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General considerations for skin test procedures in the diagnosis of drug hypersensitivity

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Diagnostic procedures in allergy diagnosis can be classified into the patient's history, *in vivo* skin testing, *in vitro* laboratory tests and provocation tests (1). In drug hypersensitivity, a reliable diagnosis is particularly difficult. The history is often not reliable since different drugs are often taken simultaneously. Test reagents are neither standardized for *in vitro* nor for *in vivo* (skin) tests and provocation tests are cumbersome, possibly harmful for the patient and possibly not sensitive enough since crucial cofactors might be absent during the procedure. Finally, the clinical picture of drug hypersensitivity is very heterogeneous, mirroring many distinct pathophysiological events. When immunologic mechanisms have been shown, either antibody or cell mediated, the reactions are referred as drug allergy (20). Drug allergy is in the vast majority due to IgE-mediated immediate-type reactions or T-cell mediated delayed-type reactions. In a large number of patients, no allergy can be proven, which may be either due to the lack of adequate test reagents or procedures, or may indicate a non-allergic pathomechanism. Thus, many doctors rely on history and some reference manuals for drug adverse event diagnosis, without attempting to prove the relationship between drug intake and symptoms or to clarify the underlying pathomechanism of the reaction. Such an attitude leads to a misunderstanding of the epidemiology and the pathophysiology of this highly relevant field.

Skin tests can be used for the evaluation of a drug hypersensitivity (2–5). The diagnostic value of skin tests has not been fully evaluated and the experience in different centres has rarely been exchanged during the

*ENDA: European Network for Drug Allergy, the EAACI interest group on drug hypersensitivity with the following additional members: Drs W. Aberer, B. K. Ballmer-Weber, A. Barbaud, A. Bircher, J. Birnbaum, P. Campi, A. de Weck, M. Drouet, J. Fernandez, T. Fuchs, E. Gomes, J. L. Guéant, C. Gutgesell, A. Kapp, M. Kowalski, G. Marone, H. Merk, D. Moneret-Vautrin, C. Pascual-Marcos, B. Przybilla, E. Rebelo-Gomes, F. Rueff, A. Sabbah, J. Sainte Laudy, M. J. Torres, D. Vervloet, B. Wedi

last decades. Thus, reliable skin test procedures for the diagnosis of drug hypersensitivity are generally missing and test concentrations are unknown or poorly validated for most drugs.

Skin tests have to be applied according to the suspected pathomechanism of the drug hypersensitivity (2–5). In immediate β-lactam drug allergy an IgE-mediated reaction can be demonstrated by a positive skin prick and/or intradermal test after 20 min (6, 7). On the other hand, non-immediate reactions to β-lactams manifesting by cutaneous symptoms occurring more than one hour after last drug intake, are often T-cell mediated and a positive patch test and/or a late-reading intradermal test is found after several hours or days (8). Moreover, skin tests have the additional capability to give insights concerning the immunologic pathomechanism.

To harmonize our drug hypersensitivity diagnostic procedures in Europe, members of ENDA (the core part of the EAACI interest group on drug hypersensitivity) have first developed a questionnaire based on a detailed history of the reaction (9). It also includes some procedures for skin tests, provocation tests and biological tests. It is available in various languages and thus utilized in different regions of Europe. Our next aim is to develop useful test procedures for the diagnosis of drug hypersensitivity, procedures which are simple and can be used in centres not specialized in drug hypersensitivity.

As a first step, we define general principles for skin testing of drugs, to establish the best skin test concentrations to be used for already well-studied substances. For other substances and through collaborative studies, we will be able to provide sensitivity and specificity data for each drug and drug concentration.

Selection of patients for skin testing

A list of common clinical symptoms, for which skin testing is recommended is listed in Table 1. For the practising allergist, skin testing with SPT, IDT and/or patch test is especially recommended in adverse drug reactions to beta-lactam antibiotics (mainly penicillins, cephalosporins). SPT and IDT are often positive to myorelaxants, insulin, protamine, heparin, streptokinase and chymopapain. It is also recommended to perform patch tests and IDT in delayed local or exanthematic adverse reactions to other antibiotics, carbamazepine, practolol, pyrazonolines and tetrazepam. Skin tests and provocation tests to local anesthetics should be performed; however, in this case the purpose is to exclude a reaction to a preparation under test conditions, rather than to confirm drug hypersensitivity.

