

# The Drug Ambassador Project

## The Diversity of Diagnostic Procedures for Drug Allergy Around Europe

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**Background:** Drug allergy is an increasingly important clinical problem. About 5–10% of patients consulting allergy centers have some form of drug allergy or pseudo allergy. At present there is no consensus concerning the best way to study and diagnose hypersensitivity reactions to drugs. This leads both to practical difficulties in diagnosing individual patients and to more general problems in comparing protocols and results from different centers.

**Methods/Data base:** The European Network for Drug Allergy (ENDA) Drug Ambassador Project aimed to collect information on the ways that different European centers approach these patients.

**Results:** The present report summarizes data collected during this project, focussing on the organization of drug allergy consultations, diagnostic protocols and the various *in vitro* and *in vivo* investigation procedures in current use. The study revealed wide variation in the diagnostic procedures used for drug allergy in clinical practice, despite the apparent consensus achieved in recommendations and position papers.

**Conclusion:** Reciprocal exchange of information and discussions based on these observations may help to achieve standardization and harmonization in this sector with significant potential benefits for patients with drug allergies.

**Keywords:** drug hypersensitivity, diagnosis, standardization

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### Introduction

Drug hypersensitivity reactions are common. They affect 5–10% of the population [1] but constitute a rather difficult topic in allergology. The clinical appearance of drug hypersensitivity reactions may mimic several diseases, which renders the diagnosis difficult. Moreover, many different drugs may cause drug hypersensitivity reactions, but the incidence of reactions to any single drug is rather low.

This makes it difficult for a single center to collect a significant number of patients with drug hypersensitivity reactions to a given drug. Collaborative efforts are therefore needed to better understand the mechanisms of such reactions and to standardize diagnostic procedures. However, to achieve effective collaboration there needs to be a degree of harmonization of investigations and diagnostic procedures. In this report, we compare drug hypersensitivity diagnostic procedures among 12 different allergology centers in Europe. The inquiry was focused on practical aspects like the organization of consultations, the protocols used to collect clinical data, the ways in which skin tests are performed with different drugs, and the laboratory tests and techniques currently in use. In addition, the availability of other resources (e.g., research projects) for the study of drug hypersensitivity reactions was investigated.

The data reveal a marked heterogeneity from center to center regarding the evaluation procedures and, as a general observation, the existence of such heterogeneity suggests that there is no one uniform way of investigating these patients. Given that there is this uncertainty, it would seem to make sense to bring people together in a more harmonized way to gather data which can be exchanged and on which relevant comparisons can be made.

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**TABLE 1**  
ALLERGY CENTERS INVOLVED IN THE STUDY

Austria	– Department of Environmental Dermatology, University of Graz, Graz
France	– Department of Allergology and Clinical Immunology, Central University Hospital of Nancy, Nancy – Dermatology Department, Hospital Fournier, Nancy – Maladies Respiratoires, Hospital Arnaud de Villeneuve, CHU de Montpellier, Montpellier
Germany	– Department of Dermatology and Allergology, Hanover Medical University, Hanover
Italy	– Department of Allergy, Clinical and Laboratory Immunology, San Giovanni di Dio, Florence
Poland	– Department of Clinical Immunology and Allergy, Faculty of Medicine, Medical University of Lodz, Lodz
Portugal	– Allergy and Clinical Immunology, Central Pediatric Hospital Maria Pia, Porto
Spain	– Allergy Department, University Hospital La Paz, Madrid
Switzerland	– Clinic for Rheumatology and Clinical Immunology/Allergology, Inselspital, Bern – Allergy Unit, Department of Dermatology, Basel University Hospital, Basel
UK	– Medical Specialities Clinical Group, University of Southampton, Southampton

**TABLE 2**  
ORGANIZATION OF DRUG ALLERGY CONSULTATIONS  
AND PATIENT NUMBERS

Centers	Organized independent drug allergy consultation in place	Number of patients seen per week
A	Yes	12 patients + 20 ST and/or DPT + 2 PT
B	No	4–10 patients
C	No	5 patients
D	Yes	12–15 patients
E	No	20 patients
F	No	2–3 patients
G	Yes	3 patients
H	No	6 patients
I	No	5–6 patients
J	Yes	30–35 patients + 40–50 ST or DPT
K	No	2–3 patients
L	No	3–4 patients

DTP = drug provocation test; PT = patch test; ST = skin tests

achieve better cooperation among the different European centers dedicated to drug allergy.

