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**Skin testing approaches for immediate and delayed hypersensitivity reactions**

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**Summary**

In evaluating adverse drug reactions (ADRs), patch tests (PTs), skin prick tests (SPTs) and intradermal test (IDTs), are useful tools for identifying responsible drugs and finding safe alternatives. Their diagnostic value depends on the clinical features of the ADR and on the drug tested. PTs have a good sensitivity in assessing acute generalized exanthematous pustulosis and drug rash with eosinophilia and systemic symptoms, while their sensitivity is lower in maculopapular exanthema and toxic epidermal necrolysis. SPTs done with all drugs except opiates, are used for immediate hypersensitivity reactions. IDTs are performed by injecting 0.02 mL of the appropriately diluted suspected drug to evaluate immediate (with immediate readings) and delayed hypersensitivity reactions (with delayed readings). IDTs appears sensitive for immediate hypersensitivity reactions to beta-lactam antibiotics, iodinated contrast media, heparins, general anesthetics, and platinum salts. A negative ST does not exclude the responsibility of a drug in the occurrence of an ADR.

**Key words:** Diagnosis, delayed hypersensitivity, drugs, immediate hypersensitivity, intradermal tests, patch tests, prick tests, provocation tests, skin tests.

**Key Points:**

- Drug patch tests are well tolerated and have a good sensitivity in assessing acute generalized exanthematous pustulosis and drug rash with eosinophilia and systemic symptoms.
- SPTs are used for immediate hypersensitivity reactions and can be done with all drugs except opiates.
- IDTs are performed by injecting 0.02 mL of the appropriately diluted suspected drug to evaluate immediate (with immediate readings) and delayed hypersensitivity reactions (with delayed readings).
- For IDTs, appropriate dilutions - summarized in this paper- have to be respected in order to avoid irritant false positive reactions.
- A negative drug skin test does not exclude the responsibility of a drug in the occurrence of an ADR.

1 Patch tests (PTs) and skin tests (STs), namely skin prick tests (SPTs) and intradermal  
2 tests (IDTs), are useful tools for diagnosing drug hypersensitivity. They can be used to  
3 demonstrate the responsibility of a drug in the occurrence of an adverse drug reaction (ADR),  
4 as well as to assess cross-reactivity among drugs and find safe alternatives.

5 In performing these tests, however, there is a lack of standardized methodological approaches  
6 and particularly inconsistency with regards to the drug concentrations (1), which make  
7 comparisons between centers difficult. Moreover, there are differences between Europe and  
8 North America in the approach to the diagnosis of drug hypersensitivity reactions (2).

9 In this article, we considered international guidelines and relevant reviews (3-5),  
10 especially more recent ones (6,7), summarizing the data concerning the diagnostic value of  
11 both STs and PTs and providing information for their adequate indication and correct  
12 performance. In any case, the reference standard to confirm or exclude drug hypersensitivity  
13 is the drug provocation test (DPT), which consists in the controlled administration of a  
14 therapeutic dose of the suspected drug (6,8,9).

15 In non-severe ADRs, negative STs and/or PTs can be followed by an ingestion challenge or  
16 DPTs. There is a broad consensus on the indication of direct DPTs (i.e., not preceded by skin  
17 testing) in children with benign nonimmediate) reactions to beta-lactam antibiotics (BLs),  
18 especially in those with mild maculopapular exanthema (MPE) (10-14). Direct DPTs with  
19 BLs were also carried out in adults assessed as low risk for true BL allergy (13,15). However,  
20 this approach was not recommended in a recent review on STs (7) because it was evaluated in  
21 a limited number of patients and the indication for direct DPTs did not agree with that of the  
22 European Academy of Allergy and Clinical Immunology (EAACI) guidelines on the  
23 diagnosis of BL allergy (12). In the latter, only adults with palmar exfoliative exanthema can  
24 be candidates for direct DPTs. Regarding immediate reactions (i.e., occurring within 1 to 6  
25 hours after the last administered dose) (16) to BLs, there is no consensus on which subjects  
26 reporting such non-anaphylactic reactions are low risk. In this connection, recently, Sabato *et*  
27 *al.* (7) demonstrated that urticarial reactions to BLs that appear within one 1 hour after the 1<sup>st</sup>  
28 dose and subside within 1 day (i.e., meeting the “1-1-1” criterion) are highly predictive of  
29 positive allergy testing.

30  
31 In this paper, we mainly referred to a recent review (7) on STs and PTs in the work-up of  
32 cutaneous adverse drug reactions (CADRs).