Symptoms and signs generally indicating drug allergy, as opposed to non-immunologic adverse reaction, are the presence of a sensitization period, reaction to low dosages of the drug, and typical symptomatology such as urticaria and anaphylaxis immediately after administration of a drug (Table 1). However, in adverse reactions to drugs, this general scheme is often unreliable, as sensitization may not be apparent and some reactions may mimic symptoms of allergy. Thus, centres with a special interest on drug allergies are encouraged to test patients with other drugs to gain and publish experience on the value of skin testing under different conditions.

There are other diseases where immunological reactions to drugs could be involved, but skin testing has generally not been found helpful. For example, renal or hepatic manifestations may occur as a part of a generalized allergic reaction (e.g., in Drug Reaction with Eosinophilia and Systematic Symptoms). However, the value of skin tests in hematological (anemia, thrombocytopenia, leukopenia), renal (e.g., glomerulonephritis) or hepatic manifestations (e.g., hepatitis) has not been proven. Also skin testing is not considered to be helpful in autoimmune diseases like systemic lupus erythematosis, bullous pemphigoid, pemphigus vulgaris, and interstitial lung disease.

An algorithm for the use of skin tests is given in Fig. 1. In immediate, possibly drug-related symptoms of urticaria/angioedema, rhinitis, conjunctivitis, bronchospasm or other anaphylactic symptoms, skin prick tests and intradermal tests are recommended. However, it has to be considered that systemic reactions during skin testing might occur (see *Testing of patients at higher risk*; below).

In non-immediate, possibly drug-related reactions of contact dermatitis, photo-contact dermatitis, exanthematous drug eruptions, urticaria/angioedema, purpura pigmentosa progressiva, leucocytoclastic vasculitis, fixed drug eruptions (testing in previously involved areas and in unaffected skin), Stevens–Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis, patch tests and/or late readings of the intradermal tests after 24, 48 and 72 h are recommended (2–5, 8, 10–12). Also in non-immediate drug hypersensitivity, systemic reactions following skin testing are known (13). In severe situations especially, skin testing has to be performed with caution (see specific chapter, *Testing of patients at higher risk*). A recurrence or elicitation of a toxic epidermal necrolysis due to skin testing has not been described in the literature.

Skin test methods

Standardized skin test methods considered in this document are the skin prick test (SPT), the intradermal test (IDT), the patch test and the photopatch test. Scratch tests are used in some centres, but will not be further considered in this paper.

Table 1 Common clinical indications for skin testing in the diagnosis of drug hypersensitivity

Patch tests can be used as first line of investigation	Skin prick tests and intradermal tests
Acute generalized exanthematous pustulosis	Anaphylaxis
Contact dermatitis	Bronchospasm
Erythema multiforme	Conjunctivitis
Exanthematous drug eruption	Rhinitis
Fixed drug eruption	Urticaria/angioedema
Photoallergic reactions	
Purpura/Leucocytoclastic Vasculitis	
Stevens–Johnson Syndrome	
Toxic epidermal necrolysis	

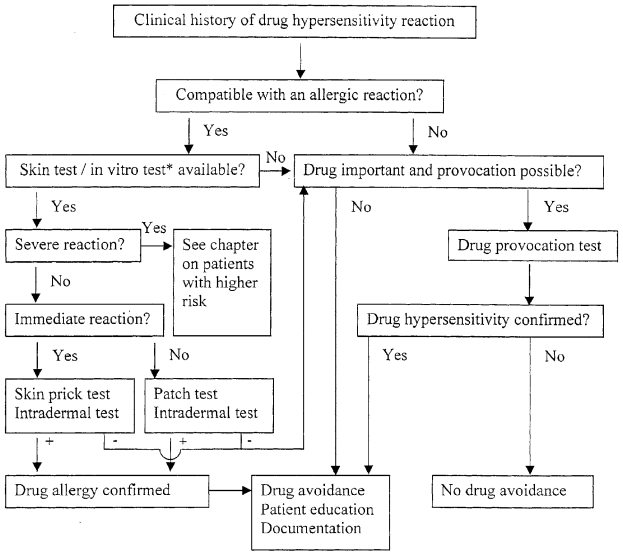

Figure 1. Algorithm for the use of skin tests in the diagnosis of drug hypersensitivities. The only in vitro test thoroughly validated is the RAST to penicillin determinants. Results of in vitro tests have to be regarded in concert with the history and results of skin tests.

