

Patch Testing for Drugs

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Adverse drug reactions occur commonly and primarily manifest in a myriad of cutaneous eruptions. The use of drug patch testing in the diagnosis of specific drug eruptions is increasing; however, a standardized approach to this methodology is currently lacking. A review of current literature was performed on the available evidence of patch testing for drugs. This review addresses the use of patch testing for specific cutaneous adverse drug reactions and for specific classes of drugs including antimicrobials, anticonvulsants, antiretrovirals, glucocorticoids, and nonsteroidal anti-inflammatory drugs. In addition, the approach to performing patch testing to drugs in the clinical arena as well as current contraindications for drug patch testing is reviewed.

Adverse drug reactions occur commonly and often present as cutaneous eruptions.¹ Methodology for diagnosis largely rests on the suspected immunopathogenesis causing the reaction. It is well documented that skin-prick testing is useful for detecting Immunoglobulin E (IgE)-mediated reactions manifesting as urticaria, angioedema, or anaphylaxis. In addition, intradermal testing has proven useful for confirming IgE-mediated reactions to β -lactam antibiotics, as well as beneficial in evaluating delayed-type cutaneous adverse drug reactions when read at 24 to 48 hours.² Patch testing (PT) is a method used primarily to evaluate type IV delayed hypersensitivity reactions.³ Patch testing with drugs has been used for the diagnosis of specific drug eruptions including drug rash with eosinophilia and systemic symptoms (DRESS),⁴ acute generalized exanthematous pustulosis (AGEP),⁵ SJS/TEN (Stevens-Johnson syndrome/toxic epidermal necrolysis), and fixed drug eruptions. The utility of PT depends on various factors including the type and formulation of the drug being tested, the vehicle used, and the immunopathogenesis eliciting the eruption.

This article reviews 3 key topics highlighted in the current literature on drug PT.

1. How to perform PT for drugs in the clinical setting as well as current contraindications for drug PT
2. The use of PT for specific drug classes including antibiotics, anticonvulsants, antiretrovirals, glucocorticoids, and nonsteroidal anti-inflammatory drugs (NSAIDs)
3. The use of PT for specific cutaneous adverse drug reactions

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The authors have no funding or conflicts of interest to declare.

DOI: 10.1097/DER.0b013e3182a0d38a

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PERFORMANCE OF DRUG PATCH TESTING

Both the European Society of Contact Dermatitis (ESCD) and the European Network on Drug Allergy (ENDA) have guidelines for performing PT for medication-induced cutaneous eruptions, which are listed in Table 1.^{6,7} The guidelines differ slightly in opinion in 3 key areas: (1) when to perform drug PT after a reaction, (2) the timing of the interpretation of PT, and (3) type of scoring system. The ESCD recommends waiting 6 weeks to 6 months after complete healing of the cutaneous adverse drug reaction, whereas the ENDA advises waiting 3 weeks to 3 months to PT. The ESCD advocates for an initial reading of the PT at 20 minutes and a delayed reading at day 7 if the reading is negative on day 4. In contrast, the ENDA recommends 2 readings, on day 2 and on day 3 or 4. The scoring systems of the International Contact Dermatitis Research Group are in effect similar to those of the European Environmental Contact Dermatitis Research Group and are outlined in Table 1.

As in PT with common allergens for evaluation of contact dermatitis, patients should avoid taking oral prednisone or other immunosuppressive medications for 1 month before testing.⁸ Patch tests should be placed on the upper back using Finn Chambers on Scanpor tape (Epitest, Tuusula, Finland) except in fixed drug eruptions where they should be performed on the residual lesional skin as well as the normal skin of the back.^{9,10}

Drug PT can be performed with the commercialized drug as well as pure substances. It is recommended to test pure drugs at a 10% dilution in petrolatum and, if possible also, at a 10% dilution in alcohol.⁶ If the pure drug cannot be obtained, then medications in their commercialized form should have their coating removed and be ground to a fine powder. This powder can then be tested as is, as well as incorporated at 30% in white petrolatum and diluted to 30% in water.⁶ Antibiotic PT is commercially available for ampicillin (5% petrolatum [pet.]), bacitracin (20% pet.), chlorotetracycline-HCl (1% pet.), clotrimazole (1% pet.), erythromycin (1 and 2 % pet.), framycetin sulfate (10% pet.), fusidic acid (2% pet.), gentamicin sulfate (20% pet.), kanamycin sulfate

TABLE 1. Comparison of Guidelines for Drug PT*

Recommendations	ESCD	ENDA
Timing of PT	6 wk to 6 mo After complete healing of cutaneous adverse drug reaction* 1 mo after discontinuation of systemic CSs*	3 wk to 3 mo
Location	Upper back	Upper back
Drug concentrations	Pure substances (10% in pet. +/- 10% in alc. or aq.) Powder from tablets and pills (30% in both pet./aq.) Liquid prep (as is and 30% aq.)	Substances diluted in 0.9% NaCl or in petrolatum to varying concentrations
PT reading	20 min, D2 (D3), D4, D7 (if PT negative on D4)	D2, D3 (D4)
Interpretation/scoring	ICDRG criteria†	EECDRG criteria‡

*Adapted from Romano et al.¹⁶

†0 = no reaction; ? = doubtful reaction; + = weak (nonvesicular) reaction; ++ = strong (edematous or vesicular) reaction; +++ = extreme reaction.

