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Skin Testing Approaches for Immediate and Delayed Hypersensitivity Reactions

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► **To cite this version:**

Annick Barbaud, Antonino Romano. Skin Testing Approaches for Immediate and Delayed Hypersensitivity Reactions. *Immunology and Allergy Clinics of North America*, 2022, 42 (2), pp.307–322. 10.1016/j.iac.2022.01.003 . hal-03892133

HAL Id: hal-03892133

<https://hal.sorbonne-universite.fr/hal-03892133>

Submitted on 22 Jul 2024

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

4
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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 1st
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/cm² 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.

1 REFERENCES

- 2 1- Phillips EJ, Bigliardi P, Bircher AJ, Broyles A, Chang YS, Chung WH, Lehloenya R,
3 Mockenhaupt M, Peter J, Pirmohamed M, Roujeau JC, Shear NH, Tanno LK, Trubiano J,
4 Valluzzi R, Barbaud A. Controversies in drug allergy: Testing for delayed reactions. *J Allergy*
5 *Clin Immunol*. 2019;143:66-73.
- 6 2- Torres MJ, Romano A, Celik G, Demoly P, Khan DA, Macy E, Park M, Blumenthal K,
7 Aberer W, Castells M, Barbaud A, Mayorga C, Bonadonna P. Approach to the diagnosis of
8 drug hypersensitivity reactions: similarities and differences between Europe and North
9 America. *Clin Transl Allergy*. 2017 Mar 13;7:7.
- 10 3- Barbaud A, Gonçalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests with
11 drugs in the investigation of cutaneous adverse drug reactions. *Contact Dermatitis*.
12 2001;45:321-8.
- 13 4- Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations
14 for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy*. 2002;57:45-51.
- 15 5- Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB et al.
16 ENDA/EAACI Drug Allergy Interest Group. Skin test concentrations for systemically
17 administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy*.
18 2013;68:702-12.
- 19 6-Broyles AD, Banerji A, Barmettler S, Biggs CM, Blumenthal K, Brennan PJ, et al. Practical
20 Guidance for the Evaluation and Management of Drug Hypersensitivity: Specific Drugs. *J*
21 *Allergy Clin Immunol Pract*. 2020;8(9S):S16-S116.
- 22 7- Barbaud A, Castagna J, Soria A. Skin tests in the work-up of cutaneous adverse drug
23 reactions - A review and update. *Contact Dermatitis*. in press.
- 24 8- Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, Brockow K, Pichler
25 WJ, Demoly P; European Network for Drug Allergy (ENDA); EAACI interest group on drug
26 hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions:
27 general considerations. *Allergy*. 2003;58:854-63.
- 28 9-Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and
29 Immunology; American College of Allergy, Asthma and Immunology; Joint Council of
30 Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy*
31 *Asthma Immunol*. 2010;105:259-73.
- 32 10-Banks TA, Tucker M, Macy E. Evaluating Penicillin Allergies Without Skin Testing. *Curr*
33 *Allergy Asthma Rep*. 2019;19:27.
- 34 11-Khan DA. Proactive management of penicillin and other antibiotic allergies. *Allergy*
35 *Asthma Proc*. 2020;41:82-9.
- 36 12- Romano A, Atanaskovic-Markovic M, Barbaud A, Bircher AJ, Brockow K, Caubet JC,
37 Celik G, Cernadas J, Chiriac AM, Demoly P, Garvey LH, Mayorga C, Nakonechna A,
38 Whitaker P, Torres MJ. Towards a more precise diagnosis of hypersensitivity to beta-lactams
39 - an EAACI position paper. *Allergy*. 2020;75:1300-15.
- 40 13-Cooper L, Harbour J, Sneddon J, Seaton RA. Safety and efficacy of de-labelling penicillin
41 allergy in adults using direct oral challenge: a systematic review. *JAC Antimicrob Resist*.
42 2021;3:123.
- 43 14- Iammatteo M, Lezmi G, Confino-Cohen R, Tucker M, Ben-Shoshan M, Caubet JC. Direct
44 Challenges for the Evaluation of Beta-Lactam Allergy: Evidence and Conditions for Not
45 Performing Skin Testing. *J Allergy Clin Immunol Pract*. 2021;9:2947-56.
- 46 15- Ramsey A, Mustafa SS, Holly AM, Staicu ML. Direct Challenges to Penicillin-Based
47 Antibiotics in the Inpatient Setting. *J Allergy Clin Immunol Pract*. 2020;8:2294-301.
- 48 16-Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, Khan
49 DA, Lang DM, Park HS, Pichler W, Sanchez-Borges M, Shiohara T, Thong BY. International
50 Consensus on drug allergy. *Allergy*. 2014;69:420-37.