Skin prick tests and intradermal tests

(1) Procedure. A SPT is done by pricking the skin percutaneously with a prick needle through an allergen solution (14). It is the safest and easiest test, but only moderately sensitive, for immediate drug reactions. An intradermal test is accomplished by injecting 0.02–0.05 ml of an allergen intradermally, raising a small bleb measuring 3 mm in diameter. The IDT is more sensitive than the SPT, but also carries a higher risk for inducing an irritative, falsely positive reaction and might even lead to an anaphylactic reaction in IgE-dependent reactions.

Certain drugs have to be discontinued prior to skin testing (Table 2). The patient should be free of infectious diseases, fever or inflammatory reactions at the time of testing, unless the skin test is urgently needed. The intake of β-adrenergic blocking agents should be discontinued (usually for 48 h,) according to their half-life of elimination, if the drug to be tested had induced an anaphylactic reaction, as these drugs may interfere with treatment of a possible systemic reaction elicited by the skin test.

SPT should be performed on the volar aspect of the forearm. If this is negative after 15–20 min, an intradermal test can be performed on the volar forearm, although other regions can be tested (however, there is no comparison for drug allergens). The pain of intradermal tests may limit their use in young children. Normally these tests are well tolerated, but in highly IgE sensitized patients generalized symptoms (urticaria and anaphylaxis) might appear.

(2) Documentation and scoring. Readings should be taken after 15–20 min if immediate reactions are analyzed, and after 24 and 72 h for evaluation of non-immediate (late) reactions. In selected cases, additional readings (e.g., after 96 h) are sometimes recommended, as time intervals between testing and positive test reactions may vary.

Immediate reactions are documented by measuring the mean diameter of the wheal (and erythema) of the test preparations and the negative control directly after the injection and after 15–20 min. Different qualitative scoring systems are available and used in different centres (14). In order to compare the results, a morphological score should be applied as well, enabling a later comparison of different scoring systems. The preferred documentation manner is by outlining the size of the injected area and of the reaction at 15–20 min on a translucent cellophane tape. As a criterion for

Table 2 Drug-free interval demanded for drugs decreasing reactivity of skin tests (adapted from (14))

Medication	Route	Immediate reaction	Non-immediate reaction	Free interval
H1-antihistamines Imipramines, phenothiazines	Oral, intravenous	+	−	5 d
β-adrenergic drugs	Oral, intravenous	+	−	5 d
Glucocorticosteroids***	Oral, intravenous	±	−	**
Long-term	Oral, intravenous	±	+	3 weeks
Short-term, high dose	Oral, intravenous	±	+	1 week
Short-term, < 50 mg pred*	Oral, intravenous	±	−	3 d
Topical corticosteroids	Topical****	±	+	> 2 weeks

*Prednisolone equivalent; ** no clinical relevance; *** withdrawal may not be possible; **** at the site of testing only.

positivity, which has been employed in the diagnosis of penicillin allergy and may be used tentatively for other drugs, reactions are considered positive when the size of the initial wheal increases by 3 mm or greater in diameter after 15–20 min and is associated with a flare (15). The mean diameter is recorded by measuring the largest and the smallest diameters at right angles to each other. Both diameters are recorded, summed and divided by 2. The area can be determined by other methods: weighing of the cellophane, planimetry and computerized scanning.

Late reactions, such as delayed or late-phase reactions, should always be examined. They are documented by the diameter of erythema, papulation/infiltrate and morphological description, such as erythematous swelling, erythematous infiltrate, erythema only, eczema with papulation and/or vesicles. Any infiltrated erythema is considered to represent a positive reaction. For later comparison and research purposes, photodocumentation and, if possible, histology may be recommended.

Patch tests and photopatch tests

(1) Procedure. In a patch test the allergen is usually fixed on the back of the patient for 1–2 days and the result is read after 1 day and/or 2–3 days (16). A photopatch test is a modification of the patch test used when photoallergic or phototoxic reactions are suspected. After one day the patch test is removed and the skin is irradiated with ultraviolet light, 5 or 10 J/cm^2 UVA (12). This test is read after two, three and four days.

