) and ImmunoCAP for detecting specific IgE are available only for a reduced number of drug allergens, and their sensitivity can be low and reduces further as the time from the CADR elapses. For T cell–mediated reactions, lymphocyte stimulation tests (LST) or lymphocyte transformation tests (LTT) with proliferation or the ELIspot (enzyme-linked ImmunoSpot) are not fully standardized concerning drug concentrations and vehicles, nor the activation molecules to study (INF-gama, IL-5, granzyme, etc.). Some of these in vitro tests can be still performed during the acute phase of CADR, but false negative results can occur, particularly in DRESS or just following an immediate reaction with consumption of specific IgE [2•].

As in vivo diagnostic methods, oral or cutaneous provocation tests are available, with particular indications and limitations. Oral provocation is considered the gold standard diagnostic test; although, it is not universally reproducible, and it has several limitations. It is better established for immediate hypersensitivity where the reaction (urticaria/angioedema/anaphylaxis) occurs within minutes and can be easily reverted by therapy. Oral provocation protocols and outcomes are not standardized in non-immediate CADR, and oral challenge is absolutely contraindicated in severe CADRs for which effective therapy is not available and where fatality can occur (SJS/TEN, DRESS and, eventually, AGEP). In delayed CADRs, there is no agreement on the protocol for oral rechallenge which varies from one to several drug administrations (up to 7 days), distinct dose schedules with different time intervals between

administrations and period of patient follow-up [5]. This is certainly not feasible when multiple drugs are possible culprits.

Cutaneous drug provocation with skin tests are a good diagnostic alternative; although, it is mandatory to adapt the type of skin test to the pattern of CADR: skin prick tests (SPT) and intracutaneous test (ICT) with immediate readings are indicated for immediate reactions, whereas patch testing (PT) and ICT with delayed readings are indicated for non-immediate CADR. They have the advantage of studying many drugs at the same time but they still have limitations concerning full standardization, available material for testing, specificity, sensitivity, and contraindications, particularly for ICT in severe CADR.

Patch testing, that we will review further, is a safe and specific tool to confirm the culprit if performed according to the guidelines [6, 7••]. Also, PT has been of considerable help in understanding pathomechanisms involved in non-immediate CADR and, in the case of abacavir, they have been crucial to confirm the association between hypersensitivity to this anti-retroviral and HLA-B*57:01 [8].

## History of Patch testing as a Cutaneous Provocation Test in CADR

Patch testing, which is mainly indicated for diagnosing contact allergy and the cause of allergic contact dermatitis (ACD), was actually first used by Joseph Jadasshon in the study of a drug reaction or a systemic contact dermatitis. In 1895, as a continuation of Neisser's studies, Joseph Jadasshon, at the University of Breslau (Germany), induced a local reaction using a patch with the gray mercury ointment in a patient with a generalized eczematous dermatitis after a mercury injection for treating syphilis. This new scientific technique ("Funktionelle Hautprufung"), presented in the Dermatology congress in 1896, is considered as the first patch test with Joseph Jadassohn as the "father" of it [9].

After Felix and Comaich published the value of PT in drug eruptions in the 1970s, severvsal isolated cases or small studies showed that PT can confirm the responsible drug in CADR, mainly with carbamazepine and penicillin. Larger studies in the 1990s and beginning of 2000 [10, 11] motivated the publication of the ESCD (European Society of Contact Dermatitis) guidelines for performing skin tests in drug eruptions [6]. Thereafter, with the availability of commercial test preparations, particularly antibiotics, anticonvulsants, and non-steroidal anti-inflammatory drugs (NSAID), PT has been used with increasing frequency in the study of drug eruptions.

## Rational for Using of Patch Testing in the Study of Non-Immediate CADR

The rationale for using PT is based on the fact that both non-immediate CADR affecting predominantly the skin and ACD from contact sensitizers share pathophysiologic mechanisms and clinical presentations. They are both caused by simple chemicals (haptens) and specific effector T cells of different phenotypes, which infiltrate the dermis and epidermis and cause maculopapular, eczematous, pustular, bullous, lichenoid, lymphomatoid, or granulomatous reactions. Moreover, some drug allergens (e.g., antibiotics) cause both ACD and non-immediate CADR. Individuals who initially develop a MPE or DRESS from

antibiotics can later suffer from occupational ACD from the same chemicals when exposed as healthcare professionals [12]. Also, an individual previously sensitized through the skin may later develop a generalized dermatitis when systemically exposed to the same drug or a cross-reactive chemical, presenting as a generalized MPE or SDRIFE [13]. Like in ACD, patch tests are highly reproducible (>80% for antibiotics), and reactivity persists for many years, as shown for antibiotics and anticonvulsants after more than 10 years [14•, 15].