33 Regarding the timing of their performance, in general, it is recommended to carry out  
34 STs and PTs at least 4 weeks and within one year after the ADR (3,4). In drug reaction with

1 systemic symptoms (DRESS), they must be done at least 6 months after the disappearance of  
2 the CADR and in the absence of high virus replication (18). Note that IgE-mediated  
3 hypersensitivity to BLs can wane over time (19). Some studies (20,21) followed patients with  
4 such hypersensitivity prospectively over 5 years and found that more than 60% of the  
5 participants who completed the studies and were initially skin test positive reverted to skin  
6 test negative with the implicated drug. Consequently, to avoid false-negative results, it is  
7 crucial to evaluate these subjects within a few months (22). On the other hand, T-cell-  
8 mediated hypersensitivity to antibiotics, including BLs, seems to be a long-lasting condition  
9 (23).

10 Some drugs or ultraviolet (UV) exposure can diminish the skin reactivity to drug STs. In  
11 immediate hypersensitivity reactions (IHRs), the use of beta-blockers is considered as a  
12 relative contraindication to skin testing. However, a study by Fung *et al.* (24) demonstrated  
13 the safety of administering SPTs to patients on beta-blocker treatment.

14 Topical corticosteroids should be stopped the week before on the site of any drug ST (3,4,7).  
15 Systemic corticosteroids have no inhibitory impact on SPTs, but have to be stopped one  
16 month before PTs or IDTs (25). Immunosuppressive drugs can affect the skin reactivity for  
17 any drug ST and should be stopped one month before testing if possible. Ultraviolet exposure  
18 should be avoided up to 4 weeks before STs and PTs.

19 In IHRs, antihistamines should be stopped 4 days (7 days for loratadine and desloratadine and  
20 tricyclic antidepressants with antihistaminic activity) before STs, but they have no impact on  
21 PT results (3,4,7). Concerning psychotropic drugs, imipramine and phenothiazines that have  
22 antihistaminic activity, but not escitalopram, fluoxetine, sertraline (25), can diminish skin  
23 reactivity to SPTs (26).

24

## 25 **DRUG PATCH TESTS**

26 PTs reproduce a delayed hypersensitivity reaction (DHR). PTs are applied to the upper back  
27 on unaffected and untreated skin, using IQ chambers (Chemotechnique, Vellinge, Sweden) or  
28 an equivalent fixed with a ‘‘hypoallergic’’ tape. They are left for 2 days, then read on day 2  
29 (30 minutes after removing the test material) and on day 4 or 5, and until after one week for  
30 those with corticosteroids. Reading result’s criteria are identical to those used for contact  
31 allergy (i.e., negative, irritant, + to ++++) (27). At least 10 negative controls are necessary to  
32 assess the specificity of a positive PT. Negative controls have been published for PTs with  
33 many drugs (7,28). PTs are particularly useful for evaluating DHRs to noninjectable drugs

1 like most anticonvulsants and non-vitamin K antagonist oral anticoagulants (29,30). However,  
2 only a limited number of molecules marketed by Chemotechnique (Vellinge, Sweden) or  
3 SmartPractice Canada are available as ready-to-use material, in which most drugs either the  
4 trade or reagent grade product are diluted at 10% in petrolatum. In most cases, it is necessary  
5 to prepare the test material by diluting the drugs in their marketed form provided by the  
6 patients themselves. As the stability of PT material has not been validated or established for  
7 most drugs, it should be prepared just before testing. PTs with the drug in its commercially  
8 available oral form can be prepared by diluting it at 30% (3) or 20% (4) in petrolatum. Ideally,  
9 a concentration of 10% of the active ingredient should be obtained. Brajon *et al.* (28) showed  
10 that the exact amount of the active ingredient in the PT material prepared by diluting  
11 commercial forms of the drugs concerned at 30% in petrolatum varied widely and 25% of that  
12 material had an active ingredient's concentration of less than 2%. From a practical point of  
13 view, since it is impossible to obtain a 10% active ingredient's concentration for each drug  
14 tested, we recommend that studies using PTs with drugs provide the exact concentration of  
15 active ingredient, so that the results obtained by different centers can be compared (28).

16 When the active ingredient is in pure form (e.g., lyophilized powder), it is recommended to  
17 dilute it at 10% in petrolatum (3).