‡0 = no reaction; ? = faint erythema; + = erythema, infiltration, possibly discrete papules; ++ = erythema, infiltration, papules, and vesicles; +++ = intense erythema, infiltration, coalescing vesicles.

D indicates day; EECDRG, European Environmental Contact Dermatitis Research Group; ICDRG, International Contact Dermatitis Research Group.

(10% pet.), neomycin sulfate (20% pet.), nystatin (2% pet.), oxytetracycline (3% pet.), streptomycin sulfate (5% pet.), sulfanilamide (5% pet.), and tetracycline-HCl (2% pet.) from allergEAZE (www.allergeaze.com). Quinoline mix, bacitracin, and neomycin sulfate are found in the T.R.U.E. Test (Thin Layer Rapid Use Epicutaneous Patch Test) (www.true-test.com). Commercialized products are also available from Chemotechnique Diagnostics (www.chemotechnique.se/).

In addition, gel jacket portions of encapsulated drugs should be tested separately, as there have been rare cases reported of drug hypersensitivity reactions to one of the excipients in the commercial preparation of the drug.¹¹ Similarly, liquid preparations of medications should be tested at full strength as well as diluted at 30% in water.⁶ Fresh preparations should be used for commercialized forms of the drugs, as the stability of many diluted products is unknown; it is recommended that preparations are made for only 1 patient and kept no more than 1 day.⁶ Using more diluted substances for PT—for example, first dilution at 0.1% to 1% and, if negative, increase up to 10%—is highly recommended to prevent a relapse of a severe cutaneous adverse drug reaction (SCAR) (DRESS, SJS, etc).^{6,12}

At least 2 vehicles should be used to prepare drug PT, petrolatum and water, to increase the likelihood of penetration of the drug into the epidermis. This methodology will decrease the rate of false-negative results. For example, studies have shown that PT with β -lactam antibiotics or pristinamycin diluted in water was negative, when concurrently the same drugs diluted in petrolatum yielded positive results in some patients.^{13,14} Similarly, steroid hormones (estrogen and progesterone) should be diluted in alcohol to increase epidermal penetration as dilution in water or petrolatum has yielded false-negative results.¹⁵ Other reasons for false-negative results include viral cofactors present at the time of

the cutaneous drug eruption, which may be absent at the time of PT; and a drug metabolite but not the parent drug as responsible agent.⁶

CONTRAINDICATIONS/CAUTIONS FOR PT WITH DRUGS

Patch testing can be performed for a wide variety of medications. Systemic reactions to PT are extremely rare¹⁶; however, immediate-type reactions on PT have been noted with various antibiotics.¹² Thus, reading PT at 20 minutes is recommended by the ESCD. Although rare, reactivation of severe cutaneous drug eruptions has been seen during drug PT. Because of concern for relapse of the drug eruption during PT with certain medications (acyclovir, carbamazepine, pristinamycin, pseudoephedrine),^{5,17–19} testing with multiple concentrations of these drugs is suggested as discussed above (starting at 1%).¹² In patients who have experienced severe life-threatening cutaneous reactions to medications, a risk-to-benefit ratio should be considered before PT. Intradermal testing promotes the recurrence of cutaneous drug eruptions more frequently than PT,¹² and this can occur even if the intradermal skin test result is negative.

Overall, PT should not be performed if a patient has sunburn because of reduced skin reactivity⁷ or if the patient is currently on oral corticosteroids (CSs) and possibly immunomodulators. However, a recent study in England²⁰ with PT for contact dermatitis in patients on immunomodulators demonstrated that patients on medications such as azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil are still capable of having positive PT reactions. Topical CSs and likely topical immunomodulators to the back should also be stopped before PT. If possible, avoid PT during pregnancy, acute viral illness with fever, and infectious diseases.⁷

USE OF PT FOR SPECIFIC CUTANEOUS ADVERSE DRUG REACTIONS

Drug Reaction, Eosinophilia, and Systemic Symptoms

Drug reaction, eosinophilia, and systemic symptoms is a type IV delayed-type hypersensitivity reaction characterized by fever, rash, and systemic symptoms including lymphadenopathy, abnormal liver function, interstitial nephritis, pulmonary and cardiac infiltrates, and hematologic abnormalities with eosinophilia and atypical lymphocytes.²¹ An estimated incidence of the disease has been reported to be between 1 per 1000 and 1 per 10,000 exposures to anticonvulsant drugs.²²