- 1 17-Sabato V, Gaeta F, Valluzzi RL, Van Gasse A, Ebo DG, Romano A. Urticaria: The 1-1-1
2 Criterion for Optimized Risk Stratification in β -Lactam Allergy Delabeling. *J Allergy Clin*
3 *Immunol Pract.* 2021;9:3697-704.
- 4 18- Barbaud A, Collet E, Milpied B, Assier H, Staumont D, Avenel-Audran M et al. A
5 multicenter study to determine the value and safety of drug patch tests for the three main
6 classes of severe cutaneous adverse drug reactions. *Br J Dermatol.* 2013;168:555-62.
- 7 19-Castells M, Khan DA, Phillips EJ. Penicillin Allergy. *N Engl J Med.* 2019;381:2338-51
- 8 20-Blanca M, Torres MJ, García JJ, Romano A, Mayorga C, de Ramon E, Vega JM, Miranda
9 A, Juarez C. Natural evolution of skin test sensitivity in patients allergic to beta-lactam
10 antibiotics. *J Allergy Clin Immunol.* 1999;103(5 Pt1):918-24.
- 11 21-Romano A, Gaeta F, Valluzzi RL, Zaffiro A, Caruso C, Quaratino D. Natural evolution of
12 skin-test sensitivity in patients with IgE-mediated hypersensitivity to cephalosporins. *Allergy.*
13 2014;69:806-9.
- 14 22-Romano A, Valluzzi RL, Caruso C, Zaffiro A, Quaratino D, Gaeta F. Evaluating
15 Immediate Reactions to Cephalosporins: Time Is of the Essence. *J Allergy Clin Immunol*
16 *Pract.* 2021;9:1648-57.e1.
- 17 23- Pinho A, Marta A, Coutinho I, Gonçalo M. Long-term reproducibility of positive patch
18 test reactions in patients with non-immediate cutaneous adverse drug reactions to antibiotics.
19 *Contact Dermatitis.* 2017;76:204-9.
- 20 24- Fung IN, Kim HL. Skin prick testing in patients using beta-blockers: a retrospective
21 analysis. *Allergy Asthma Clin Immunol.* 2010;6:2.
- 22 25- Isik SR, Celikel S, Karakaya G, Ulug B, Kalyoncu AF. The effects of antidepressants on
23 the results of skin prick tests used in the diagnosis of allergic diseases. *Int Arch Allergy*
24 *Immunol.* 2011;154:63-8.
- 25 26- Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG et al.
26 Practical guide to skin prick tests in allergy to aeroallergens. *Allergy.* 2012;67:18-24.
- 27 27- Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M et al. European
28 Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on
29 best practice. *Contact Dermatitis.* 2015;73:195-221.
- 30 28- Brajon D, Menetre S, Waton J, Poreaux C, Barbaud A. Non-irritant concentrations and
31 amounts of active ingredient in drug patch tests. *Contact Dermatitis.* 2014;71:170-5.
- 32 29-Romano A, Viola M, Gaeta F, Rumi G, Maggioletti M. Patch testing in non-immediate
33 drug eruptions. *Allergy Asthma Clin Immunol.* 2008;4:66-74.
- 34 30-Cortellini G, Carli G, Franceschini L, Lippolis D, Farsi A, Romano A. Evaluating
35 nonimmediate cutaneous reactions to non-vitamin K antagonist oral anticoagulants via patch
36 testing. *J Allergy Clin Immunol Pract.* 2020;8:3190-3.
- 37 31- Assier H, Valeyrie-Allanore L, Gener G, Verlinde Carvalh M, Chosidow O, Wolkenstein
38 P. Patch testing in non-immediate cutaneous adverse drug reactions: value of extemporaneous
39 patch tests. *Contact Dermatitis.* 2017;77:297-302.
- 40 32- Indradat S, Veskitkul J, Pacharn P, Jirapongsananuruk O, Visitsunthorn N. Indradat S.
41 Provocation proven drug allergy in Thai children with adverse drug reactions. *Asian Pac J*
42 *Allergy Immunol.* 2016 ;34:59-64.
- 43 33- Bruusgaard-Mouritsen MA, Jensen BM, Poulsen LK, Duus Johansen J, Garvey LH.
44 Optimizing investigation of suspected allergy to polyethylene glycols. *J Allergy Clin Immunol.*
45 in press.
- 46 34- Barbaud A, Weinborn M, Garvey LH, Testi S, Kvedariene V, Bavbek S, Mosbech H,
47 Gomes E, Aberer W, Elberink HNGO, Torres MJ, Ponvert C, Ayav C, Gooi J, Brockow K.
48 Intradermal Tests With Drugs: An Approach to Standardization. *Front Med (Lausanne).*
49 2020;7:156.
- 50