Positive PT in CADR often reproduces the clinical and histopathologic aspects of the acute eruption, with spongiform pustules in AGEP (Fig. 1) [16, 17], epidermal necrolysis in TEN [18], or FDE (Fig. 2), a lymphomatoid reaction in DRESS or vacuolar degeneration of epidermal basal cells with T cell exocytosis and mononuclear and eosinophil perivascular infiltration in DRESS and MPE (Fig. 3) [19]. Accordingly, mononuclear cells isolated from positive PT in CADR from amoxicillin, carbamazepine, lamotrigine, and other drugs

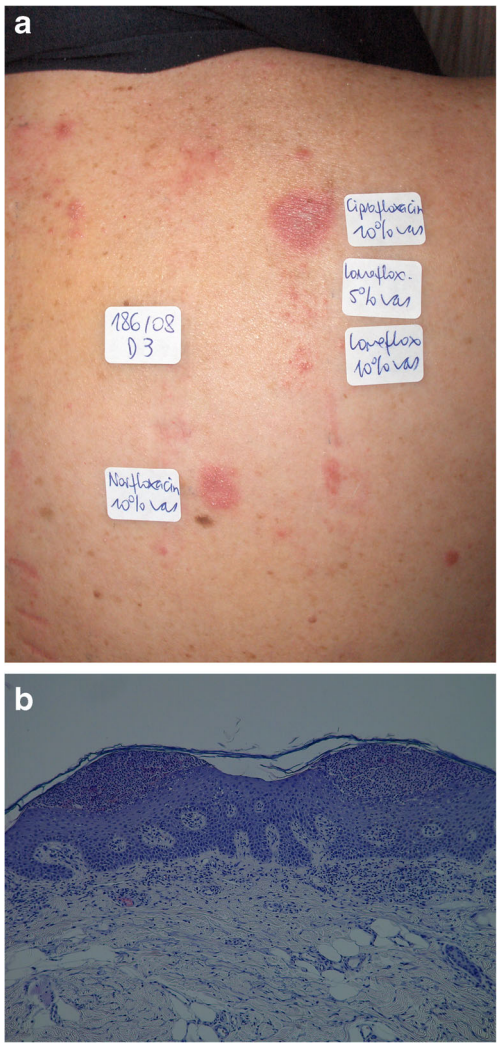


**Fig. 1.** In a case of AGEP from ciprofloxacin, positive patch tests to ciprofloxacin, norfloxacin, and lomefloxacin, with pustules on day 3 (**a**) and histopathology of the patch test showing two spongiform subcorneal pustules (H&E)

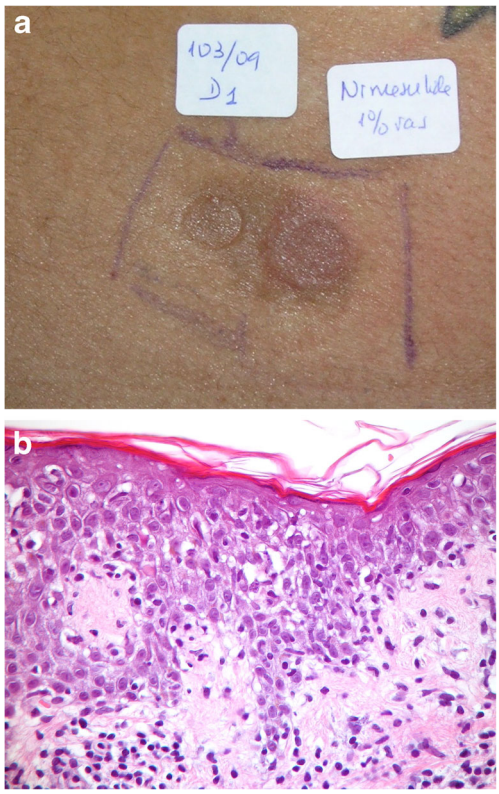


**Fig. 2.** **a** Positive patch test to nimesulide at day 1 in a residual pigmented area in a case of fixed drug eruption, with a negative reaction to diclofenac, an another possible culprit. **b** Histopathology of the patch test (H&E) with vacuolar degeneration of the basal layer, apoptotic keratinocytes, and lymphocyte exocytosis, which also reproduces the histology of the acute reaction