Among the recently published literature, there are several large prospective studies that assessed the usefulness of PT in various cutaneous adverse drug reactions (Table 2) including DRESS syndrome.^{11,18,23} Barbaud et al¹⁸ performed the largest multicenter prospective study looking at the usefulness and safety of patch tests in SCARs. Utilizing PT protocols according to the ESCD guidelines, this study emphasized the utility of PT for DRESS syndrome. Among the 72 patients with a history of DRESS syndrome, 46 cases (64%) had positive patch tests. One of 72 patients developed a maculopapular exanthem on her arms with PT. Two patients were included twice in the positive patch test group, which may lead to a slightly increased sensitivity of PT but likely not a significant impact on the results. To ensure that positive reactions were not irritant reactions, the authors compared the agents that gave positive results to a local database, which included patients tested with PT for the same agents. Utilizing this control method enhances the validity of drug PT in DRESS syndrome.

Whereas the aforementioned study used multiple medications for PT, a recent study²³ looked at the clinical value of PT specifically for carbamazepine-induced SJS/TEN and DRESS. They found similar positive patch test results among the 2 groups with a slightly higher percentage of positive patch tests in the DRESS group; however, this group had a smaller number of PT performed. All negative results on day 2 remained negative on day 4; however, the authors do not mention whether the negative patch tests were then read on day 7 as recommended by the ESCD. The authors comment on the lack of irritant reactions among all the cases including the 10 controls used. The readings were performed according to standardized scoring criteria (International Contact Dermatitis Research Group). This study suggests that PT with carbamazepine is both safe and useful in carbamazepine-induced SJS/TEN or DRESS.

Santiago et al¹¹ studied more than 50 patients with DRESS induced by multiple agents. This study showed a significantly lower sensitivity of PT for DRESS, with only 32% positive PT reactions. However, the authors do not mention the dilutions used, and it is possible that false-negative results may have occurred that could have contributed to the lower number of positive results found in this study compared with more recent ones. Interestingly, in the group of 33 patients with anti-epileptic-induced DRESS

studied, 51.5% of PTs were positive (compared with 32% in the total group), and carbamazepine was responsible for two thirds of those cases. None of the 19 patients patch tested with allopurinol nor the 9 tested with oxypurinol in several concentrations and vehicles developed a positive reaction, suggesting these agents are not useful for testing.

A recent systematic review from Canada²¹ analyzed the use of PT for the diagnosis of anticonvulsant hypersensitivity syndrome (also known as DRESS syndrome) in which only reactions related to aromatic anticonvulsant drugs were reviewed.²¹ The authors found that depending on the drug being tested, the positive predictive value (PPV) of the PT was as high as 80% to 90%. In addition, the PPV of PT for DRESS syndrome appears higher than the negative predictive value, indicating that other confirmatory tests should be performed in the event of a negative PT to a concerning agent.²⁴ The usefulness of PT was highest for specific drugs (carbamazepine and phenytoin).²⁵ Similarly, a study performed by Galindo et al,²⁶ who applied PT to 15 patients with various systemic adverse drug reactions, found a PPV of 75% for PT to carbamazepine and 60% for PT to phenytoin, whereas PPV for PT to phenobarbital and lamotrigine was only 25%.²⁶

SJS/TEN and AGEF

Within the spectrum of adverse drug reactions, SJS/TEN and AGEF lie at the more severe end. The studies looking at the utility of PT in SJS/TEN and AGEF have considerably smaller sample sizes owing to the lower incidences of these reactions. In the previously mentioned multicenter study to determine the usefulness of drug patch tests for SCARs, 23.5% (4/17) of those with SJS/TEN were positive compared with 64% (46/72) of patients with DRESS and 57.8% (26/45) of those with AGEF. The authors noted that the type of drug and form of reaction affected the utility of the patch test. For example, carbamazepine was positive in 11 of 13 DRESS cases, but none of 5 SJS/TEN cases. As noted in the previous section, this study followed PT protocols according to the ESCD guidelines and also used adequate controls to rule out irritant reactions. In addition, Wolkenstein et al²⁷ demonstrated limited usefulness of PT in SJS/TEN. They followed the ENDA guidelines in regard to the timing of the drug patch tests (3–8 weeks after reaction); however, reading of the patch tests did not follow standardized guidelines. The authors reported that the patch tests were read after 3 days and did not mention whether they were interpreted on days 2/4 or 7. They patch tested 59 patients with cutaneous adverse drug reactions (SJS/TEN, AGEF, and other cutaneous drug eruptions) and found only 9% (2/22) of SJS/TEN cases had a relevant positive test compared with 50% (7/14) of cases of AGEF. The authors concluded that PT for SJS/TEN had a low sensitivity and was more useful for diagnosis of AGEF, which is consistent with recent literature.¹⁸ Conversely, in the previously mentioned study by Lin et al,²³ PT with carbamazepine and other structurally related aromatic anticonvulsants was found to be safe and useful for carbamazepine-induced SJS/TEN.