- 1 35- Garvey LH, Ebo DG, Mertes PM, Dewachter P, Garcez T, Kopac P, Laguna JJ, Chiriac
2 AM, Terreehorst I, Voltolini S, Scherer K. An EAACI position paper on the investigation of
3 perioperative immediate hypersensitivity reactions. *Allergy*. 2019;74:1872-84.
- 4 36- Torres MJ, Trautmann A, Böhm I, Scherer K, Barbaud A, Bavbek S, Bonadonna P,
5 Cernadas JR, Chiriac AM, Gaeta F, Gimenez-Arnau AM, Kang HR, Moreno E, Brockow K.
6 Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity.
7 *Allergy*. 2021;76:1325-39.
- 8 37-van der Poorten MM, Van Gasse AL, Hagendorens MM, Faber MA, De Puyseleir L, Elst
9 J, Mertens CM, Romano A, Ebo DG, Sabato V. Nonirritating skin test concentrations for
10 ceftazidime and aztreonam in patients with a documented beta-lactam allergy. *J Allergy Clin
11 Immunol Pract*. 2021;9:585-8.e1.
- 12 38-van der Poorten MM, Hagendorens MM, Faber MA, De Puyseleir L, Elst J, Mertens CM,
13 Romano A, Ebo DG, Sabato V. Nonirritant concentrations and performance of ceftaroline
14 skin tests in patients with an immediate β -lactam hypersensitivity. *J Allergy Clin Immunol
15 Pract*. 2021;9:4486-8.e2.
- 16 39- Brož P, Harr T, Hecking C, Grize L, Scherer K, Jaeger KA, Bircher AJ. Nonirritant
17 intradermal skin test concentrations of ciprofloxacin, clarithromycin, and rifampicin. *Allergy*.
18 2012;67:647-52.
- 19 40- Kuyucu S, Mori F, Atanaskovic-Markovic M, Caubet JC, Terreehorst I, Gomes E et al.
20 Hypersensitivity reactions to non-betalactam antibiotics in children: an extensive review.
21 *Pediatr Allergy Immunol*. 2014;25:534-43.
- 22 41- Lobera T, Audicana MT, Alarcón E, Longo N, Navarro B, Muñoz D. Allergy to
23 quinolones: low cross-reactivity to levofloxacin. *J Invest Allergol Clin Immunol*.
24 2010;20:607-11.
- 25 42- Perrin-Lamarre A, Petitpain N, Trechot P, Cuny JF, Schmutz JL, Barbaud A. Toxidermies
26 aux glycopeptides. Résultats du bilan immuno-allergologique dans une série de huit cas. *Ann
27 Dermatol Venereol*. 2010;137:101-5.
- 28 43- Bonadonna P, Lombardo C, Bortolami O, Bircher A, Scherer K, Barbaud A et al.
29 Hypersensitivity to proton pump inhibitors: Diagnostic accuracy of skin tests compared to
30 oral provocation test. *J Allergy Clin Immunol*. 2012;130:547-9.
- 31 44- Brockow K, Romano A, Aberer W, Bircher AJ, Barbaud A, Bonadonna P et al. Skin
32 testing in patients with hypersensitivity reactions to iodinated contrast media - a European
33 multicenter study. *Allergy*. 2009;64:234-41.
- 34 45- Lerondeau B, Trechot P, Waton J, Poreaux C, Luc A, Schmutz JL, Paris C, Barbaud A.
35 Analysis of cross-reactivity among radiocontrast media in 97 hypersensitivity reactions. *J
36 Allergy Clin Immunol*. 2016;137:633-5.
- 37 46- Rosado Ingelmo A, Doña Diaz I, Cabañas Moreno R, Moya Quesada MC, García-Avilés
38 C, García Nuñez I, Martínez Tadeo JI, Mielgo Ballesteros R, Ortega-Rodríguez N, Padiá
39 Vilchez MA, Sánchez-Morillas L, Vila Albelda C, Moreno Rodilla E, Torres Jaén MJ.
40 Clinical Practice Guidelines for Diagnosis and Management of Hypersensitivity Reactions to
41 Contrast Media. *J Invest Allergol Clin Immunol*. 2016;26:144-55.
- 42 47-Clement O, Dewachter P, Mouton-Faivre C, Nevoret C, Guilloux L, Bloch Morot E, et al.
43 Immediate Hypersensitivity to Contrast Agents: The French 5-year CIRTACI Study.
44 *EClinicalMedicine*. 2018;1:51 - 61.
- 45 48- Scherer K, Tsakiris DA, Bircher AJ. Hypersensitivity reactions to anticoagulant drugs.
46 *Curr Pharm Des*. 2008;14:2863-73.
- 47 49- Soria A, Baeck M, Goossens A, Marot L, Duveille V, Derouaux AS, et al. Patch, prick or
48 intradermal tests to detect delayed hypersensitivity to corticosteroids? *Contact Dermatitis*.
49 2011;64:313-24.

