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Urticaria and Atopic Dermatitis (S Jacob, Section Editor)

Patch Testing in the Diagnosis of Medication Allergy

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Opinion statement

In evaluation of medication allergy, the utility of drug patch testing is dependent on both the type of drug reaction and the suspected causal drug. Epicutaneous patch tests reproduce T cell-mediated delayed hypersensitivity; thus, eruptions at least partially mediated by T cells can be confirmed by positive drug patch test (DPT) responses in some patients. These include acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug eruptions (FDE), macular drug reactions ("morbilliform" or "exanthematous" reactions), and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Currently, literature supports that specific drugs, including antiepileptics and certain antibiotics, are most likely to produce diagnostic patch test results. However, drug patch testing cannot be used reliably for all medications. We suggest that standardized international guidelines should be developed and implemented to improve the comparability of results from drug patch testing reported in literature. Furthermore, an organized, systematic research strategy should be executed in order to gain further understanding of how and when drug patch testing can be used most effectively.

Introduction

Cutaneous adverse drug reactions are a commonly encountered challenge for physicians, as they comprise 1–2 % of all outpatient and 5–10 % of all inpatient encounters [1]. These adverse drug reactions can be categorized as either type A or type B. Type A reactions are "augmented" reactions that are predictable based on the pharmacology of the ingested drug. These are the most common side effects and are dose-dependent. Type B reactions are "bizarre" reactions, which cannot be expected based on the drug pharmacology [2]. Patients

who experience type B drug reactions are often prescribed multiple medications and have confounding medical conditions, which makes determining the causal agent challenging. A decision regarding the medication that induced the reaction commonly relies on chronologic temporal and clinical information. Other than oral rechallenge, which can frequently cause subsequent life-threatening relapse, there is no [designated or accepted] definitive diagnostic test to determine the specific causal agent. Drug patch testing has been suggested as a useful, and often safer, diagnostic test in these situations.

Drug patch testing can reproduce T cell-mediated delayed hypersensitivity caused by the exposure to the medication. Drug patch testing is generally considered low risk to the patient, with only moderate reexposure to the possible culprit drug in the majority of cases. Despite the relative safety of drug patch testing, systemic relapse of some conditions following drug patch testing has been documented in the literature. In addition, commercialized preparations for drug patch testing have limited availability in the USA making drug patch testing difficult to standardize. The purpose of this review is to discuss the utility of drug patch testing in medication allergy, to explore limitations to drug patch testing, and to identify clinical situations in which drug patch testing can provide useful diagnostic information.

Method of drug patch testing

Currently, there are many potential sources of variability between studies reporting drug patch testing in the literature. However, the European Society of Contact Dermatitis (ESCD) and European Network for Drug Allergy (ENDA) have produced guidelines to standardize procedure of drug patch testing with medications that are commercially available. The ESCD suggests that patient information, drug intake history, and clinic characteristics of the reaction should be documented in all drug skin testing. When specifically undertaking drug patch testing, the testing should be performed at least 6 weeks to 6 months after the resolution of the drug reaction [3]. On the other hand, the ENDA guidelines suggest that patch testing should be conducted 3 weeks to 3 months after cutaneous reaction [4]. Drug patch testing should be postponed until cessation of systemic corticosteroids or immunosuppressive therapy has surpassed 1 month to avoid false-negative test results. Drug patch testing should generally be performed on the upper back. If the cutaneous reaction is a fixed drug eruption, drug patch testing should be performed on both upper back and affected areas (when feasible). According to the ESCD, the test should be read at 20 min (to rule out urticarial eruption), day 1, day 2, and day 4. If a negative test result is read at day 4, the tested site should be read again at day 7. Skin prick tests, followed by intradermal tests with delayed readings can be considered as additional diagnostic tests if drug patch testing is negative [3]. ENDA endorses two patch test readings, the first on day 2 and the second either on day 3 or 4 [4]. In the absence of a specific reason to select one guideline over another, we favor using the guidelines produced by the ESCD given the presence of early and delayed readings in those guidelines, which may increase the likelihood of detecting relevant results. Additionally, if urticarial drug eruption has been excluded firmly by history and/or skin prick testing, it is reasonable to consider bypassing the 20-min reading.