## Data Collection

Twelve centers (herewith randomly designated by the capital letters A–L), all part of the European Network for Drug Allergy (ENDA) and dealing with drug allergy, from nine European countries (Austria, France, Germany, Italy, Poland, Portugal, Spain, Switzerland, and the UK) were contacted and agreed to a 3- to 5-day visit of the “drug allergy ambassador” (EG). The centers visited are listed in Table 1. On visiting each center, the drug allergy ambassador collected data, including:

- organization of the drug allergy unit/consultation;
- selection of patients and clinical history protocols in use;
- *in vivo* investigation procedures (especially details about skin tests);
- *in vitro* laboratory resources (routine and research procedures).

The data were intended to provide a guideline for future work and also urge efforts to harmonize practices in this field.

## Organization of the drug allergy consultation

*Is there a separate, dedicated drug allergy clinic? How many patients are seen per week? Do you take all referred patients or do you select them? Do you use the ENDA questionnaire?*

Four centers do have dedicated drug allergy clinics and eight see such patients in the course of ordinary allergy clinics. Within those specialized clinics, the range seems to be 3–35 patients, so they do not all see large numbers of patients (see Table 2).

The availability of similar standardized methods and reagents is essential if we wish to compare clinical results from different groups, to validate diagnostic procedures in laboratory tests, or to enhance our understanding of the pathophysiology of drug hypersensitivity reactions. Precise information about the work performed in each country/center is also important in order to implement clinical and laboratory research and to

**TABLE 3**  
TYPES AND ORDER OF SKIN TESTING

Centers	Order of performing skin tests	Comments
A	1. Prick 2. ID	Patch test (sometimes)
B	1. Prick (Allerg and LA) 2. Scratch 3. ID (Allerg and LA) 4. Scratch/patch	Patch test (sometimes)
C	1. Prick 2. ID (Allerg and LA) 3. Patch	Scratch patch test (sometimes); Order can be: prick, patch, and ID, during the first reading of patch test
D	1. Prick (Allerg, Amox/clav, Cef, LA/GA) 2. ID (Allerg, Amox/clav, Cef and LA/GA)	Patch test (sometimes for $\beta$ -lactams)
E	1. Prick 2. ID	Patch test (sometimes)
F	1. Patch test 2. Prick	ID (sometimes)
G	1. Prick 2. ID	Patch test (sometimes)
H	1. Scratch test 2. ID (Allerg, Pen G and LA) 3. Scratch Patch test 4. Patch	All on the same day
I	1. Patch test ( $\beta$ -L and sometimes NSAIDs) 2. Prick test (NSAID, LA, GA, Allerg) 3. ID (NSAID, LA, GA, Allerg)	
J	1. Prick test ( $\beta$ -L, Ery, Strepto, Trim, Sulpho, Propy, Phenyl, Dipyr, LA, GA) 2. ID ( $\beta$ -L, Strepto, Trim, Sulpho, Genta, Propy, Dipyr ) 3. Patch test ( $\beta$ -L)	
K	1. Prick test (for most of the suspected drugs) 2. ID (Allergopen and insulin)	No patch
L	1. Prick test (PG, Pyrazo, Lidoc) 2. ID (PG, Pyrazo, Lidoc)	No patch

Allerg = Allergopen; Amox/clav = amoxicillin + clavulanic acid;  $\beta$ -L =  $\beta$ -lactams; Cef = cefuroxime; Dipyr = dipyrone; Ery = erythromycine; GA = general anesthetics; Genta = gentamycin; ID = intradermal test; LA = local anesthetics; Lidoc = lidocaine; Pen G = penicillin G; Phenyl = phenylbutazone; Propy = propyphenazone; Pyrazo = pyrazolones; Strepto = streptomycin; Sulpho = sulphonamides; Trim = trimethoprim

All centers accept patients without selection, independent of the time interval since the reaction and the probability of a real drug-related event. However, in some settings, access to a consultation was limited by the specific profile of the department to which the allergy center was affiliated (pediatric, adults, dermatology, etc.).

Most centers do not use the ENDA questionnaire [2] regularly because it is considered too complex and impractical. In two centers, the clinical protocol in use is adapted from the

original ENDA questionnaire. In one center, a translation of the ENDA questionnaire exists but is not used.