Patch testing should not be done in patients after prior strong UV-exposure (e.g., after holidays at the seaside), because the test reactivity is usually diminished. Demanded drug-free intervals for certain drugs are listed in Table 2. Large doses of topical glucocorticosteroid treatment away from the test site may have the same effects as low doses of systemic glucocorticosteroid treatment. The patient should be free of infectious diseases, fever or inflammatory reactions at the time of testing.

Patch test are done on the upper back on unaffected, untreated and uncleaned skin (no prior rinsing with alcohol) using Finn Chambers or an equivalent fixed with a ''hypoallergic'' tape. Immediate reactions to the drug should be ruled out by the clinical history before the patch tests are applied.

The patch test should be applied for 2 days until results comparing 1 and 2 day application is available. Further patch tests with longer durations of application might be indicated in special cases.

(2) Documentation and scoring. Readings should be done at least at two consecutive times: 48 h and 72 h. It still has to be determined whether applications of patch tests for 24 h and readings after 24 and 72 h yield the same results. Additional readings, for example in hospitalized patients, after 96 h or more might also be needed in some cases. Scoring is done according to international standards (12, 16). Sometimes reactions occur earlier or much later (as in the case of corticosteroids and phenylephrine). Patients should be instructed to report to the doctor if they notice a reaction at any time. Scoring is done according to the *European Environmental and Contact Dermatitis Research Group* patch test and photopatch test classifications (Table 3) (12, 16).

Best time interval between drug hypersensitivity and skin testing

There is a consensus of opinion that skin tests should be performed after a time interval which allows resolution of clinical symptoms, clearance from the circulation of the incriminated drugs and anti-allergic medications. However, it is not known whether the reactivity might be higher (e.g., cellular hyperreactivity) or lower (e.g., initial histamine depletion of mast cells or tolerance) if skin tests are performed directly after the reaction (within the next few days). It is also not known to what extent the sensitization to a drug decreases over time. Thus, many groups carry out tests after some minimal time interval of, for example, three weeks, but not after more than three months, if possible.

Testing of patients at higher risk

There are some patients experiencing systemic reactions after percutaneous and epicutaneous skin testing. Patients who have been hospitalized because of an allergic reaction and/or who had a life-threatening drug hypersensitivity, including anaphylaxis and severe skin reactions (e.g., toxic epidermal necrolysis, severe bullous exanthemas, vasculitis, Stevens–Johnson Syndrome) or systemic reactions (e.g., hypersensitivity syndrome) are at risk, even if there is a long time interval between the drug hypersensitivity and skin testing (17). Case-control studies gathering such data from different centres are needed to evaluate precisely the exact risk factors. In

Table 3 Scoring of patch test reactions (modified from (16))

Clinical picture	Score	Conclusion
Faint erythema only	? or + ?	Doubtful reaction
Erythema, infiltration, possibly discrete papules	+	Weak positive reaction
Erythema, infiltration, papules, vesicles	+ +	Strong positive reaction
Intense erythema, infiltration, coalescing vesicles	+ + +	Extreme positive reaction
	–	Negative reaction
	IR	Different irritant reactions
	NT	Not tested

+, + +, + + + are regarded as positive skin test reactions and – as a negative skin test reaction.

such high risk patients a risk-benefit analysis has to be done: is the skin test necessary? Are all precautions taken in case of some reactions occur? The risk-benefit analysis has to be made by the allergist in regard to the clinical reaction, the possibilities of treatment for a possible adverse reactions, the risk for the patient and the importance of the drug. If ever possible, pregnant women should not been tested. The drug should initially be tested with a higher dilution of the test preparations (e.g., 1/10–1/100000). Although not validated as well, an open application can be performed initially in very severe immediate reaction. The next concentration step has to be applied only if the higher dilution has yielded a negative result. In severe, nonimmediate reactions it has to be considered to extend the time interval between tests and not to perform intradermal test with the highest concentration before performing patch tests.