Formulation of drug to be tested

Whenever possible, the ESCD recommends that the pure form of the drug ingested by the patient should be used for drug patch testing. The pure

substance should be tested at a 10 % dilution in both petrolatum and alcohol, if possible. The commercial form of the drug can be used as the test agent if the pure form is unobtainable. The coating of pills should be removed and the remaining pill should be ground to a powder. Powder within the capsules can be tested as is but should be added to petrolatum at 30 % or diluted to 30 % in water. A capsule can be broken and the contents tested as is. Liquid medications should be tested as is and simultaneously tested diluted to 30 % in water. Although systemic relapse is not frequently reported in literature, cautious patch testing with acyclovir, carbamazepine and pseudoephedrine is recommended to avoid this serious complication [3]. High-risk reactions and drugs should be tested with commercialized form of the drug or the pure substance, first diluted at 0.1 % and, if negative, at higher concentrations of 1 up to 10 % [3]. ENDA guidelines advise that substances be diluted in 0.9 % NaCl or in petrolatum to concentrations supported by previous patch test studies [4]. Petrolatum remains best-studied, most reliable vehicle for patch testing. Multiple alternatives have been proposed but require further study to determine their role in patch testing [5].

The intrinsic quality of the medication to act as an irritant should be considered when choosing concentrations for drug patch testing. High concentrations of a drug can cause cutaneous irritation, making results of drug patch testing difficult to interpret [6].

Several key practical points about drug patch testing are summarized in Table 1.

Utility of patch testing for medication allergy: our strategy

To determine whether drug patch testing will be useful, consider using the algorithm in Fig. 1. The first step is to take a clinical history (with detailed chronology) and attempt to identify the type of reaction that occurred in a patient. If the reaction was immediate (e.g., urticarial), or occurred within minutes to hours, then skin prick testing should be performed. If the reaction was not immediate, the next step is to determine whether the reaction was in the "T cell-mediated" group, which includes acute generalized exanthematous

Table 1. Key practical points about drug patch testing

Timing	-When possible, 3 weeks to 6 months following resolution of cutaneous reaction
	-At least 1 month after cessation of systemic immunosuppression
Location	-Upper back (when feasible)
	-Upper back and affected site for FDE
Reading schedule	-At 20 min (optional, to detect urticarial eruption)
	-Delayed readings at days 1, 2, and 4 (ESCD) OR days 2 and 3 or 4 (ENDA)
	-Consider skin prick testing and/or intradermal test if DPT negative
Formulation to be tested	-Pure substance at 10 % dilution (in petrolatum and in alcohol, if possible)
	OR
	-Commercially available substance at 30 % dilution

For evaluation of high-risk cutaneous reactions, test at dilutions of 0.1 %, then 1 and 10 % in observed setting