that were cultured in vitro are drug-specific T cells and exhibit phenotypic and functional characteristics similar to those cells that circulate in the blood or infiltrate the skin during the acute CADR [20]. Therefore, PT can also be used to study pathomechanisms involved in CADR, namely, cells and mediators responsible for the effector phase of the reaction.

## When and How to Perform Patch Tests in CADR

PT cannot be performed during the acute phase of the CADR. It is recommended to wait at least 6 weeks after complete resolution of the CADR and perform PT within the next 6–12 months [6, 7]. Nevertheless, positive PT in non-immediate CADR, like in ACD, can be reproduced >10 years later, as shown at least for antibiotics and carbamazepine [14•, 15]. Therefore, PT can be performed after 12 months and be used as a retrospective diagnosis. This is different from immediate reactions where both specific IgE in the serum and SPT tend to fade with time.

PT is usually performed as in the study of ACD, with application of the allergens in patch test chambers on the back for 48 h and reading at day (D) 2 or D3 and D4 to D7, according to ICDRG guidelines. In FDEs, PTs are applied for 24 h on an inactive, residual lesion and, as a control, in duplicate on the

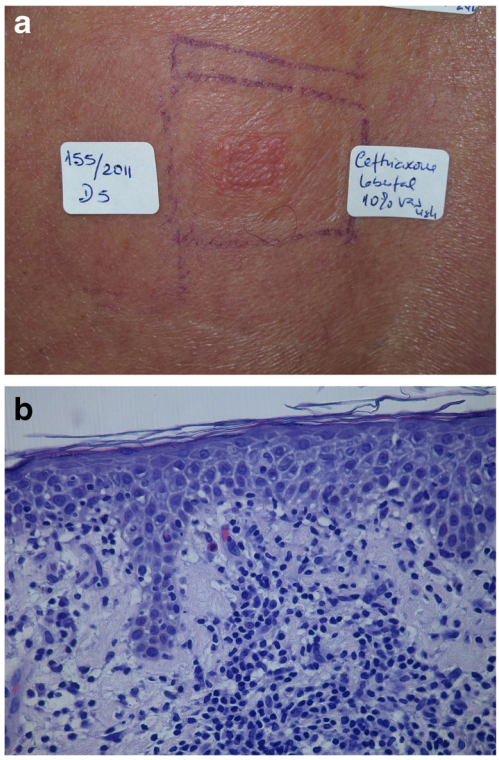


**Fig. 3.** **a** Positive patch test reaction to ceftriaxone at 10% pet manipulated from the powder of the intravenous drug observed at day 3 in a case of maculopapular exanthema. **b** Histopathology of the patch test (H&E) showing a dermal perivascular infiltrate of mononuclear cells and eosinophils, vacuolar degeneration of the basal layer, and lymphocyte exocytosis

normal back skin. Readings are performed at D1 and D2, or at D3 if previously negative [21]. As an alternative, especially in areas where occlusion or application of a patch test chamber is difficult, an open test with the culprit drug can also induce positive reactions [22]. In systemic drug photosensitivity, photopatch tests are recommended, as in photoallergic contact dermatitis, using mainly UVA irradiation at a dose of 5 J/cm$^2$ [23].

There are systemic drugs already prepared at 10% in petrolatum and commercialized as allergens for PT, mainly antimicrobials, anticonvulsants, and nonsteroidal anti-inflammatory drugs (NSAIDs). They have been widely tested in many control and exposed individuals and showed to be safe and specific for diagnostics, but they represent a very limited number of allergens within the extensive list of drugs that can be responsible for non-immediate CADR.