TABLE 2. PT in DRESS Syndrome

Type of Study	No. Patients	No. Controls	Drug(s)	Concentration (% Unless Otherwise Indicated)	Vehicle	Timing of PT	Frequency of a Positive Result	Relapse
Prospective, multicenter (Barbaud et al ¹⁸)	Total of 134	Compared with negative patch tests with same drug in a European database	Multiple β -lactams (14 cases), vancomycin (4 cases), pristinamycin (3 cases), quinolones (1 case), amikacin (1 case), pyrimethamine (1 case), acyclovir (2 cases) carbamazepine (11/13 suspected cases), proton pump inhibitors (5 cases), fludione (2 cases), spironolactone (2 cases), celecoxib (1 case)	10–30	Petrolatum	Up to 12 mo following resolution of SCAR	64% (46/72)	One
Prospective, single center (Santiago et al ¹¹)	84	67	Multiple	Pure drug and appropriate dilution	Petrolatum	6 wk to 6 mo	32.1% (18/56)	0
Prospective, single center (Lin et al ²³)	26	10	Aromatic anti-epileptic drugs: CBZ, CBZ-10,11-epoxide, lamotrigine, (Lamictal), oxcarbamazepine, phenytoin	10%; 30%	Petrolatum	4 wk to 17 mo	62.5% (10/16 CBZ-SJS/TEN group) 70% (7/10 CBZ DRESS group) with 30% CBZ	0

CBZ indicates carbamazepine.

Fixed Drug Eruption

Fixed drug eruptions are a common form of cutaneous adverse drug reactions. Characteristic clinical features of a fixed drug eruption are healing with residual hyperpigmentation and recurrence of similar lesions at the same sites with readministration of the causative agent.²⁸ The drugs commonly implicated include NSAIDs, sulfonamides, barbiturates, salicylates, tetracyclines and phenolphthalein.²⁹ In a recent case report, 2 cases of fixed drug eruption caused by etoricoxib, a selective cyclooxygenase isoenzyme (COX) 2 inhibitor, were confirmed by PT with this drug. In both cases, a positive reaction was observed on residual pigmented lesions 24 and 48 hours after PTs were performed, but not on noninvolved skin.³⁰ The authors utilized standardized allergens and, when not possible, appropriately diluted the powder of commercial pills in petrolatum according to the ESCD guidelines. However, controls were not used in this study, nor did the authors indicate that they evaluated for irritant reactions. In addition, there was no mention of what scoring system was used to interpret the patch test readings. Therefore, although this case report highlights a common finding seen in recent prospective studies¹² (ie, importance of performing PT on lesional skin), the results may not be generalizable.

In a prospective cohort study examining the cross-reactivity of sulfonamide-based drugs causing fixed drug eruptions, PT was positive in 5 of 25 patients who also had a positive controlled oral challenge testing.³¹ Although administering controlled oral challenge testing enhances the specificity of the drug patch tests, this study had many flaws. It did not follow any established protocol for PT application or interpretation. The vehicle used was dimethyl sulfoxide, and the readings took place on days 1 and 2. Positive results may have been missed because more delayed readings were not obtained. The likelihood of obtaining positive PT was increased among patients who had a residual lesion present at the time of testing, which is consistent among currently published studies. In a recently published retrospective 20-year review of patients with fixed drug eruptions who underwent PT for etiologic diagnosis, 21 patients (40.4%) had positive patch tests on pigmented lesions, 20 of those to NSAIDs (nimesulide, piroxicam, and etoricoxib) and 1 to an antihistamine (cetirizine).³²

Overall, the usefulness of PT for specific cutaneous drug eruptions largely depends on the type of adverse reaction and the implicated medication. Larger randomized controlled studies are needed to further evaluate the sensitivity and specificity of PT in delayed-type eruptions. Secondary to the low incidence of some of these cutaneous adverse reactions, these studies will likely need to be multicenter to have a large-enough sample size to generate reliable results. Overall, PT seems useful and safe. Unanimously, the literature shows that PT for fixed drug eruptions diverges from the standard application of PT to the upper back and should also be performed on lesional skin to obtain a reliable result.