- 1 50- Patel A, Bahna SL. Immediate hypersensitivity reactions to corticosteroids. *Ann Allergy*
2 *Asthma Immunol.* 2015;115:178-82.
- 3 51- Barbaud A, Waton J. Systemic Allergy to Corticosteroids: Clinical Features and Cross
4 Reactivity. *Curr Pharm Des.* 2016;22:6825-31.
- 5 52- Dumond P, Franck P, Morisset M, Sainte Laudy J, Kanny G, Moneret-Vautrin DA. Pre-
6 lethal anaphylaxis to carboxymethylcellulose confirmed by identification of specific IgE--
7 review of the literature. *Eur Ann Allergy Clin Immunol.* 2009;41:171-6.
- 8 53- Barbaud A. Place of excipients in systemic drug allergy. *Immunol Allergy Clin North Am.*
9 2014;34:671-9.
- 10 54- Shuster S, Borici-Mazi R, Awad S, Houlden RL. Rapid desensitization with intravenous
11 insulin in a patient with diabetic ketoacidosis and insulin allergy. *AACE Clin Case Rep.*
12 2020 ;6:e147-e150.
- 13 55- Pasteur J, Favier L, Pernot C, Guerriaud M, Bernigaud C, Lepage C, Jouve JL, Isambert N,
14 Collet E. Low Cross-Reactivity Between Cisplatin and Other Platinum Salts. *J Allergy Clin*
15 *Immunol Pract.* 2019;7:1894-900.
- 16 56- Guyot-Caquelin P, Granel F, Kaminsky MC, Trechot P, Schmutz JL, Barbaud A. False
17 positive results can occur on delayed reading of intradermal tests with cisplatin. *J Allergy Clin*
18 *Immunol.* 2010;125:1410-1.
- 19 57- Bavbek S, Pagani M, Alvarez-Cuesta E, Castells M, Dursun AB, Hamadi S, Madrigal-
20 Burgaleta R, Sanchez-Sanchez S, Vultaggio A. Hypersensitivity reactions to biologicals: An
21 EAACI position paper. *Allergy.* in press.
- 22 58- Novelli S, Soto L, Caballero A, Moreno ME, Lara MJ, Bayo D, Quintas A, Jimeno P,
23 Zamora MI, Bigorra T, Sierra J, Briones J. Assessment of Confirmed Clinical
24 Hypersensitivity to Rituximab in Patients Affected with B-Cell Neoplasia. *Adv Hematol.* 2020
25 Jun 11;2020:4231561.
- 26 59- Rocchi V, Puxeddu I, Cataldo G, Del Corso I, Tavoni A, Bazzichi L, Bombardieri S,
27 Migliorini P. Hypersensitivity reactions to tocilizumab: role of skin tests in diagnosis.
28 *Rheumatology (Oxford).* 2014;53:1527-9.
- 29 60-Téту P, Hamelin A, Moguelet P, Barbaud A, Soria A. Management of hypersensitivity
30 reactions to Tocilizumab. *Clin Exp Allergy.* 2018;48:749-52.
- 31 61- Poreaux C, Bronowicki JP, Debouverie M, Schmutz JL, Waton J, Barbaud A. Managing
32 generalized interferon-induced eruptions and the effectiveness of desensitization. *Clin Exp*
33 *Allergy.* 2014;44:756-64.
- 34 62- Ewan PW, Dugué P, Mirakian R, Dixon TA, Harper JN, Nasser SM. BSACI guidelines
35 for the investigation of suspected anaphylaxis during general anaesthesia. *Clin Exp Allergy.*
36 2010;40:15-31.
- 37 63- Mertes PM, Laxenaire MC, Lienhart A, Aberer W, Ring J, Pichler WJ, Demoly P.
38 Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *J*
39 *Investig Allergol Clin Immunol.* 2005;15:91-101.
- 40 64- Mertes PM, Malinovsky JM, Jouffroy L; Working Group of the SFAR and SFA, Aberer
41 W, Terreehorst I, Brockow K, Demoly P; ENDA; EAACI Interest Group on Drug Allergy.
42 Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical
43 practice. *J Investig Allergol Clin Immunol.* 2011;21:442-53.
- 44 65- Dreskin SC, Halsey NA, Kelso JM, Wood RA, Hummell DS, Edwards KM, Caubet JC,
45 Engler RJ, Gold MS, Ponvert C, Demoly P, Sanchez-Borges M, Muraro A, Li JT, Rottem M,
46 Rosenwasser LJ. International Consensus (ICON): allergic reactions to vaccines. *World*
47 *Allergy Organ J.* 2016;9:32.
- 48 66-Amsler E, Autegarden JE, Gaouar H, Frances C, Soria A. Management of immediate
49 hypersensitivity reaction to glatiramer acetate. *Eur J Dermatol.* 2017 Feb 1;27(1):92-95.