For patch testing other culprits, the drug has to be prepared locally, preferably from the commercial preparation used by the patient, usually by dissolving the powder of the drug in petrolatum and/or in water. Whenever possible, the active drug should be in the final preparation at a concentration of 10% [7••]; therefore, it is preferable to use the powder of drugs for parenteral use where most of the powder corresponds to the active principle. Otherwise, the powder of the capsules or tablets can be used, but in the last option, after diluting the powder in petrolatum, there is a high risk of having very little active drug in the final preparation [24]. Also, the pill can be smashed into a fine powder and just be placed in the test chamber with a drop of water and/or petrolatum [25].

Whenever a patch test is positive with such a preparation, it is recommended to have serial dilutions and test, at least, 10–20 controls, preferably previously exposed individuals.

It is recommended to test always all the possible culprits, including drugs for pain or fever used during surgery or an acute infection, as in the case of metamizol frequently used in in-patients during surgical procedures shown to be responsible for recurrence exanthema in these settings [26]. In DRESS, drugs initiated after the onset of the fever or rash and that are suspected of aggravating the reaction, should also be tested as some individuals become sensitized to antibiotics or other drugs, apart from the main culprit (Fig. 4) [14•]. Also, as positive patch tests can be observed with cross-reactive drugs, it is recommended to test the whole series of related chemicals (e.g., a whole series of antibiotics, of proton-pump inhibitors, etc.). This is important to give possible advice on alternative drugs to be safely used by the patient or to orient oral provocation with drugs that do not react on PT and confirm their safety.

## Patch Testing Safety, Specificity, and Sensitivity in CADR

PT has revealed to be a safe diagnostic test, even in severe CADR like DRESS or TEN [18, 27, 28••]. There are very exceptional reports of immediate reactions when PT is incorrectly used to study anaphylaxis and of reactivation of the CADR, particularly when the patch test concentrations are not respected in severe CADR (e.g., pristinamycin or rifampicin in DRESS) [29]. Active sensitization by PT with drug is very seldom reported, even with penicillins.

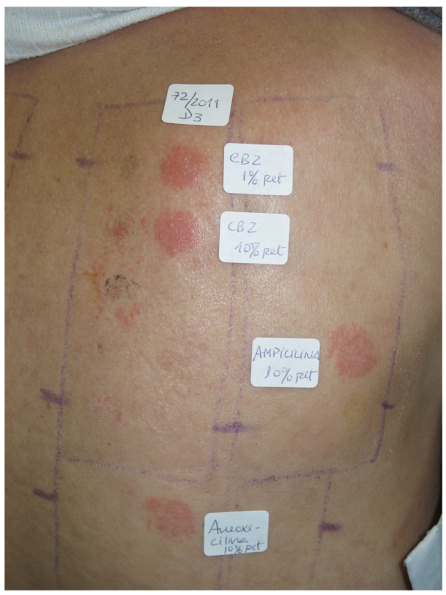


**Fig. 4.** In a case of DRESS induced by carbamazepine and further aggravated by amoxicillin used during the initial phase shows positive patch tests both to carbamazepine tested at 1 and 10% in pet. and amoxicillin at 10% pet. (Chemotechnique Diagnostics®, Vellinge, Sweden)

Patch test safety is superior to the intracutaneous test and oral provocation; therefore, testing in non-immediate drug eruptions should start with a patch test, followed, if necessary, by an intracutaneous test with a delayed reading and oral provocation [6].

No false positive reactions have been found when PT with commercialized drug allergens. Very few false positive/irritant reactions were observed with in-house preparations, namely, with the powder of the pills of spironolactone (Aldactone®), colchicine, captopril (Lopril®), chloroquine (Nivaquine®), celecoxib (Celebrex®) tested at 30% pet, and with omeprazole (Mopral®) tested at 30% aq [24]. Therefore, negative patch test in control patients are needed to validate positive reactions obtained with drugs prepared in-house.

A high reproducibility, isolation of drug-specific T cells from positive PT and clinico-histopathologic resemblance between the PT and the acute eruption, further strengthen patch test specificity. Therefore, if a positive patch test is not apparently relevant for the CADR that motivated PT, it is mandatory to perform a careful review of the patient file and look for hidden uses of the drug or a related chemical within the possible latency period for the reaction or to ask for previous episodes of CADR where the drug may have been involved (past/retrospective relevance).