### Skin Testing

*Who are the candidates for skin testing? Do you usually hospitalize patients for drug testing?*

All centers adhere to the recommendations given in the position paper on skin test procedures [3] regarding patient selec-

tion and drug-free intervals demanded for testing. Most centers have an age limit for skin testing (ST) in children, the lower age limit varies from 0 to 12 years. In two centers, patients were admitted to hospital for skin testing but the other centers perform the tests within an outpatient consultation.

*What kind of skin testing is performed? In which order?*

Most centers perform skin prick and intradermal (ID) tests for immediate-type reactions and patch tests for delayed-type reactions to drugs, but some centers do not perform all these tests on a routine investigation, and in two centers patch tests are not done at all. Usually, the diagnostic investigation starts with the prick test followed by (the more sensitive) ID and then patch testing if indicated (e.g., for delayed-type reactions to amoxicillin). In contrast, two centers start with patch tests in most cases. Three centers additionally use scratch and scratch/patch techniques that are not generally listed in the literature [3]. Table 3 summarizes the skin tests performed, the order in which they are commonly used, and the most commonly tested drugs.

*At which site(s) do you perform skin tests? Who performs them? Who reads them?*

The forearm is the most common site for performing prick and ID tests, while the back and the upper arm are routinely used in some centers. The back is used for patch tests in most centers but in one center the arm is also used. Scratch and scratch/patch tests are done on the back or the forearm.

In most of the centers visited, nurses perform the skin tests and doctors read the results. In some centers, doctors do all the work while in others, nurses perform the tests and also read the results. Sometimes it depends on the type of ST – ID tests are more frequently performed by doctors than prick or patch tests.

## Skin Test Procedures

The materials used for the different kinds of skin testing vary widely from center to center. For prick and scratch tests, 25- to 27-gauge needles and several different metallic or plastic prick lancets are in use. Needles of 25 to 29 gauge are used to perform ID tests. Most centers employ Finn chambers for patch tests, while Leukotest, Van der Bend, Hayes, and Curatest chambers are also used.

The volume of solution injected for the ID tests varies from 0.02 ml to 0.1 ml. In one center, the volume is not prescribed; the aim is to create a 4-mm papule. Another aspect which revealed marked differences were the reagents used for negative and positive controls of skin testing. Saline was the negative control most commonly used for prick and scratch tests, but commercial negative control solutions from several suppliers (Stallergenes, ALK, Hollister Stier) as well as locally produced phenolated and glycerol-saline solutions were also used. As

positive controls, 0.9% codeine or histamine (2 mg/ml or 10 mg/ml) were employed. In some centers, both codeine and histamine are used in every patient.

For ID tests, saline, commercial diluents, and locally made solutions were used as negative controls. For positive control, 0.01 mg/ml to 1 mg/ml histamine was used in some centers, but the majority do not include any positive control for ID testing. For patch tests, the controls were performed with saline, petrolatum, phosphate-buffered saline (PBS), or alcohol; in some cases no control was used.

*What kind of drug reagents are used for the tests? At which concentrations? In which vehicles?*

The recommendations as delineated in the position paper [3] regarding the test preparations, test vehicles, solutions, and test concentrations were generally considered in all centers.

Most centers use some commercial form of the different drugs such as syrup, pills, the content of capsules, powder, preparations for topical use and intravenous (IV) preparations, which are the preferred ones. For liquid preparations, the native product is usually used for the prick test, while different dilutions (in saline, water, or other appropriate diluents for specific drugs) of the commercial IV preparation are used for ID testing. A number of products, concentrations, and vehicles are used for patch tests, the most common ones being petrolatum or saline. The only commercial drug test preparation used in every center is the Allergopen kit for  $\beta$ -lactam immediate-type allergy. In one center, a commercial kit (Insulin Allergy Kit from Novo Nordisk) is used to study reactions to insulin. Details of the dilutions used in each center are shown in Table 4.

*When are the results read?*

Prick, scratch and ID tests are usually read 15–30 min after testing. Two centers examine skin test sites for delayed responses, one of these reviews at 2, 6, and 24 h and the other just reviews at 24 h. The remaining ten centers ask patients to phone in if they notice any late response.

Patches are applied for 24, 48, or 72 h, differing from center to center despite the general recommendation to leave patches not more than 48 h (danger of irritancy or even sensitization) [5]. Readings are done at 48 and 72 h in most centers. A later reading is done in some centers, especially when drugs are tested where very late reactions are common (i.e., amoxicillin). The reading 72 h after application, however, is done in all centers. In two centers, a reading after 20 min is also done frequently, especially when substances are tested that might cause contact urticaria such as many antibiotics, phenothiazines, benzocaine, or benzoyl peroxide. In all centers, patch test patients are advised to contact the center if they note a reaction after the last reading.