PATCH TESTING WITH SPECIFIC MEDICATIONS

Antibiotics

Numerous studies show that patch test positivity to antibiotics is higher in patients with delayed type of drug eruptions, particularly erythrodermic, eczematous, and maculopapular rash. Osawa and colleagues³³ evaluated 242 patients with delayed-type drug eruptions. Patch testing was positive in 62 (31.5%) of 197 patients tested. The patch test positivity was highest in erythrodermic and eczematous-type cutaneous reactions.

Grandhe and colleagues³⁴ patch tested 30 patients (aged 22–69 years) with multiple cutaneous manifestations including maculopapular rash (43%), fixed drug eruption (27%), generalized eczema (20%), and urticaria (10%), with 18 antibacterial agents including cephalosporins, fluoroquinolones, penicillin G, amoxicillin, piperacillin, and co-trimoxazole. Six of 13 patients with a history of maculopapular rash had a positive reaction to at least 1 antibiotic on PT. None of the 20 negative control patients had positive test reactions. Thus PT to antibiotics can be considered as it has a fairly high positivity rate, especially with certain types of cutaneous manifestations. From this study, it appears that false-positive rates may be low.

Numerous studies also show that within antibiotic classes there is a higher rate of positivity to PT with aminopenicillins, cephalosporins, pristinamycin, and clindamycin compared with macrolides, tetracyclines, and quinolones. In a large study of 826 patients³⁵ who were patch tested for suspected systemic drug allergy and with a history of an exanthem (95%), a positive PT reaction to 1 or more drugs was seen in 89 (10.8%), most often to β -lactams, clindamycin, and trimethoprim. β -Lactams tested positive in 3.9% (39/1008), sulfonamides in 2.9% (15/518), and clindamycin in 19% (12/63). There were no reactions in any of the tests to macrolides, tetracyclines and quinolones tested. There were no reactions in the 20 negative controls. Again, this study had an adequate number of negative controls, suggesting low false-positive rates. Similarly, in a retrospective analysis by Seitz et al³⁶ on 37 patients with a history of delayed hypersensitivity symptoms related to treatment of a fluoroquinolone antibiotic, PT was negative in all. Patch testing was performed by crushing tablets (250 mg ciprofloxacin, 200 mg ofloxacin, 250 mg levofloxacin, and 400 mg moxifloxacin) and suspending in 1 mL saline solution. Patch testing was removed after only 1 day and read after days 2, 3, and 4. However, 2 of 28 patients developed a rash when the agent was given by an oral challenge. One must note that PT was used with only 1 vehicle (saline), and the patch was removed after only 24 hours.

Although aminopenicillins and maculopapular rash have been most studied with PT, numerous case reports of other antibiotics with unusual cutaneous manifestations are seen in the literature. Chaabane et al³⁷ report a case of AGEF after cefotaxime confirmed by a positive patch test. Endo et al³⁸ report a case of a morbilliform drug eruption in a patient with acute myelogenous leukemia. The patient was patch tested to vancomycin, meropenem, and

piperacillin-tazobactam 10% in petroleum, with a strong positive reaction to meropenem.

β-Lactam Antibiotics

Various studies looked specifically at β-lactam antibiotics. Although the cutaneous manifestations were varied, several well-controlled studies with drug challenges looked at patients with primarily maculopapular reactions to this class of medications.

Patriarca et al³⁹ evaluated 30 patients with cell-mediated allergy to β-lactams defined as (1) history of adverse reactions (maculopapular rash and urticaria) to aminopenicillins (86.4%) and penicillin G (9.1%); (2) normal serum total IgE; (3) negative serum-specific IgE antibodies to penicillin G and V, amoxicillin, and ampicillin; (4) negative skin tests to a variety of β-lactams; and (5) positive patch test to at least 1 antigenic determinant from a wide variety of β-lactam preparations. Tolerance challenges were done in patch-negative β-lactams. Three separate groups of patients on the basis of clinical history, patch test, and tolerance challenge pattern were identified: (1) those with allergy to the side chain of aminopenicillins (16 patients, 53.3%); (2) those with allergy to the thiazolidine ring (3 patients, 10.0%); and (3) those with undetermined site (11 patients, 36.7%). Cross-reactivity among different molecules (defined as positive challenge in patch-negative to β-lactams) was low (4.8%), showing a very high negative predictive value (95.2%) of the patch test in excluding the occurrence of a cross-reactivity.

In 1995, Romano and colleagues⁴⁰ assessed 195 subjects with histories of adverse reactions to aminopenicillins, using skin tests with penicilloyl polylysine, minor determinant mixture, benzylpenicillin (PG), amoxicillin, and ampicillin (read after 20 minutes and 48 hours); patch tests with PG, amoxicillin, and ampicillin; and specific IgE for penicilloyls G and V. Thirty-three of the 60 subjects reporting maculopapular reactions had delayed intradermal and patch test positivity for ampicillin and amoxicillin, and 3 were also positive for PG. Diagnoses were confirmed with oral challenges in 18 of 33 patients who had a positive PT and a history of a maculopapular rash. All 18 of the orally challenged patients developed a maculopapular rash within 6 to 24 hours. Of those with a negative PT and a history of a maculopapular rash, 59% of the patients (16/27) had a negative challenge. This suggested a calculated negative predictive value of at least 59% and a sensitivity of at least 62%, based on worst-case scenarios.