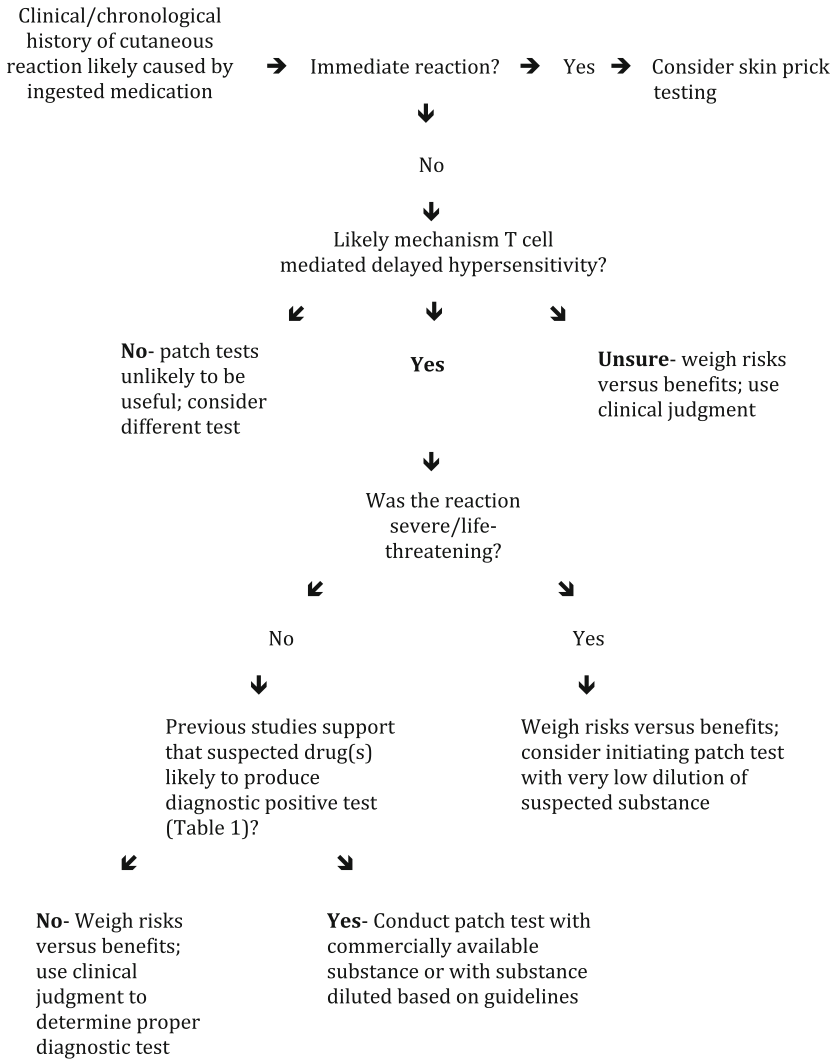

Fig. 1. Recommended algorithm for use of drug patch testing in the diagnosis of medication allergy.

pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug eruptions (FDE), morbilliform/exanthematous eruption, and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). If not, then drug patch testing is unlikely to be useful. If yes, then drug patch testing is reasonable, with utility often linked to the suspected causative drug(s) and specific reaction types. If uncertain, then it is possible that drug patch testing will be helpful in some cases, but positive results may be less likely. Regardless of the likelihood of a positive test, the risks and benefits of drug patch testing should always be considered in the context of the severity of the individual patient's reaction and the need to identify the causative drug for future therapy decisions. Since determining the type of drug reaction is a critical step, we discuss the utility of patch testing with specific drugs based on the type of drug reaction (summarized in Table 2).

Table 2. Alphabetized summary of evidence for patch testing to diagnose drug allergy

AGEP	DRESS	SJS/TEN	FDE	Macular drug reaction
Amoxicillin (useful, strong evidence)	Acyclovir	Amoxicillin	Carbocisteine	**Amoxicillin (useful, strong evidence)**
Amoxicillin-clavulanic acid	**Allopurinol (*not useful, strong evidence)**	**Carbamazepine (useful, strong evidence)**	Cetirizine	**Ampicillin (useful, strong evidence)**
Ampicillin	Amikacin	Ceftriaxone	**Etoricoxib (useful, strong evidence)**	Carbamazepine
Beclometasone	Amoxicillin	Esomeprazole	**Nimesulide (useful, strong evidence)**	Ciprofloxacin
Benzocaine	Amoxicillin-clavulanic acid	Ibuprofen	Ibuprofen	Clindamycin
Carbamazepine	**Carbamazepine (useful, strong evidence)**	Lamotrigine	Meprobamate	Diclofenac
Cefotaxime	Ceftriaxone	Phenobarbital	Meropenem	Hydroxyzine
Ceftriaxone	Celecoxib	Procaine benzylpenicillin	Mesna	Pristinamycin
Celecoxib	Citalopram	Ramipril	**Paracetamol-dextropropoxyphene (controversial)**	Rifampin
Cephedrine	Clobazam	Sulfonamide	Pefloxacin	
Clindamycin	Cloxacillin	Tetrazepam	**Piroxicam (controversial)**	
Diltiazem	Dicloxacillin	Vancomycin	Pristinamycin	
Enoxaparin	Diltiazem		Promethazine	
Fluindione	Enoxaparin		Tenoxicam	
Hydroxyzine	Esomeprazole		**Trimethoprim-sulfamethoxazole (controversial)**	
Iodixanol	Fluindione			
Ioversol	Imipenem-cilastatin			
Paracetamol-dextropropoxyphene	Iodixanol			
Phenobarbital	Lamotrigine			
Prednisone	Olanzapine			
Pristinamycin	Pantoprazole			
Tetrazepam	Piperacillin/ tazobactam			
Varenicline	Phenobarbital			
	Phenytoin			
	Pristinamycin			
	Pyrimethamine			
	Spironolactone			
	Tenoxicam			
	Tetrazepam			
	Tixocortol			
	Topiramate			
	Vancomycin			