Sensitivity of drug patch tests in CADR is highly variable and depends on the phenotype of the CADR and particularly on the culprit drug. Some drugs never induce positive patch tests (e.g., allopurinol or its metabolite oxypurinol) whereas others, like carbamazepine (Fig. 4), induce more than 80% of positive PT reactions in different types of CADR [27]. The incapacity to form the culprit drug metabolite when the drug is applied on the skin or the absence, during PT, of the concomitant "danger signals" that were present during the CADR (viral infection and immune activation), are possible explanations for the low patch test sensitivity. Eventually, an insufficient epicutaneous penetration from the patch test (incorrect vehicle or drug concentration) can also be responsible for false negative patch tests; although, intracutaneous tests with delayed readings do not significantly increase sensitivity of skin tests, particularly in the case of penicillins [30].

It is, nevertheless, difficult to ascertain the real sensitivity of PT in CADR, as the considered gold standard (drug rechallenge) has several limitations, and it is not always performed, namely, in severe CADR due to safety concerns. Also, studies show a wide range of drug PT sensitivity depending on the selection of patients (certain or possible drug imputability) and methods used to suspect or further confirm causality.

Apart from carbamazepine, patch tests are very frequently positive in drug eruptions from abacavir (Fig. 5), tetrazepam, diltiazem, and pristinamycin, whereas positive patch tests occur in 20–30% of non-immediate CADR from aminopenicillins (Fig. 6) [30, 31], clindamycin (Fig. 7) [32], or fluorquinolones (Fig. 1), and still less often with other drugs.

Considering only non-immediate immune-mediated reactions sensitivity of the drug PT is highly dependent on the phenotype of the eruption. Positive PT are observed in 1/3 to one half of the patients with MPE, FDE, AGEP, DRESS [28••], and more frequently in systemic contact dermatitis induced by drugs, but percentages of positive PT in other eruptions, like TEN and SJS, are much lower (<10%) [33].

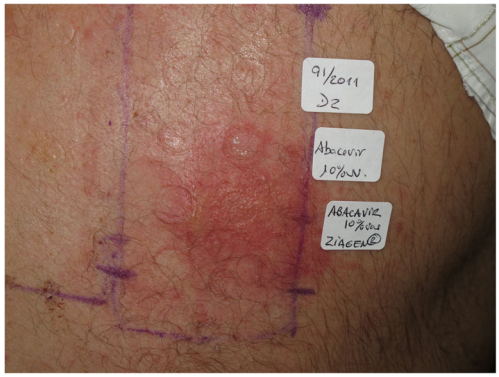


**Fig. 5.** Positive patch test to abacavir in a HLA-B*57:01 patient with HIV infection who developed an hypersensitivity reaction with exanthema, fever, and gastrointestinal symptoms

## Drug Patch Testing in Evaluating Cross-Reactivity

In non-immediate CADRs patch testing can be used to study cross reactivity among drugs, sometimes with very interesting results.

In maculopapular exanthema, amoxicillin and ampicillin always cross-react in PT (Fig. 6) but cross-reactivity is not often extensive to benzylpenicillin or carbapenems neither to cephalosporins [30, 31]. A similar pattern is usually confirmed by oral challenge. There is also frequent cross-reactivity within the group of cephalosporins (Fig. 8), fluorquinolones (Fig. 1), and between pristinamycin and virginiamycin [34].

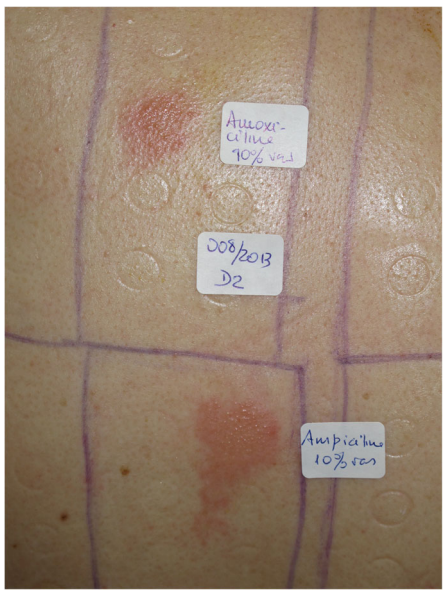


**Fig. 6.** Cross-reactions between amoxicillin and ampicillin 10%pet in a case of maculopapular exanthema from amoxicillin (Chemotechnique Diagnostics®)