Antiretrovirals

Medications used for the treatment of HIV have been implicated in delayed hypersensitivity syndromes. Patients infected with HIV have a higher frequency of drug allergies and are exposed to multiple medications (antibiotics, antimycobacterials, antiretrovirals, etc) during their treatment.⁴¹ Abacavir, a nucleoside analog used for HIV treatment, is associated with a hypersensitivity syndrome characterized by fever, rash, malaise, nausea, vomiting,

and diarrhea.⁴² In a review of 7 patients who developed abacavir hypersensitivity syndrome based on symptoms, all had positive PT to both 1% and 10% abacavir in petrolatum.⁴² In the PREDICT-1 study, 100 HIV-positive patients tolerating abacavir for 6 to 10 weeks had negative PT.⁴³ HLA testing for *HLA-B*5701* and PT testing for abacavir have high correlation. A retrospective case-control study (SHAPE) found that *HLA-B*5701* was present in 100% of 47 patients with positive PT.⁴⁴ In the PREDICT-1 data, all 100 patients tolerating abacavir with negative PT to the drug did not carry the *HLA-B*5701* mutation. In an Italian study, 10 of 20 HIV-positive patients with a history of an adverse skin reaction while on highly active antiretroviral therapy that contained abacavir tested positive to PT and *HLA-B*5701* mutation⁴⁵; none of the 60 HIV-positive controls on highly active antiretroviral therapy with abacavir had positive reactions to PT.

Thus, it appears that a positive result in a patient who had a clinically consistent hypersensitivity reaction is indicative of a true-positive result. There were no reports of false-positive results in patients who had PT to abacavir and had tolerated the medication in the HIV-positive controls.^{42,43,45} A negative result on PT, however, cannot rule out a hypersensitivity reaction to abacavir, and it is not suggested that the drug be reintroduced if PT is negative. Most studies used 1% to 10% abacavir diluted in petrolatum with positive results noted at these concentrations (Table 3). Reading of PT varied from 24 to 96 hours; although positive results were noted at 24 hours, we suggest PT is read at 48 hours and 72 to 96 hours per the ESCD guideline recommendations.

Anticonvulsants

Most evidence for anticonvulsants and PT comes from experience with carbamazepine, and even then the literature is focused mostly on case reports and series. There is also variation seen with carbamazepine itself, depending on the type of skin eruption involved. As already discussed, in a recently published multicenter prospective study,¹⁸ PT was positive to carbamazepine in 11 of 13 patients with DRESS but in none of 5 patients with SJS/TEN. However, a Taiwan study²³ found similar positive PT results to carbamazepine in DRESS and SJS/TEN. A 1+ or stronger reading was seen in 10 (62.5%) of 16 patients diagnosed with SJS/TEN and 7 (70%) of 10 patients diagnosed with DRESS.

Patch testing to carbamazepine has been attempted with concentrations varying from 1% to 30% in petrolatum. In the study of Santiago et al,¹¹ all patients who tested positive to carbamazepine were positive to all concentrations used; increasing the concentration to 20% did not increase their yield. However, in the study of Romano et al,⁴⁶ 1 of 6 patients with PT positive to carbamazepine was positive only at concentrations of 15% to 20%. The ESCD suggests using a concentration of 1% to 10% carbamazepine in petrolatum for PT; one may consider increasing to concentrations of 15% to 20% if history is suggestive and a negative PT result has been obtained at lower concentrations. In the 7 studies reviewed for PT to carbamazepine, only one mentioned a

TABLE 3. Abacavir PT

Study	No. Patients	No. Controls	Vehicles Used	PT Read	Results	Reactivation of Rash
Phillips et al ⁴²	7	7; 2 HIV-negative never exposed to drug; 5 HIV-positive tolerating drug	1% and 10% abacavir in petrolatum in patients 1–3 and HIV controls; 0.1%, 1%, 5%, 10%, 15%, 25% abacavir in petrolatum in patients 4–7 and HIV-positive controls	48 and 96 h (patients 1–3), 1, 24, 48, and 96 h (patients 4–7)	Positive in all 7 patients and negative in all 7 controls. All positive to 1% and 10% abacavir	No
Mallal et al ⁴³	61	100	Modified from the protocol of Phillips et al but not stated explicitly	Not stated	23 had positive PT test; 38 had negative PT test. PT negative in all HIV-positive controls tolerating the drug	Not stated
Saag et al ⁴⁴	199		1% and 10% abacavir	24 and 48 h	47 had positive PT	No patients had PT stopped or discontinued
Giorgini et al ⁴⁵	20	60 HIV-positive tolerating drug; 20 HIV negative	1%, 10% abacavir in petrolatum and abacavir as in HIV-positive patients; HIV-negative patients in petrolatum only	20 min, days 2, 3, and 4	Positive in 10/20 patients; negative in all 60 HIV-positive controls	No

patient who experienced reactivation of rash with PT (Table 4). None of the controls used in these studies had positive PT to carbamazepine, suggesting a low risk of false-positive results.