- 1 67- Santiago F, Gonçalo M, Vieira R, Coelho S, Figueiredo A. Epicutaneous patch testing in
2 drug hypersensitivity syndrome (DRESS). *Contact Dermatitis*. 2010;62:47-53.
- 3 68- Andrade P, Brinca A, Gonçalo M. Patch testing in fixed drug eruptions--a 20-year review.
4 *Contact Dermatitis*. 2011;65:195-201.
- 5 69- Barbaud A; Groupe FISARD de la SFD. Investigations allergologiques dans les
6 érythèmes pigmentés fixes. Méthode recommandée par le groupe FISARD de la SFD
7 [Allergological investigations in fixed pigmented erythema. Method recommended by the
8 FISARD (drug eruptions) group of the French Dermatology Society]. *Ann Dermatol*
9 *Venerol*. 2018;145:210-3. French.
- 10 70- Gonçalo M, Ferguson J, Bonevalle A, Bruynzeel DP, Giménez-Arnau A, Goossens A et al.
11 Photopatch testing: recommendations for a European photopatch test baseline series. *Contact*
12 *Dermatitis*. 2013;68:239-43.
- 13 71-Romano A, Blanca M, Torres MJ, Bircher A, Aberer W, Brockow K, Pichler WJ, Demoly
14 P; ENDA; EAACI. Diagnosis of nonimmediate reactions to beta-lactam antibiotics. *Allergy*.
15 2004;59:1153-60.
- 16 72- Blanca M, Romano A, Torres MJ, Fernández J, Mayorga C, Rodriguez J, Demoly P,
17 Bousquet PJ, Merk HF, Sanz ML, Ott H, Atanasković-Marković M. Update on the evaluation
18 of hypersensitivity reactions to betalactams. *Allergy*. 2009;64:183-93.
- 19 73-Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Caruso C, Quaratino D. Cross-reactivity
20 and tolerability of aztreonam and cephalosporins in subjects with a T cell-mediated
21 hypersensitivity to penicillins. *J Allergy Clin Immunol*. 2016;138:179-86.
- 22 74- Soria A, Hamelin A, de Risi Pugliese T, Amsler E, Barbaud A. Are drug intradermal tests
23 dangerous to explore cross-reactivity and co-sensitization in DRESS? *Br J Dermatol*.
24 2019;181:611-2.
- 25 75-Trubiano JA, Chua KYL, Holmes NE, Douglas AP, Mouhtouris E, Goh M, et al. Safety of
26 cephalosporins in penicillin class severe delayed hypersensitivity reactions. *J Allergy Clin*
27 *Immunol Pract*. 2020;8:1142-6.e4.
- 28 76-Copaescu A, Mouhtouris E, Vogrin S, James F, Chua KYL, Holmes NE, Douglas A,
29 Slavin MA, Cleland H, Zubrinich C, Aung AK, Goh MSY, Phillips EJ, Trubiano JA;
30 Australasian Registry of Severe Cutaneous Adverse Reactions (AUS-SCAR). The Role of In
31 Vivo and Ex Vivo Diagnostic Tools in Severe Delayed Immune-Mediated Adverse Antibiotic
32 Drug Reactions. *J Allergy Clin Immunol Pract*. 2021;9:2010-5.e4.
- 33 77- Desroche T, Poreaux C, Waton J, Schmutz JL, Menetre S, Barbaud A. Can we allow a
34 further intake of drugs poorly suspected as responsible in drug reaction with eosinophilia and
35 systemic symptoms (DRESS)? A study of practice. *Clin Exp Allergy*. 2019;49:924-8.
- 36
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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 ² 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*
ANTIBIOTICS		
Beta-lactams		
Amoxicillin, ampicillin and other semisynthetic penicillins	20 mg/mL	
Aztreonam	2 to 20 mg/mL	
Benzylpenicilloyl-poly-L-lysine	6×10^{-5} mol/L	
Benzylpenicilloyl-octa-L-lysine	8.64×10^{-5} mol/L	
Sodium benzylpenilloate	1.5×10^{-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	
Quinolones		
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	
Macrolides		
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
Others		
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	
PERIOPERATIVE DRUGS		
Neuromuscular blocking agents		
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
Anesthetic agents		