Test preparations, test vehicles and solutions

Specific standardized skin test reagents are commercially available only for penicillins. Penicilloyl-Polylysine (PPL) and Minor Determinant Mixture (MDM) (Allergopen, Allergopharma, Steinbeck, Germany) have been specifically developed for skin testing of suspected drug allergy to penicillins and validated procedures do exist. However, when tested according to the recommendations of the manufacturer these reagents are negative in SPT and IDT, it is recommended to test also the culprit β-lactam preparation. For this, as for all other drugs, test material is normally restricted to drugs commercially available on the market. Because of better standardization, skin testing should be encouraged in the form of preparations for parenteral administration. If the reaction occurred with the oral preparation, this should be tested also by patch and skin prick tests as it may contain different constituents. Initial testing using a suitable dilution can be performed with the whole culprit medication suspected to have elicited the drug hypersensitivity reaction (see *Test concentrations*). In the case of a positive test reaction, it is possible that either an active ingredient or a drug additive is responsible for the reaction and both must be tested separately. It should be attempted to identify the relevant constituent of the drug preparation that leads to a reaction .

For patch testing, intradermal testing and the skin prick test, preparations for parenteral (mostly intravenous) route should be diluted in 0.9% NaCl. Pharmacological data concerning the application of parenteral preparations in the skin are not known. For intradermal tests, sterile solutions are obligatory. For non-hydrosoluble drugs a stock solution can be prepared in dimethyl-sulfoxide (DMSO) and further diluted down with 0.9% NaCl. A negative control with the same concentration of DMSO is needed in these cases.

For skin prick tests and patch tests of drugs that are only available as a tablet, not in a soluble form, the tablets can be smashed in a mortar and diluted with 0.9% NaCl or petrolatum. There is some experience of this method in certain groups (1–3). The tablets should be weighed and the concentration of the active ingredient should be determined. Test concentrations should be given in mg drug/ml vehicle and optimal test concentrations for individual drugs should be calculated for the future.

For patch tests, substances should be diluted in 0.9% NaCl or in petrolatum, depending on the solubility and toxicity of the preparation (e.g., with acidic preparations). There are no data in the literature which compare both vehicles systematically. Thus we do not know if the reactivity to a drug in a sensitized individual tested at 5% in petrolatum is equivalent to the reactivity tested at 50 mg/ml of 0.9% NaCl.

Test concentrations

A skin test reaction to a drug tested in a concentration that does not cause a reaction in a sufficient number of controls is indicative of a drug allergy. Sometimes test concentrations for some drugs can be found in the literature (Table 4). If not, one may begin to test the compound in a similar concentration as a related drug for which there are data in the literature. Ideally, molar concentrations of the drug are given, but for practical purposes concentrations in mg drug/ml vehicle are more often used.

For other drugs, the optimal test concentration is unknown and must be determined. The optimal test concentration is the highest concentration of a particular drug, which does not give any skin reaction (irritative reactions are not rare) in a group of never-exposed subjects and a group of already-exposed but non-allergic individuals (see *Controls* below), but may be positive in patients with drug allergy. Whether this concentration relates to the serum or skin concentration of the drug when one takes a therapeutic dose of this medication is not known.

In immediate reactions, gradually increasing concentrations are tested in the patient to titrate the concentration causing a positive test reaction. Appropriate concentrations for testing with fresh preparations have not been well studied in large groups of patients and controls. Thus, the starting dilution (sometimes as low as 1/100 000) is not clearly defined for most drugs and also depends on the severity of the reaction (see below *Patients at higher risk*). Initially the skin prick test is done with a low concentration (usually not lower than 1/100 of the

Table 4. Patch test concentrations used in the literature and in the practice

Antibiotic	DKG[1]	De Groot (18)	Barbaud (2)	Others (8, 18)
Penicillin G	5% pet	Pure 1% pet 10000 iU pet	Pure in powder with sodium citrate*	Romano: 5000 iU/g pet Bruynzeel: 20% w/w
Other penicillins	5% pet	Pure 1% pet	Pure in powder*	Romano: 5% pet (20 controls) Bruynzeel: 20% w/w
Cephalosporins	5% pet	20% pet or pure 0.5% water	Pure in powder*	Bruynzeel: 20% w/w
Cotrimoxazole	Trimethoprim 5% pet Sulfamethoxazol 5% pet	Sulfonamide (not specified): 5% pet	80 mg/ml in water	
Tetracycline-HCl	2% pet	3% pet 5% pet	Doxycycline: 20 mg/ml in water	
Gentamycin sulfate	20% pet	20% pet		
Ciprofloxacin, ofloxacin	5% pet		Norfloxacin: in powder from pill*	
Erythromycin	1% pet	1% pet 5% pet 10% pet	Pure in powder*	
Pristinamycine			Pure in powder*	
Carbamazepine			Pure in powder*	