Scratch/patch tests are applied for 24 or 48 h (with no uniform procedure in the single center) and readings are performed immediately after removal as well as 24 and 48 h thereafter.

**TABLE 4**  
DRUG REAGENTS AND CONCENTRATIONS USED

Centers	Test type, drug reagents and concentrations
A	Prick – native ID – from 1:100 to native Patch – 30% in petrolatum or 30% aqueous; 10% if the molecule is pure; sometimes pure
B	Prick – native ID – from 1:1,000 to 1:10 for LA; native for Allerg Patch – 10–50% in petrolatum; 0,25–40% in PBS; from 4% in saline to pure
C	Prick – native ID – from 1:1,000 to 1:10; from 1:5 to native for LA Patch – 1–20% in petrolatum; 1% in alcohol
D	Prick – from 1:100 to native ID – from 1:1,000 to 20mg/ml Patch – commercial preparations in petrolatum from FIRMA; 25% in saline
E	Prick – native ID – from 1:1,000 to 1:10; sometimes native Patch – most often 30% in petrolatum; sometimes pure
F	Prick – native (diluted if immediate reaction) ID – from 1:10,000 to native Patch – 30% in petrolatum or 30% aqueous; 10% if molecule is pure; sometimes in alcohol
G	Prick – native ID – from 1:100 to native Patch – 30–50% in saline; native
H	Prick – from 1:100 to native for Allerg, Amox, Amp; 1,000 U for Pen G Scratch – suspected drugs native in powder ID – from 1:100 to native for Allerg; 1,000 U for PG Patch – from 1:100 to native for Allerg; 1,000–200,000 U for PenG; Amox, Amp and suspected drugs native in powder Scratch/Patch – same as for scratch
I	Prick – native for Allerg; 1 mg/ml solution of ASA and Parac; native for LA and GA ID – from 1:10 to native for Allerg, ASA, Parac; native for LA; from 1:2,000 to 1:10 for different GA Patch – Amox and Amp 5% in Vaseline
J	Prick – native for Allerg; 10,000 <b>UI</b> Pen G; Amp, Amox, Cefac, Ery, Strepto, Trim, Sulph, ASA, Parac, Phenyl: all 10mg/ml; Propy: 200 mg/ml; Dipyr: 20 mg/ml; native for LA ID – native for Allergopen; 10,000 <b>UI</b> Pen G; Amp, Amox, Cefalo, Strepto, Trim, Sulpha, ASA, Parac, Dipyr: all 1 mg/ml Patch – 50% in petrolatum
K	Prick – from 1:10 to native for most drugs ID – native for Allerg, 5 <b>UI/ml</b> Insulin (Insulin Allergy Kit)
L	Prick – 1,000 <b>U</b> for Pen G; native for LA; 0.001–1% solutions for Pyrazo ID – 1,000 <b>U</b> for Pen G; native for LA; 0.001–1% solution for Pyrazo

**[Please check units given in bold.]**

Allerg = Allergopen; Amox = Amoxicillin; Amp = Ampicillin; **ASA = [Please define]**;  $\beta$ -L =  $\beta$ -lactams; Cef = cefuroxime; Cefac = cefaclor; Cefalo = cefalotone; Dipyr = dipyrone; Ery = erythromycin; GA = general anesthetics; Genta = gentamycin; ID = intradermal test; LA = local anesthetics; Lidoc = lidocaine; Parac = paracetamol; Pen G = penicillin G; Phenyl = phenylbutazone; Propy = propyphenazone; Pyrazo = pyrazolones; Strepto = streptomycin; Sulpho = sulphonamides; Trim = trimethoprim

*What are the positivity criteria? How are results recorded?*

The criteria for positive prick and ID results are markedly different from center to center, as summarized in Table 5. Most cen-

ters measure the prick and ID reactions and register results in mm; some use a 1+ to 4+ grading system. Some centers keep a permanent record, either by tracing the wheal and transferring the outline to paper with adhesive tape while other centers take photographs.