All nonbolded medications without parenthetical comments have few (four or less) positive DPTs reported in cohort studies or single case reports. Medications that show particularly high, low, or controversial utility in drug patch testing are bolded with following comments added:
- **Useful, strong evidence:** At least two or more published reports supporting patch testing, one of which must be large cohort study with five or more positive drug patch tests
- **Not useful, strong evidence:** More than one cohort studies reporting zero (0) positive DPTs with medication (despite it being deemed the causative medication for that reaction)
- **Controversial:** Literature provides conflicting data

Acute generalized exanthematous pustulosis

AGEP is a cutaneous adverse drug reaction that is mediated by release of GM-CSF and IL-8 with recruitment of neutrophils. The mechanism of this drug reaction involves delayed hypersensitivity, which the DPT is able to replicate [7••]. The reported positive DPT results range between 50 and 60 %. In a multicenter study, drug patch testing identified the causal drug in 58 % of people with an AGEP reaction. In addition, only one systemic reaction was induced by the use of drug patch testing [8]. Older research also supports DPT with AGEP drug reactions, as 7/14 patients developed positive reactions in one study [9]. In a patient who developed AGEP following oral intake of amoxicillin-clavulanic acid, drug patch testing revealed a strong pustular reaction to ampicillin, amoxicillin, and amoxicillin/clavulanic acid and a weak reaction to penicillin [10]. In another patient with AGEP caused by amoxicillin-clavulanic acid, drug patch testing showed multiple positive responses to several β-lactam antibiotics. It has been suggested that a T cell-mediated response to β-lactams common ring may be involved in the pathogenesis of the multiple DPT reactions [11]. Positive DPTs following AGEP reactions caused by hydroxyzine, benzocaine, cefotaxime, and celecoxib have also been documented [12–16]. Although a systemic response to DPT is rare, induction of an AGEP-like systemic reaction by acetaminophen DPT has been reported when patch testing was used to determine the cause of a case of AGEP [17].

Drug reaction with eosinophilia and systemic symptoms

The mechanism of DRESS most likely is multifactorial involving abnormalities of drug detoxification enzymes that cause accumulation of reactive drug metabolites, reactivation of viruses, and a genetic predisposition with HLA antigens. Several major studies demonstrate variable utility of patch testing in DRESS with reported sensitivities ranging from the mid 60s to 32 %. In a multicenter study, drug patch testing seems to be of value with DRESS, as 64 % of tests gave a positive result. Carbamazepine produced positive DPTs in 11/13 patients. However, drug patch testing did not produce a positive reaction when allopurinol or salazopyrin was suspected [8]. Interestingly, that study demonstrated a higher percentage positive test results compared to a Portuguese study using the same methodology. The Portuguese study found only 32 % of DPTs had a positive result after DRESS as 56 patients were studied with a positive patch test reaction seen in 18 patients overall. Of the positive patch tests, 17/18 were with antiepileptics and 1/18 with tenoxicam. In the antiepileptic group, carbamazepine alone was responsible for 13/17 positive reactions (76.5 %). Patch tests with allopurinol and its metabolite produced a negative patch test in all cases attributed to this drug [18]. A different cohort of 444 patients demonstrated an overall 22.4 % positive result of drug patch testing (when multiple types of drug reactions were studied). In patients with DRESS syndrome, 9/16 tested patients (56.3 %) had positive results; of these, 8/9 reacted to carbamazepine [19•].

Two studies examined cohorts of patients with DRESS attributed to antiepileptic drugs. In Canada, the authors reported a PPV of 80 to 90 % depending on antiepileptic drug [20]. The second study reported strong PPV with carbamazepine (PPV of 75 %) and phenytoin (PPV of 60 %). Very low positive test results were associated with phenobarbital (PPV 25 %) and lamotrigine (PPV 25 %) [21]. Of all the antiepileptic drugs associated with DRESS, carbamazepine is the most widely supported in the literature to produce a positive DPT. A study specifically examining carbamazepine-induced cutaneous adverse drug reactions found that 7/10 carbamazepine-induced DRESS patients had a positive DPT when carbamazepine diluted to 30 % was tested [22•]. In a detailed case report of an 8-year-old girl with DRESS syndrome who underwent drug patch testing with carbamazepine 6 weeks after her cutaneous reaction resolved, the carbamazepine-induced positive skin reaction was observed at 48 h [23].