18 Some drugs, such as captopril (at 1% in pet.), celecoxib (if tested >10% in pet.), chloroquine  
19 (at 30% in pet.), misoprostol (if tested > 1% in pet.), and sodium valproate (at 1% in pet.),  
20 have been reported as irritant (7). Some centers have pharmacy services that dilute drugs for  
21 patch testing. Assier *et al.* (31) demonstrated that material prepared by physicians led to  
22 results equivalent to those obtained with the ready-to-use products commercialized by  
23 Chemotechnique.

24 A control PT has to be done with the vehicle (e.g., petrolatum, alcohol) used to dilute the drug  
25 for the preparation of the PT material.

26

## 27 **DRUG SKIN PRICK TESTS**

28

29 SPTs can be done with any form of commercialized drug, usually, in undiluted form: pills  
30 reduced to very fine powder, capsule contents, liquid, or injectable solutions (1). In SPTs, a  
31 small drop of reagent is applied on volar forearm skin, and a standardized 1-mm-tipped lancet  
32 (pricker) is passed through the drop and perpendicularly inserted into the skin. (3,4,7,26).  
33 Reactions to SPTs are considered positive when the diameter of the wheal is at least 3 mm  
34 greater than that of the negative control and is surrounded by erythema, 20 minutes after the

1 prick. A positive control is done with histamine at 10 mg/mL. As a negative control, normal  
2 saline and/or any other solvent employed to dilute are used. SPTs can be performed with all  
3 drugs except opiates. If there is a global shortage of a drug (e.g., biologicals, COVID 19  
4 vaccines), it could be possible to perform a prick-to-prick test by dipping the lancet in the  
5 drug solution residual of the vials already used and then carrying out the skin puncture with it.  
6 Non-specific degranulation is observed in SPTs with certain antibiotics or anesthetic drugs at  
7 the usual concentrations. The highest nonirritating concentrations for SPTs are reported in  
8 Table 2. SPTs are useful for evaluating IHRs. In effect, although they have a sensitivity of  
9 6.9%, they have a very good specificity (98.8%) and a good negative predictive value (85.7%)  
10 (32).

11 Seldom late positive responses to SPTs have been reported in MPE, DRESS, and acute  
12 generalized exanthematous pustulosis (AGEP) (7,18). A SPT causes a delayed positive  
13 reaction when there is erythema and infiltration at the puncture site after 1 or 2 days (3,4).

14 SPTs with additives can be done by diluting them as follows: polyethylene glycol (PEG) 3000  
15 at 50% water/volume, PEG 6000 at 50% water/volume, and polysorbate 80 at 20%  
16 water/volume (33).

17

## 18 **DRUG INTRADERMAL TESTS**

19 IDTs are performed and interpreted differently in drug allergy centers. Recently, a multi-  
20 center study standardized an IDT method that helped reduce variability, allowing for a more  
21 reliable comparison of results between physicians and centers (34). According to this study  
22 (34), the recommended volume to be injected intradermally on the volar forearm is 0.02 ml. It  
23 produces a small superficial bleb approximately 5 mm in diameter. For intradermal  
24 administrations, a tuberculin syringe is used, which contains only 0.02 ml of the reagent  
25 solution and has a flat-ended plunger.

26 The diameter of the injection papule (wheal) should be measured immediately after injection  
27 ( $W_i$ ) and then at 20 minutes ( $W_{20}$ ). At that time, the IDT is considered positive if the  
28 diameter of the measured wheal ( $W_{20}$ ) is greater than or equal to the diameter of the  $W_i + 3$   
29 mm and if there is surrounding erythema that has also to be measured.

30 In subjects with DHRs, IDTs can be positive on delayed readings (e.g., after 1-3 days). Any  
31 late responses to IDT should be documented by the diameter of the erythema and the  
32 infiltration, as well as a morphological description. Patients are advised to return to show any  
33 positive responses appearing within 1 week after IDT, as well as to take pictures of positive or  
34 doubtful IDTs (12).

1 For IDTs, sterile injectable solutions are obligatory. In most cases, dilutions of reagents are  
2 done in normal saline. Performing a positive control with histamine at 1 mg/mL is not  
3 mandatory if a positive control SPT is performed. As a negative control, normal saline and/or  
4 any other solvent employed to dilute are used.