**TABLE 5**  
POSITIVITY CRITERIA AND RECORDING OF RESULTS

Centers	Positivity criteria	Recording methods
A	Prick – 3 mm papule with erythema ID – 3 mm more than negative control papule	Recorded with tape Recorded with tape
B	Prick – 3 mm papule ID – 5 mm papule and 10 mm erythema	Scale from + to ++++ Measured in mm
C	Prick – 3 mm papule ID – 3 mm papule	Scale from + to ++++ Scale from + to ++++
D	Prick – 3 mm papule ID – 5 mm papule with erythema or the initial papule of 3 mm (any flare seen on a late observation will be considered a positive late reaction)	Measured in mm Measured in mm
E	Prick – > 50% of the papule of the positive control ID – 2 × the initial papule	Measured in mm Measured in mm
F	Prick – 3 mm ID – 2 × the initial papule	Measured in mm Measured in mm Photo sometimes
G	Prick – 3 mm papule ID – 3 mm more than initial papule	Recorded with tape Recorded with tape
H	Prick – 3 mm papule with erythema Scratch – comparison with histamine scratch ID – 5 mm papule and 10 mm erythema	Scale from + to ++++ Scale from + to ++++
I	Prick – subjective evaluation taking into account the papule, erythema, and pruritus ID – subjective evaluation taking into account the papule, erythema, and pruritus	Recorded with tape Recorded with tape
J	Prick – 2 mm papule ID – 2 mm larger than negative control papule	Measured in mm Measured in mm
K	Prick – > 3 mm papule ID – > 7 mm papule or increase of more than 2 mm of initial papule or more than 5 mm over the negative control	Measured in mm Measured in mm
L	Prick – > 3 mm papule ID – 5 mm papule	Recorded with tape Recorded with tape

All centers use the ICDRG criteria for the interpretation of patch test reactions [5].

The reading of patch results is more uniform – the International Contact Dermatitis Research Group (ICDRG) scale is generally used [5].

*Do you have data on the use of skin tests in healthy controls / drug-exposed controls?*

Most centers have some data about different drugs and the different types of tests. Four centers have a few data about prick and ID tests with several drugs in healthy drug-exposed controls. Only one center has some data especially concerning prick and ID for  $\beta$ -lactams, while another has data on pyrazolones. Again, one center has results about the use of patch and scratch/patch results in healthy persons and drug-exposed controls, while two centers also have data on patch tests in healthy drug-exposed individuals. Based on these experiences, the appropriate concentrations of test solutions are determined locally in each center; these differ among the various centers.

*Have there been adverse reactions to skin testing?*

Most centers report very low frequencies of adverse reactions to skin testing ranging from 0.1% to 1% of the total number of investigations performed, but provide no details about selected groups of patients. In three centers, where immediate-type reactions to  $\beta$ -lactams are tested frequently, higher numbers of adverse reactions are observed (10%, 6%, and 15%), especially in patients with positive ID tests for  $\beta$ -lactams.

*Do you repeat skin tests?*

None of the centers visited repeats skin tests on a routine basis. Those investigators reporting repetition of skin tests specified two different reasons, one being equivocal results (negative result despite positive history or positive result when testing for “safe” alternatives), the second being systematic repetition

**TABLE 6**  
DRUG PROVOCATION TESTS

Centers	Procedure
A	Yes, if tests are negative or not considered conclusive according to the literature
B	Not routinely
C	Yes, with drug alternatives
D	Yes, with drug alternatives
E	Not routinely except for aspirin
F	Yes, with drug alternatives of the same group (after ST with these drug alternatives)
G	Yes, if tests are not conclusive and no previous life-threatening reaction reported, otherwise with drug alternatives
H	Yes, if negative ST and negative laboratory results
I	Yes, if negative ST and RAST, starting with drug alternatives but also with the culprit drug if no previous life-threatening reaction reported
J	Yes, if negative ST and RAST for $\beta$ -lactams with the culprit drug With the culprit drug or alternative drugs if ST not done or not conclusive and no previous life-threatening reaction reported
K	Rarely, unless there are no alternative drugs and the clinical history and ST results are not clear Bronchial challenge with ASA for NSAID intolerance
L	Rarely with the culprit drug, unless there are no alternative drugs, otherwise with drug alternatives Bronchial and nasal challenge with ASA for NSAID intolerance

ASA = [Please define]; NSAID = nonsteroidal antiinflammatory drug; RAST = radioallergosorbent test

as performed by just one institution (argument: “resensitization” might occur with each new course of therapy) [6].

When testing for drug allergy retrospectively, one has to keep in mind that the extent of sensitization to a drug decreases over time; a test being performed more than three months after the reaction might thus lead to a negative reaction [3] but cause boosting and by that a positive reaction when testing again a few days later [6].