[1]DKG: German contact allergy group (test concentrations in German practice).
*All these preparations were tested pure and diluted to 30% in water and in petrolatum.
pet = in petrolatum (vaselin); w/w = watery solution.

intravenous preparation). If no reaction occurs, 10-fold increases in the test concentration are done until a positive reaction is seen. If no reaction can be elicited by the skin prick test, intradermal testing starts with a dilution of 1/100 of the skin prick test concentration and the concentration is increased in logarithmic steps (1/10, 1/1) until the final concentration is reached with a positive test reaction after 20 min The final concentration should be validated (see *Controls* below). In the case of beta-lactam antibiotics validated test concentrations, as well as data on sensitivity, specificity, and comparison with results of in-vitro tests, exist and have been published (2, 6, 7, 8).

In non-immediate reactions, patch tests can be performed with the vehicles and concentrations given in Table 4. However, there is a need for further validation of the optimal vehicle and test concentrations. Only those test concentrations are listed, for which sufficient experience seems to exist (Table 4) (2, 8, 18, 19). If more than one test concentration and in addition a watery test vehicle are listed, the higher concentrations and the watery solution have to be validated against eliciting unspecific test reactions in exposed non-allergic individuals.

Controls

All test methods can produce irritative reactions, which are not indicative of an allergy, but reflect an irritant potency of the drug and its preparation. To study the specificity of the test preparation and procedure, data should be present for as many patients as possible who tolerate the drug (already exposed, non allergic individuals). It is also recommended to test a number of never-exposed controls (at least 10) to exclude irritation, if this is acceptable to the ethical committee. The most important outcome is the highest concentration of a drug, which can be used for skin testing without producing a positive unspecific (irritative) reaction. From the clinical experience on contact sensitizing drugs it is known that there is a remote possibility of sensitizing individuals. Although orally taken drugs have less sensitizing potency than contact sensitizing agents, as most drugs are chemically not reactive, this is a remote possibility to be considered.

Interpretation of test results

The negative predictive value of skin tests is generally low. This may be partly due to the fact that physiologic metabolites rather than the active drug itself is responsible for the reaction and because many drugs are haptens, which have to be conjugated with a carrier protein before becoming an allergen. Thus, a negative skin test to a drug alone is unreliable for ruling out drug allergy. In the case of a negative skin test, one should consider proceeding to more hazardous drug provocation tests after carefully evaluating the risks and the benefits in the specific patient (Fig. 1).

On the contrary, even when a proper technique and proper drug material are employed, a positive skin test result does normally indicate the diagnosis. The positive predictive value of a skin test tends to be high, provided that a sufficient number of controls have been tested negative with exactly the same methodology (6). As for positive skin tests with other allergens, the result should be always interpreted together with the clinical history

and *in-vitro* test results when available. When there is a specific reaction to a skin test, plus a corresponding clinical history, the patient is advised to avoid thereafter the relevant drug and related drugs (e.g., aminoglycoside antibiotics) (Fig. 1) and an 'allergy pass' may be issued. In centres that are interested in drug allergies, however, even in the light of a positive skin test, it is prudent to confirm the diagnosis by use of a provocation test, in order to gain and publish information about false positive and false negative skin test reactions, as well as positive and negative predictive values for specific drugs and clinical manifestations. Also provocation tests or desensitization protocols to the culprit drug, or provocation to alternative drugs, may be attempted in specific cases when satisfactory substitutes are not available or in patients with 'multiple drug intolerance syndrome'.

Ethical considerations and informed consent

The issue of obtaining data concerning the irritative effects of drugs on skin, tested in unexposed non-allergic controls as described above, requires approval from local ethical committees, as well as the validation of different skin tests by provocation tests. The second ethical issue to consider regards the collection, storage and distribution of data in a database of the results of drug hypersensitivity tests and diagnosis, including skin tests. It will be one of the future goals of ENDA to collect data on exposed individuals with good tolerance of a drug, to bypass the necessity of having new controls in each different centre.

Skin testing for the detection of drug allergy is commonly used in different centres. Skin testing of patients for a possible allergic reaction to a drug probably does not require authorization by a local ethical committee, but it does require patient informed consent. Please contact your local ethical committee before proceeding in your centre. Of course skin testing in the context of clinical studies requires the agreement of the local ethical committee, since sensitization and adverse systemic reactions may occur.

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