5 The initial dilution of the IDT reagents depends on the severity of the index reaction. In IHRs,  
6 IDTs should be performed after ensuring the negativity of SPTs. As in the diagnosis of IHRs  
7 to BLs (12), the suggested sequence of STs is as follows: (a) SPT (1/10 and the highest  
8 nonirritating concentrations) at intervals of 20 minutes, and if SPTs are negative (b) IDTs  
9 (1/100 of the highest nonirritating concentration, 1/10, and the highest nonirritating  
10 concentration) at intervals of 20 minutes. The procedure is stopped when a positive ST is  
11 found. In evaluating subjects who suffered severe anaphylactic reactions, starting  
12 concentrations of ST reagents should be at least  $10^{-3}$  of the highest nonirritating ones to avoid  
13 systemic reactions (2). In any case, it is advisable to perform IDTs in a hospital setting.

14 In low-risk patients, the work-up can be simplified by performing SPTs and IDTs directly  
15 with the highest nonirritating concentrations.

16 IDTs can induce false-positive results mainly due to irritating reagent concentrations. An  
17 EAACI position paper provided information on drug concentrations for skin testing (5). Table  
18 2 shows the highest nonirritating concentrations for drug prick and intradermal testing  
19 recommended in this and other EAACI position papers (5,12,35), as well as in practice  
20 parameters (36) and relevant reviews (7). Note that these concentrations were determined in  
21 studies where IDTs were performed using many different techniques. Moreover, these  
22 concentrations were defined only regarding IHRs (5). For IDTs, the highest nonirritating  
23 concentration of many drugs might not be similar to that which evokes a T-cell response after  
24 6 to 24 hours. This is particularly true for drugs such as fluoroquinolones and vancomycin,  
25 which intrinsically cause direct release of histamine and in which the sensitivity of IDTs using  
26 the lowest concentrations to avoid non-IgE-mediated mast-cell activation by IDTs is very  
27 poor ().

28 Regarding STs with the main drugs, amoxicillin, amoxicillin-clavulanic acid, and ampicillin  
29 can be tested at concentrations up to 20 mg/mL, like other semisynthetic penicillins,  
30 aztreonam, and all cephalosporins except cefepime (12,37,38). Macrolides (39,40), rifampicin  
31 (39) or quinolones (39,41) can be very irritant. IDTs with diluted solutions are of interest with  
32 glycopeptides (42). They could be of value in IHRs to proton pump inhibitors (43).

33 IHRs to iodinated contrast media (ICM) can be assessed by SPTs with undiluted products and  
34 by IDTs with dilutions 1:10 (36,44,45). In DHRs, PTs can be useful and delayed-reading



1 IDTs can be done with undiluted ICM (36). For STs with gadolinium derivatives, dilutions  
2 1:10 (46) or undiluted products (47) can be used.

3 Heparin and heparinoids can be tested diluted 1:10 or undiluted (48). Nevertheless, STs are  
4 contraindicated in subjects with an index reaction of necrosis at the site of heparin injection.  
5 As the positive reaction is often delayed, readings should also be performed after 72 hours or  
6 later.

7 Corticosteroids can be tested diluted 1:10 (49-51). STs with corticosteroids at high  
8 concentrations, mainly with those with long-lasting effects, can induce skin atrophy (49).  
9 Allergy to excipients, mainly carboxymethylcellulose or polysorbate, should be considered  
10 and investigated. Carboxymethylcellulose can be tested by SPTs and IDTs at a concentration  
11 of 10 mcg/mL (52,53). Insulins are tested diluted at 1:10 (54). Immediate-reading IDTs with  
12 platinum salts at concentrations from 0.1 to 1 mg/mL, depending on the salt, are specific (55);  
13 however, a non-specific erythematous infiltration can occur at 24 hours with these IDTs.  
14 Therefore, their delayed readings do not appear to be specific, as published with carboplatin at  
15 1 mg/mL (56) and observed with oxaliplatin (7).

16 IDTs with biologicals and cytokines are of little use (57). For STs with anti-tumor necrosis  
17 factors, specificity thresholds have been reported at the following concentrations: infliximab  $\leq$   
18 2 mg/mL, adalimumab  $\leq$  50 mg mL, and etanercept  $\leq$  5 mg/mL (7). Some articles have  
19 reported studies in which IDTs were performed with rituximab (57,58) or tocilizumab  
20 (57,59,60). IDTs with interferons were thought to be non-specific, but they appear to be  
21 interesting, with good positive and negative predictive value (NPV) (61) in evaluating  
22 generalized exanthemas due to these molecules. The thresholds for the specificity of IDTs are  
23 reported in Table 2.