Other drugs demonstrate variable reactivity on drug patch testing for DRESS syndrome. For example, DRESS is rarely caused by piperacillin/tazobactam; as such, one group documented four cases with only one positive patch test [24].

Fixed drug eruption

Fixed drug eruptions commonly are associated with antibiotics, anticonvulsants, and nonnarcotic analgesics (nonsteroidal anti-inflammatories). In numerous small studies and case reports, drug patch testing has demonstrated utility in identifying the cause of FDE when tests are performed on lesional skin, but not normal skin. Researchers in France found DPTs performed on lesions of FDE were positive in 12/19 cases tested. Medications inducing FDE that had positive DPTs include carbocisteine, paracetamol, pefloxacin, piroxicam, pristinamycin, tenoxicam, and trimethoprim–sulfamethoxazole [25]. A retrospective study reported that DPTs on previous lesions allowed the identification of the causative drug in 21/52 patients (40.4 %) studied with FDE. DPTs were positive in one case with cetirizine and in 20/47 (42.6 %) with NSAIDs, including nimesulide, piroxicam, and etoricoxib. In all the cases, nonlesional DPTs were negative. None of the 7 patients tested with trimethoprim–sulfamethoxazole, none of the 8 tested with paracetamol, and none of the 15 cases due to other antibiotics had positive lesional DPTs [26]. In another cohort including 55 patients with FDE, there was only a 20.0 % positive patch test result rate. In 33/55 patients, patch tests were performed both on normal skin and on the affected site. However, 22 patients were tested only on normal skin because of difficulty applying the drug to the affected sites. It is likely that the 20 % positive patch test result was negatively affected by this limitation, as positive results are more likely when materials are applied to lesional skin [19•]. The cross-reactivity of sulfonamide antibiotics associated with FDE was analyzed in a prospective study in which 5/25 patients with a positive oral challenge test also had a positive patch test. If residual FDE was present, patch testing was performed in both normal and lesional skin. Patients with patch test performed in residual reaction had a higher likelihood of positive test result [27]. Patch testing has also been conducted in a cohort composed of 30 patients with a likely history or diagnosis of adverse drug reaction to antimicrobials. Of the patients with FDE, positivity of patch testing to lesional skin was 50 %, which was the highest percentage of all the reaction types studied [28].

There are numerous published case reports that support the use of drug patch testing to diagnose specifically etoricoxib-induced FDE [29–31]. In one case report, a patient with FDE following ingestion of etoricoxib had a positive DPT to etoricoxib and a negative result to celecoxib, which allowed the physicians to provide a safe alternative therapeutic medication [32]. Further case reports of medication induced FDE confirmed by positive drug patch testing includes nimesulide, meprobamate, ibuprofen, mesna, and promethazine [33–37].

Macular/morbilliform (exanthematous) drug reaction

The mechanism behind macular/morbilliform/exanthematous drug reaction involves the release of toxic mediators from cytotoxic T cells. In a large cohort of 444 patients who underwent drug patch testing, there was a positive patch test rate of 23.9 % in maculopapular eruptions; however, the results were not broken down into individual casual agents and response to patch test [19•]. The use of drug patch testing to diagnosis maculopapular drug reactions secondary to various antibiotics is supported by several major studies. In a cohort study composed of 30 patients with a likely history or diagnosis of adverse drug reaction to antimicrobial medications, maculopapular eruptions produced a 46 % positive patch test rate [28]. A study by Romano et al. investigated 60 patients with reported maculopapular reactions following ingestion of aminopenicillins. Delayed hypersensitivity in 33/60 patients was confirmed by positive patch test and delayed intradermal patch test positivity [38]. A subsequent study by Romano evaluated 241 patients, 173 of which reported maculopapular rash following ingestion of aminopenicillins. Of these subjects, 90 patients had a positive patch test attributed to aminopenicillins [39]. A different study used diagnostic patch testing in 30 patients who had developed maculopapular exanthemas likely induced by clindamycin. Patch tests were performed with clindamycin 10 % in petrolatum; only 9/30 had a positive patch test. However, 0/50 control patients patch tested with clindamycin produced a positive patch test. Although sensitivity is low at 30 %, the patch tests in this clinical series were highly specific [40]. In study focusing on pristinamycin and adverse drug reactions, 12 of the 18 patients with a history of maculopapular drug reactions had a positive patch test [41]. Another study included a group of 21 patients with history of cutaneous adverse drug reactions, 16 of which had experienced maculopapular eruptions. Of the 16 patients, 8 had positive DPTs, 4 to ciprofloxacin, 2 to diclofenac, and 1 to ampicillin and carbamazepine [1]. A case report of a 45-year-old woman who developed pruritic generalized morbilliform reaction while on vancomycin, meropenem, and piperacillin-tazobactam used drug patch testing to test possible casual medications. Possible offending medications mixed in 10 % petroleum and standard screening trays were used for drug patch testing. The DPT of meropenem revealed strong positive reaction at early and delayed time points [42]. Another case report described the case of a 70-year-old woman with morbilliform rash following ingestion of prednisone, hydroxyzine, and cetirizine. Patch tests were negative for all corticosteroids tested, but the