One may also consider testing with known drug metabolites of carbamazepine to increase yield.⁴⁷ In a study of 13 patients who had skin reactions (maculopapular rash) to carbamazepine who were patch tested to the parent drug and carbamazepine 10,11-epoxide, 2 patients reacted to the metabolite but not the parent drug.⁴⁷ Overall, 10 of 13 patients had positive PT to carbamazepine and/or its metabolite.

Variance in the incidence of positive PT to carbamazepine in comparison to other anticonvulsants may be due to its lipophilic properties and a favorable value for transdermal permeation (K_{oct} = N-octanol/water partition coefficient).²¹

Nonsteroidal Anti-Inflammatory Drugs

Cyclooxygenase 2 inhibitors are increasingly used for pain relief because of their lower rate of gastrointestinal adverse effects seen with other nonsteroidals. The cutaneous reactions to cyclooxygenase 2 inhibitors vary and include maculopapular drug eruptions, AGEP, SJS/TEN, erythema multiforme, and DRESS. A 52-year-old woman taking etoricoxib developed erythematous pruritic plaques on her neck, forearm, and finger.⁴⁸ Patch testing performed with etoricoxib 1% and 5% in petrolatum was positive at locations of previous lesions but negative on nonlesional skin. Patch testing was also performed in 10 healthy controls and was negative. Patch testing to celecoxib was also positive in a 61-year-old woman with multifocal fixed drug eruption using 10% petrolatum 2 months after eruption⁴⁹ but negative in a 57-year-old woman with fixed drug eruption with positive oral rechallenge.⁵⁰ Nonsteroidal anti-inflammatory drugs have also been implicated in the development of AGEP. There are multiple case reports of AGEP caused by celecoxib and valdecoxib.^{51–53} In a case report of a Korean woman taking celecoxib who developed AGEP,⁵¹ PT was performed 3 months after the reaction. She was tested to celecoxib 5% in normal saline and petrolatum along with capsule contents diluted to 5% in normal saline and petrolatum. The patient had a vesicular reaction to celecoxib 5% in normal saline and an erythematous reaction to celecoxib 5% in petrolatum; the patient did not react to other antibiotics or NSAIDs that were concurrently placed, and 2 healthy controls did not react to the celecoxib either. In other case reports, PT to celecoxib was also positive in a 79-year-old woman who developed erythema multiforme,⁵⁴ a 76-year-old man with maculopapular eruption,⁵⁵ a 70-year-old woman with maculopapular eruption,⁵⁶ and a 29-year-old woman with DRESS on both celecoxib and antituberculosis drugs,⁵⁷ whereas it was negative in a 53-year-old woman with photoallergic drug eruption both via PT and photo-PT.⁵⁸ (Table 5)

It is important to note that false-positive reactions may be seen when performing PT to celecoxib; it is suggested that capsule contents be tested at concentrations no higher than 5% to 10%.¹²

TABLE 4. Carbamazepine PT

Study	No. Patients	No. Controls	Vehicles Used	PT Read	Results	Reactivation of Rash
Lee et al ⁴⁷	13	39	10% carbamazepine in petrolatum; carbamazepine epoxide 1 µg/mL in ethanol	Days 2 and 4	7 positive to CBZ alone; 2 positive to CBZ-epoxide; 1 positive to both: none of controls positive to either	Not stated
Barbaud et al ¹⁸	18	—	Commercial form of drug 30% diluted or 10% diluted in petrolatum	Days 2 and 4	11/13 positive with DRESS; 0/5 positive in SJS/TEN	1 Patient
Santiago et al ¹¹	33	50	1%, 5%, 10% in all patients and 20% in 20 patients	Days 2 and 3 or 4	13/18 PT positive where carbamazepine was suspected agent	No
Lammintausta et al ³⁵	37	—	20%–30% Diluted in petrolatum and/or saline	Days 2 and 3 or 4	7/37 positive	Not stated
Romano et al ⁴⁶	8	34	5%, 10%, 15%, and 20% carbamazepine in petrolatum	Days 2 and 3	6/8 positive	Not stated
Galindo et al ²⁶	8	20	5% in petrolatum	Days 2 and 4	6/8 positive	Not stated
Lin et al ²³	26	10	30% or 10% diluted in petrolatum	Days 2 and 4	10/16 positive SJS/TEN; 7/10 positive DRESS	No

Legend: D indicates Day; DRESS, Drug Rash with Eosinophilia and Systemic Symptoms.