24 For IDTs with general anesthetics, the same method should be adopted. Some guidelines  
25 recommended an injection of 0.03 mL (62), others a volume of 0.03 mL to 0.05 mL (63) or  
26 0.02 mL to 0.05 mL (64), but a recent EAACI position paper recommended a volume of 0.02  
27 mL, as for other IDTs (35).

28 STs with some drugs are irritating and can induce false positive results. STs with vaccines are  
29 not standardized and their specificity is discussed. False positive results are frequent in  
30 delayed readings and should not be considered. In case of IHRs, SPTs or prick-to-prick tests  
31 with the undiluted vaccine and, when available, its excipients (e.g., gelatin, egg, PEG) can be  
32 done. However, IDTs with vaccines diluted 1:10 and even 1:100, mainly with influenzae  
33 vaccine, frequently induce irritative reactions (65). False positive results have also been

1 reported with IDTs performed with glatiramer acetate at a concentration of 200 mcg/mL, and  
2 in some cases at that of 20 mcg/mL. For STs with this molecule, the specificity threshold has  
3 not yet been determined (66). Finally, a recent practical guidance for the evaluation and  
4 management of drug hypersensitivity (6) provided information on STs with a huge number of  
5 drugs, including antivirals, antifungals, and antimalarials.

## 6 **NEGATIVE PREDICTIVE VALUE OF DRUG SKIN TESTS**

7 Since STs and DPTs are not standardized, it is difficult to compare the results regarding the  
8 NPV of STs across the literature. For BLs, the NPV of STs is around 90%, depending on the  
9 type of hypersensitivity and the method used for DPTs (12). For ICM, the NPV varies from  
10 80% to 97.3% (36).

## 11 **DRUG SKIN TESTS AND PATCH TESTS HAVE TO BE ADAPTED ACCORDING** 12 **TO THE CLINICAL FEATURES AND THE DRUG INVOLVED**

13 The diagnostic value of STs and PTs depends on the ADR clinical features and on the drug  
14 tested. STs are useful for identifying the responsible drug only in IgE- or T-cell-mediated  
15 reactions. They are not useful in some ADRs such as those to nonsteroidal anti-inflammatory  
16 drugs with a cross-reactivity pattern, bradykinin-induced angioedema due to angiotensin-  
17 converting enzyme inhibitors, and sartans, as well as reactions to dipeptidyl peptidase-4  
18 inhibitors, as such reactions are not caused by allergic hypersensitivity. Moreover, STs have  
19 no diagnostic value in drug-induced auto-immune diseases or pruritus.

20 In IHRs, as for BLs (12), STs have to be adapted to the risk profile of the patient. STs have  
21 been reported as useful with many drugs but mainly with BLs, ICM, gadoterate meglumine,  
22 general anesthetics, insulins, proton pump inhibitors, corticosteroids, and platinum salts. PTs  
23 are not recommended. In case of anaphylactic shock, PTs are absolutely contraindicated as  
24 they have a poor value in IHRs, but mainly because they can re-induce the shock.  
25 Anaphylactic shocks induced by PTs have been reported with BLs, neomycin, gentamicin,  
26 bacitracin, and diclofenac (7).

27 Regarding DHRs, recently, an international consensus on their diagnosis was reached (1) and  
28 its adapted conclusions are summarized in Table 1. Drug PTs have a rather low sensibility and  
29 are of value for evaluating MPE, systemic contact dermatitis, symmetric drug-related  
30 intertriginous and flexural exanthema, or flexural exanthema, eczematous reactions at  
31 injection sites, AGEP, DRESS, and Stevens-Johnson syndrome/toxic epidermal necrolysis

1 (SJS/TEN) (1,7). Many drugs have been reported to have positive results when evaluated by  
2 PTs, but PTs performed with allopurinol, salazopyrin, or paracetamol are mostly or ever  
3 negative (18,67).

4 In MPE, delayed-reading IDTs have the highest sensitivity. Delayed positive IDT results have  
5 been reported mainly with BLs, glycopeptides, heparins, ICM, and corticosteroids.

6 In fixed drug eruptions (FDEs), PTs are applied in duplicate on the back but also on the site of  
7 eruption (residual sometimes pigmented lesion; i.e., “*in situ* PTs”) and read at day 1 or 2  
8 (68,69). If *in situ* PTs are negative an *in situ* repeated open application test can be done (69).  
9 The preparation for the *in situ* PT is given to the patient and applied to a surface of 2 cm x 2  
10 cm, once a day for 1 week. In case of negative STs, a DPT can be done in benign FDE, but it  
11 is absolutely contraindicated in generalized bullous FDE.