antihistamine patch tests demonstrated positivity for hydroxyzine, demonstrating the utility of DPTs in that setting [43]. Additional case reports have described positive patch testing to hydroxyzine, as well as vancomycin [44, 45].

Stevens-Johnson syndrome/toxic epidermal necrolysis

The mechanism of SJS/TEN involves keratinocyte death caused by granulysin released by cytotoxic T cells and NK cells. In the Barbaud multicenter study, patch testing in patients with SJS/TEN do not seem as useful as compared to patch testing with other skin reactions. Only 4/17 DPTs produced a positive result [3]. Another older study showed 2/22 patients had a positive test, representing low sensitivity. However, there were no false positives, thus supporting a high specificity [9]. In the Ohtoshi cohort of 444 patients undergoing DPTs, there was a positive patch test rate of 14.3 % in SJS/TEN, but the results were not broken down into individual drugs that induced the reaction [19•]. When specifically examining carbamazepine induced SJS/TEN, a different study found positive patch test reactions to carbamazepine diluted to 30 % in 10/16 patients [22•]. In addition to these large studies, a case series has described three cases in which the causal agent of SJS/TEN was identified by drug patch testing. One patient had patch testing with procaine benzylpenicillin and ceftriaxone each at 5 % in petrolatum according to the guidelines stated by Barbaud's methodology [3] and patch tests with procaine benzylpenicillin were the only positive. In another case, diagnostic patch testing following SJS/TEN with ibuprofen were performed following Brockow et al. guidelines [4] and yielded a positive result. Finally a patient who developed SJS/TEN over a 3 week period under went drug patch testing 10 months following the reaction with carbamazepine, paracetamol, and ceftriaxone. The carbamazepine patch test was read as positive. This series concluded that drug patch testing was useful in determining causal agent [46].

Risk of systemic reactivation

Generally, the risk of systemic flare reactions following drug patch testing is considered low [8]. In a large multicenter study, systemic reactions following DPT were rare. Of the 45 patients diagnosed with AGEP, there was only one documented systemic reaction following DPT, occurring with pristamycin. In the same study, of the 72 and 17 cases of DRESS and SJS/TEN, respectively, there were no reported systemic reactions to DPT, although this remains a possible and potentially serious risk when performing DPT to determine the cause of DRESS and SJS/TEN [8]. In addition to the multicenter study, systemic relapse of AGEP following DPT with acetaminophen and paracetamol have been reported [47, 17]. Adverse cutaneous reactions to DPT have also been documented with carbamazepine and pseudoephedrine [47]. Although uncommon in the general population, chronic immunosuppression or immune dysregulation may increase the risk of systemic reactions to DPT; systemic relapse

has been documented predominately in patients who are infected with HIV/AIDs [48, 49].

Summary: results vary depending on the suspected drug reaction

The diagnostic value of drug patch testing has variable support based on published literature, but may be valuable in certain clinical scenarios with specific drugs that are highly likely to induce the specific type of reaction suspected. Of note, there is a lack of standardization in data collection, methodology and reporting of results, which could contribute to this variation. In addition, patch testing has been employed by some clinicians in cutaneous reactions mediated by mechanisms other than type IV delayed hypersensitivity. However, we believe that the mechanism of the drug reaction should be considered before using DPTs as a diagnostic test.

Compliance with Ethical Standards

Conflict of Interest
Kerrie Grunnet and Dr. Jake Turrentine 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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This study supports the use of drug patch testing as a diagnostic test for carbamazepine induced SJS/TEN and DRESS.

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