Corticosteroids

Reactions to CSs can comprise both delayed hypersensitivity reactions and type I mediated reactions including urticaria/angioedema and anaphylaxis. Allergy to topical CSs affects 0.5% to 5.8% of patients⁵⁹ and is more common than type I mediated reactions. Patients are sensitized mostly via skin, airborne, and intravenous routes.⁶⁰ Testing needs to be catered to reaction type with PT used for allergic contact dermatitis (ACD) and skin-prick testing for type I mediated reactions. Patch testing to CS is complicated by the therapeutic anti-inflammatory nature of the CS itself, which may cause false-negative results if tested at too high concentration.¹⁶ Risk factors attributed to the development of delayed hypersensitivity to CS include chronic venous leg

ulcers, stasis dermatitis, and contact dermatitis (in particular, patients with a history of ≥ 2 positive PT results and multiple medicament sensitivities). Suspicion must arise for ACD to CS when the dermatitis fails to respond to CS and/or when dermatitis worsens with treatment.⁶⁰ Patch testing for CS allergy should include the groups of simultaneously reacting or cross-reacting CSs,⁶¹ as well as the vehicle and preservatives in the preparations. Patch testing should include tixocortol pivalate, budesonide, and hydrocortisone 17-butyrate along with the patient's own commercial steroid⁶⁰; 90% of ACD to CSs will be detected by using tixocortol pivalate, budesonide, triamcinolone, and the patient's commercial steroid.^{62,63} Patch test to CS has become increasingly feasible secondary to commercially available formulations ranging from concentrations of 0.1% to 1% in petrolatum

TABLE 5. Selected Case Reports of PT to Celecoxib

Article	PT Results	PT Concentration	Other
Bellini et al ⁴⁹	PT positive	10% in petrolatum and dimethyl sulfoxide involved and uninvolved skin	
Bandyopadhyay et al ⁵⁰	PT negative	20% in petrolatum to lesional and non lesional skin	Read at 48, 72, and 96 h; oral challenge positive
Shin et al ⁵¹	PT positive	5% normal saline and petrolatum; capsule contents 5% in normal saline and petrolatum	PT positive to 5% celecoxib in both normal saline and petrolatum; 2 controls negative
Arakawa et al ⁵⁴	PT positive	Not stated	
Grob et al ⁵⁵	2 patients: 1 patient PT positive	Not stated	LTT positive in other patient
Alonso et al ⁵⁶	PT positive (2 positive)	10% petrolatum	Read at days 2 and 4; 5 control patients negative
Lee et al ⁵⁷	PT positive	10% and 50% petrolatum	PT positive both concentrations
Yazici et al ⁵⁸	PT negative	10/100 petrolatum with UV-A phototherapy	

LTT indicates lymphocyte transformation test.

(www.allergeaze.com). Patch test readings for ACD to topical CS usually require a third patch reading at day 7; about one third of ACD to CS would be missed without this late reading.⁶⁴ Positive PT to CS may indicate only topical sensitization, and oral administration of the CS may be tolerated.¹⁶ However, once a patient has been sensitized to CS by skin contact, administration of the CS via oral, intravenous, intramuscular, or inhalation rarely can provoke systemic contact dermatitis.⁶⁵

CONCLUSIONS

Although there are increasing reports and a number of recent studies on the use of patch tests in drug hypersensitivity diagnosis, there remains a lack of a standardized approach to define the population, clinical manifestation, drug to patch test, and patch test materials to make PT to drugs a standard of care. To date, based on the data reviewed, we conclude that there are sufficient data to suggest the following:

1. Patch testing to drugs has a role in delayed hypersensitivity drug reactions and has a higher positivity in patients presenting with maculopapular rash, erythroderma, and nonimmediate cutaneous reactions including AGEF, DRESS, fixed drug eruption, and systemic contact dermatitis from drugs, with some evidence for SJS/TEN.
2. In drug PT for fixed drug eruptions, it is necessary to perform PT on lesional skin versus nonlesional skin to reduce false-negative results, as many cases have reported negative PT results on nonlesional skin.
3. Patch testing seems to work best with aromatic anticonvulsants and various antibiotics (aminopenicillins) but does not appear to work consistently with a wide range of drugs.
4. There are limited standardized antigens available for use, including antimicrobials, anticonvulsants, and CSs.
5. A systematic research effort is required to resolve current inconsistencies and to encourage greater utilization of this potentially important diagnostic methodology.

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