12 In investigating a drug-induced photosensitivity, both PTs and photo patch tests with the  
13 suspected drug have to be performed. It is recommended to test with a 1% concentration of an  
14 active ingredient, but only at 0.1% for phenothiazines (70). The irradiation for drug photo  
15 patch tests is performed at Day 2 with a 5 Joules/cm<sup>2</sup> UVA (70). A non-irradiated control PT  
16 is also applied. The reading is done two days after the irradiation. Criteria for positive results  
17 are identical to those used for PTs with haptens (i.e., negative, irritant, + to +++) (27).

18 Regarding severe DHRs, such as SJS/TEN, DRESS, AGEP, and bullous exanthemas, as  
19 stated in some European guidelines (3,4,12,71,72), PTs with the suspected drugs should be  
20 used as the first line of investigation (i.e., prior to STs). In the case of positive responses to  
21 PTs, STs should be avoided, whereas in the case of negative results, IDTs might be performed,  
22 starting with a lower concentration of the drug concerned (e.g., 1 mg/mL for semisynthetic  
23 penicillins). In some studies (Barbaud 2013, Romano 2016), this approach proved to be safe  
24 and useful not only for identifying the responsible drugs (18), but also for detecting any cross-  
25 reactivity and finding safe alternatives (73). Specifically, in the 72 patients with DRESS, 45  
26 with AGEP, and 17 with SJS/TEN of a multicenter study (18), PT sensitivity was 64%, 58%,  
27 and 24%, respectively. Of the 11 patients with AGEP and 4 with DRESS associated with BLs  
28 who were negative to PTs, 4 and 3 were positive to delayed-reading IDTs, respectively.  
29 Nevertheless, the use of IDTs in evaluating severe DHRs to drugs remains controversial, even  
30 though recent studies on subjects with such reactions confirmed and emphasized their safety  
31 and usefulness, in particular, for exploring cross-reactivity and co-sensitization in DRESS  
32 (74-77).

1 For an alternative or suspected low-imputable drug, if irreplaceable and negative to STs, a  
2 graded DPT can be discussed by specialists involved in severe cutaneous ADRs (77).

3  
4 **IN CONCLUSION**, in order to compare the results from one center to another, it is  
5 time to consider standardizing drug skin testing methods. For PTs, is essential to report results  
6 with reference to the concentration of the active ingredient. For IDTs, the only way is to work  
7 on a known allergen dose and not on injection-wheal diameters. Therefore, a controlled  
8 volume injected in IDTs seems to be the best method. We always have to keep in mind that a  
9 negative ST does not exclude the responsibility of a drug in the occurrence of a CADR.

### 11 **Clinics Care Points**

12  
13 ° In case of positive drug skin tests, in order to ensure specific results, please give 10 negative  
14 control results from your experience or literature.

15 ° In non severe adverse reactions, drug skin tests have to be done before drug provocation  
16 tests, but can be avoided before provocation in children with non-severe delayed reactions or  
17 in adults with palmar exfoliative exanthema.

18  
19 ° Drug patch tests reproduce a delayed hypersensitivity reaction, use it for delayed cutaneous  
20 adverse drug reactions and not in case of anaphylaxis (not useful and able to reinduce an  
21 anaphylactic shock).

22 ° Drug patch tests are applied on the back, but in fixed drug eruption they also have to be  
23 applied in duplicate on the site of eruption (residual sometimes pigmented lesion; i.e., “in situ  
24 patch tests”)

25 ° In immediate hypersensitivity reactions, as for betalactam antibiotics, skin tests have to be  
26 adapted to the risk profile of the patient.

27 ° For IDTs, sterile injectable solutions are obligatory, do not use crushed pills even with  
28 filtration of the solution.

29 ° IDTs have to be done with a controlled volume of 0.02 mL, not based on a given diameter  
30 of the injection wheal (bleb).

31 ° A negative drug skin test does not exclude the responsibility of a drug in the occurrence of  
32 an adverse drug reaction.