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 [¶]
Midazolam	0.05 mg/mL	5 mg/mL
Propofol	1 mg/ml	10 mg/mL
Thiopental	2.5 mg/mL	25 mg/mL
Reversal agents		
Sugammadex	10 mg/mL	
Opiates		
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 [¶]
Remifentanil	0.005 mg/mL	0.05 mg/mL
Sufentanil	0.0005 mg/mL	0.005 mg/mL
Local anesthetics		
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	
CHEMOTHERAPEUTIC DRUGS		
Paclitaxel	0.03 mg/mL	
Docetaxel	0.1 mg/mL	
Platinum salts	1 mg/mL [‡]	
Carboplatin	1 mg/mL	
Cisplatin	0.1 mg/mL	
Cisplatin	1 mg/mL	
Oxaliplatin	0.5 mg/mL	
Oxaliplatin	1 mg/mL	
CORTICOSTEROIDS		
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	
HEPARINS	diluted 1:10	
INSULINS	diluted 1:10	
CYTOKINES, BIOLOGICAL AGENTS		
Anti-TNF		
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	
Interferons	undiluted	
Nonsteroidal anti-inflammatory drugs (NSAIDs)		
Diclofenac	2.5 mg/mL	
Ketoprofen	2 mg/mL	
Piroxicam	2 mg/mL	
Pyrazolones and other injectable NSAIDs	0.1 mg/mL	
CONTRAST MEDIA		
Iodinated contrast media	diluted 1:10 for immediate reactions, maybe undiluted for delayed reactions	
Gadolinium derivatives	diluted 1:10	
PROTON PUMP INHIBITORS		
Esomeprazole	0.4 or 4 mg/mL	
Omeprazole	0.4 or 4 mg/mL	
Pantoprazole	0.4 or 4 mg/mL.	
MISCELLANEOUS DRUGS, EXCIPIENTS, DYES		
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).