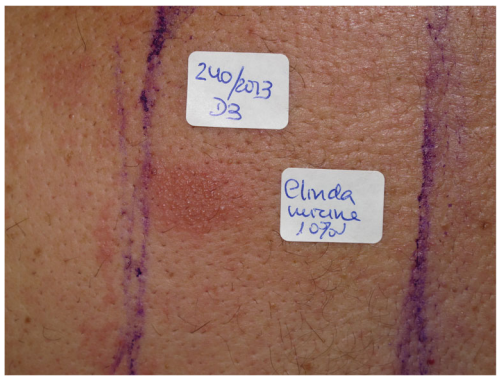


**Fig. 7.** Positive patch test to clindamycin (10% pet) (Chemotechnique Diagnostics®) at day 3 in a case of maculopapular exanthema in a patient treated for severe bacterial skin infection

On the other hand and contrary to occupational ACD from benzodiazepines, in drug eruptions PT and oral provocation confirm the absence of cross-reactions between tetrazepam and diazepam and other benzodiazepines [35, 36].

When patch testing in lesional skin in FDEs, the presence or absence of cross-reactions between related chemicals have also been documented with good correlation with oral exposure. Positive cross-reactions have been described by PT with the three piperazine anti-histamine H1 derivatives (hydroxyzine, cetirizine, and levocetirizine) [37] and the oxicam NSAIDs (tenoxicam, piroxicam, and often also meloxicam) [38]. On the opposite, among the coxibs, etoricoxib, and celecoxib, which actually have different chemical structures, no cross-reaction occurs either with PT or oral exposure [39].

Cross-reactivity or its absence can also be studied with photopatch tests: aryl-propionic NSAIDs which share a benzophenone structure and cause photoallergic contact dermatitis (ketoprofen, suprofen, and tiaprofenic acid) show cross-reactions among them and with the lipid-lowering agent, fenofibrate, which also has a benzophenone structure and causes systemic photosensitivity [23]. Concerning the oxicams, piroxicam, and tenoxicam which were shown to cross-react in FDE, do not cross-react on photopatch tests or during clinical treatments [40].

A positive cross-reaction on PT can be important to advise patient concerning drugs to avoid. On the other hand, a negative cross-reaction on PT

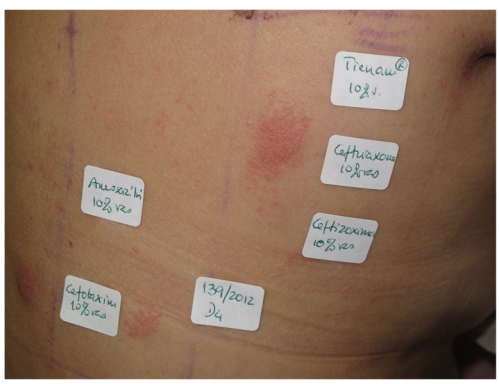


**Fig. 8.** Positive patch tests different cephalosporins tested at 10% pet, namely, cefotaxim and ceftriaxone (Chemotechnique Diagnostics®)

does not exclude the possibility of causing a CADR, but may indicate a possible safe drug to perform oral provocation.

## Conclusion

Cutaneous drug provocation with patch testing is a simple, safe, and highly reproducible diagnostic test to confirm the culprit drug in non-immediate CADR. Several studies support the high specificity of the PT; however, its sensitivity is much lower than in the study of ACD and depends both on the phenotype of the CADR and the culprit drug. Therefore, a negative PT cannot exclude a culprit drug, but a positive PT can confirm a drug among possible culprits suspected based on clinical algorithms, even after a long-time interval has elapsed (retrospective diagnosis). PT is also useful to study cross-reactivity among drugs. Moreover, as PT seems to reproduce in miniature the clinical aspects and histopathology of the acute eruption, it can be used to study pathophysiologic mechanisms involved in the effector immune response.

In a step-wise investigation of non-immediate CADR, patch testing has a definitive place in confirming the etiologic diagnosis and, especially in severe CADR, it should be performed before an intracutaneous test or an oral provocation.

## Compliance with Ethical Standards

**Conflict of Interest**
Margarida Gonçalo declares that she has no conflicts 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.

## Publisher's Note



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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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