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**Table 1: Use of Skin Prick Tests, Intradermal Tests, and/or Patch Tests in Immediate or Delayed Drug Reactions**

	Patch tests	Prick tests	IDT	Provocation tests
Urticaria/ angioedema, anaphylaxis	Not useful, can be dangerous	Useful (immediate reading)	Useful (immediate reading)	Adapted to the low- or high-risk profile of the patient (12)
Maculopapular exanthema	Useful	Limited value (DR)	Useful (DR)	After negative skin tests with delayed readings in low-risk subjects (12) NPV of 90%.
Generalized eczema (Contact reaction)	Useful	Limited value (DR)	Useful (DR)	After negative delayed skin test with delayed readings. NPV unknown
SDRIFE	Useful (positive in 36-82%)	Limited value (DR)	Useful (DR)	After negative skin tests with delayed readings. NPV unknown
Fixed drug eruption	Useful if applied on the area of eruption (68,69)	Not useful	Not useful	At full dose when patch tests or repeated application tests are negative. NPV unknown.
Generalized bullous fixed drug eruption	Maybe useful	Contraindicated	Contraindicated	Contraindicated
Acute generalized exanthematous pustulosis (AGEP)	Useful, sensitivity up to 58% (18)	Limited value (DR)	Potentially useful (DR)	Contraindicated with suspected drugs and cross-reactive ones
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Useful, sensitivity 32-64% depending on the tested drug (18,67) Advised 6 months after disappearance of DRESS	Limited value (DR)	Delayed reading at 24 hours (18,74)	Contraindicated with highly suspected drug and cross-reactive ones (1,77)
SJS/TEN	Low sensitivity (<30%)	Unknown value (DR)	Contraindicated with the suspected drugs	Contraindicated.
Photosensitivity	Photopatch tests with a 5 Joule/cm <sup>2</sup> UVA irradiation	No value	No value	No value without exposure to UV
Vasculitis	No value	No value	No value	Contraindicated

DR: Delayed reading (i.e., after 24 to 48 hours).

SDRIFE: Symmetrical drug-related intertriginous and flexural exanthema.

SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis.

*Data from Refs 1 and 7*

1 **Table 2:** Highest nonirritating concentrations recommended for drug prick and intradermal  
 2 testing [According to published literature, mainly from Brockow et al. (5), EAACI position  
 3 papers (12,35,36) and a recent update on drug skin tests (7)].

4

	Intradermal tests	Skin Prick Tests*
<b>ANTIBIOTICS</b>		
<b>Beta-lactams</b>		
Amoxicillin, ampicillin and other semisynthetic penicillins	20 mg/mL	
Aztreonam	2 to 20 mg/mL	
Benzylpenicilloyl-poly-L-lysine	$6 \times 10^{-5}$ mol/L	
Benzylpenicilloyl-octa-L-lysine	$8.64 \times 10^{-5}$ mol/L	
Sodium benzylpenilloate	$1.5 \times 10^{-3}$ mol/L	
Benzylpenicillin	10,000 IU/mL	
Cefepime	2 mg/mL	
Cephalosporins other than cefepime	20 mg/mL	
Clavulanic acid	20 mg/mL	
Imipenem-cilastatin	0.5 mg/mL – 0.5 mg/mL	
Ertapenem and meropenem	1 mg/mL	
<b>Quinolones</b>		
Ciprofloxacin	0.006 mg/mL	
Levofloxacin	0.025 mg/mL	
Ofloxacin	0.05 mg/mL	
Pefloxacin	no IDT	0.32 mg/mL
Rifampicin	2 mcg/mL	
<b>Macrolides</b>		
Azithromycin	0.01 mg/mL	
Clarithromycin	0.05 mg/mL	
Erythromycin	0.01 to 0.05 mg/mL	5 mg/mL
Rovamycin	37.5 U/mL	37,500 IU/mL
<b>Others</b>		
Clindamycin	15 mg/mL	
Cotrimoxazole	0.8 mg/mL	
Gentamycin	4 mg/mL	
Rifampicin	0.002 mg/mL	
Tobramycin	4 mg/mL	
Vancomycin	0.005 to 0.05 mg/mL	
<b>PERIOPERATIVE DRUGS</b>		
<b>Neuromuscular blocking agents</b>		
Atracurium	0.01 mg/mL	1 mg/mL
Cisatracurium	0.02 mg/mL	2 mg/mL
Mivacurium	0.002 mg/mL	0.2 mg/mL
Pancuronium	0.02 mg/mL	2 mg/mL
Rocuronium	0.05 mg/mL	10 mg/mL
Suxamethonium	0.1 mg/mL	10 mg/mL
Vecuronium	0.04 mg/mL	4 mg/mL
<b>Anesthetic agents</b>		

Etomidate	0.2 mg/mL	2 mg/mL
Ketamine	0.1 mg/mL	100 mg/mL
S-Ketamine	0.25 mg/mL	25 mg/mL <sup>¶</sup>
Midazolam	0.05 mg/mL	5 mg/mL
Propofol	1 mg/ml	10 mg/mL
Thiopental	2.5 mg/mL	25 mg/mL
<b>Reversal agents</b>		
Sugammadex	10 mg/mL	
<b>Opiates</b>		
Alfentanil	0.05 mg/mL	0.5 mg/mL
Fentanyl	0.0005 mg/mL	0.05 mg/mL
Morphine	0.005 mg/mL	1.0 mg/mL <sup>¶</sup>
Remifentanil	0.005 mg/mL	0.05 mg/mL
Sufentanil	0.0005 mg/mL	0.005 mg/mL
<b>Local anesthetics</b>		
Articaine	2 mg/mL	
Bupivacaine	0.25 mg/mL	
Chloroprocaine (ester derivative)	1 mg/mL	
Levobupivacaine	0.75 mg/mL	
Lidocaine	1 mg/mL	
Mepivacaine	2 mg/mL	
Prilocaine	2 mg/mL	
Ropivacaine	1 mg/mL	
<b>CHEMOTHERAPEUTIC DRUGS</b>		
Paclitaxel	0.03 mg/mL	
Docetaxel	0.1 mg/mL	
<b>Platinum salts</b>	1 mg/mL <sup>‡</sup>	
Carboplatin	1 mg/mL	
Cisplatin	0.1 mg/mL	
Cisplatin	1 mg/mL	
Oxaliplatin	0.5 mg/mL	
Oxaliplatin	1 mg/mL	
<b>CORTICOSTEROIDS</b>		
Betamethasone	0.4 mg/mL	
Cortivazol	2.5 mg/mL	
Dexamethasone	0.4 mg/mL	
Hydrocortisone	1 mg/mL	
Hydrocortisone hemisuccinate	5 mg/mL	
Triamcinolone	4 mg/mL	
Methylprednisolone	4 mg/mL	
Prednisolone	2.5 mg/mL	
<b>HEPARINS</b>	diluted 1:10	
<b>INSULINS</b>	diluted 1:10	
<b>CYTOKINES, BIOLOGICAL AGENTS</b>		
<b>Anti-TNF</b>		
Adalimumab	50 mg/mL	
Etanercept	5 mg / mL	

Infliximab	2 mg/mL	
Infliximab	10 mg/mL	
Omalizumab	1.25 mcg/mL	
Rituximab	10 mg/mL (7 negative controls)	
Tocilizumab	0.2 mg/mL or 20 mg/mL (10 negative controls) 1.62 mg/mL	
<b>Interferons</b>	undiluted	
<b>Nonsteroidal anti-inflammatory drugs (NSAIDs)</b>		
Diclofenac	2.5 mg/mL	
Ketoprofen	2 mg/mL	
Piroxicam	2 mg/mL	
Pyrazolones and other injectable NSAIDs	0.1 mg/mL	
<b>CONTRAST MEDIA</b>		
<b>Iodinated contrast media</b>	diluted 1:10 for immediate reactions, maybe undiluted for delayed reactions	
<b>Gadolinium derivatives</b>	diluted 1:10	
<b>PROTON PUMP INHIBITORS</b>		
Esomeprazole	0.4 or 4 mg/mL	
Omeprazole	0.4 or 4 mg/mL	
Pantoprazole	0.4 or 4 mg/mL.	
<b>MISCELLANEOUS DRUGS, EXCIPIENTS, DYES</b>		
Paracetamol/Acetaminophen	1 mg/mL	
Chlorhexidine	0.002 mg/mL (sterile uncolored alcohol-free solution)	
Fluorescein	diluted 1:10 (10 mg/mL in our experience)	
Carboxymethylcellulose	0.01 mg/mL	
Hydroxyethyl starch	6 mg/mL	
Methylene blue	0.1 mg/mL	
Patent blue	0.25 mg/mL	
<i>Polyethylene glycol (PEG)/Macrogol</i>		
PEG 300		undiluted
PEG 3000		50% water/volume
PEG 2000		50% water/volume
PEG 6000		50% water/volume
Polysorbate 80		20% water/volume

1

2 \*Highest nonirritating concentrations when undiluted drugs can be irritant.

3 †Possibly irritant.

4 ‡Can induce false positive results on delayed readings (56).