### Drug Provocation Test

*Do you perform provocation tests? Which are the indications? Do you look for alternative drugs?*

All centers perform provocation tests, but the goals differ. Whereas some of the centers consider the drug provocation test (DPT) the “gold standard,” and apply it quite generously, others use it almost exclusively to define safe alternatives to the suspected trigger of an adverse reaction under investigation. The general guidelines used at each center are presented in Table 6.

In most institutions, DPT with the suspected drug is performed only if case history, laboratory tests, and skin tests do not lead to unequivocal results – and only when the drug under investigation is an “important” one. Nonsteroidal antiinflammatory drugs may be termed an exception, since most centers

agree that skin testing for these drugs is not relevant, *in vitro* testing not reliable in most instances, and case history usually not helpful because these drugs are commonly taken in combination with antibiotics or other drugs.

Testing for alternative drugs, either from the same group (e.g., ceftriaxone in a patient reacting to another cephalosporine) or from a nonrelated group, has high priority since it is common belief in all institutions that recommendations for “safe” alternatives should only be given after exposure-proven safety.

In all centers, patients are provided with a written report, including the most likely diagnosis and the recommended drug alternatives.

### Laboratory Findings

*Do you perform parallel laboratory studies? Which ones? When? Are these used routinely or only for research purposes?*

All institutions perform laboratory tests, but the number of relevant and commercial tests is limited. Detection of immunoglobulin E (IgE) antibodies is the first step in the evaluation after immediate-type reactions if tests kits are available; this is currently true only for  $\beta$ -lactams, insulin, gelatine, suxamethonium, adrenocorticotrophic hormone (ACTH), protamine, and chymopapaine.

**TABLE 7**  
LABORATORY STUDIES

Centers	Laboratory studies used routinely (Ro) or for research only (Re)	Comments
A	Re – FAST/Basotest for all positive results	Results do not influence clinical decision
B	Ro – RAST for $\beta$ -lactams Re – LTT	All results taken into consideration
C	Ro – RAST for $\beta$ -lactams Re – LTT, CAST	
D	Ro – RAST for $\beta$ -lactams Re – Specific IgE to drugs that bind to sepharose used as solid phase; tryptase if <b>DPT [okay?]</b> positive	All results taken into consideration
E	Ro – RAST for $\beta$ -lactams (RIA NH4+), tryptase, histamine Re – Histamine release test, basophil (CAST) and lymphocyte activation test	
F	Ro – RAST for $\beta$ -lactams Re – Lymphocyte activation test if the diagnosis is highly probable	
G	Ro – RAST for $\beta$ -lactams	Results taken into consideration
H	Ro – RAST for $\beta$ -lactams and all the drugs available Re – CAST for NSAID	All results taken into consideration
I	Ro – RAST for $\beta$ -lactams Re – Tryptase before and after challenge	
J	Ro – RAST for $\beta$ -lactams Re – Basotest, LTT, cytokines	Not considered for diagnostic purposes
K	Ro – RAST for $\beta$ -lactams and some GA	
L	Ro – RAST for $\beta$ -lactams Re – LTT, Basotest, 15-HETE for study of NSAID reactions	Not considered for diagnostic purposes

CAST = cellular antigen stimulation test; GA = general anesthetics; HETE = hydrox-yeicosatetraenoic acid; LTT = lymphocyte transformation test; NSAID = nonsteroidal antiinflammatory drug; RAST = radioallergosorbent test

Techniques like the lymphocyte transformation test (LTT) [7], the sulfidoleukotriene release test (cellular antigen stimulation test – CAST) [8], and a flow-cytometric basophil activation test (e.g., Basotest<sup>®</sup>) [9] are widely used for research purposes. In most centers, patients are selected for such tests according to the clinical characteristics of the reaction. Although mainly evaluated for research purposes only, the results of these investigations are taken into account for further clinical decisions in most centers; however, only three centers say they do so. Table 7 summarizes the laboratory work performed in each center and the techniques commonly used for research purposes.

### Ethical Issues

*Do you ask for written informed consent? Ethics committee approval?*

Most centers think it is not necessary to ask for the patient's written informed consent to perform skin testing but do ask patients to sign such consent for provocation challenge, although this is quite variable. In two centers, patients do not have to sign

for any procedure, while two others even ask for patients' signature for prick tests. At most centers, it is believed that the investigations are the only way of making the diagnosis; the procedures are not considered experimental and therefore do not need the approval of an ethics committee unless they are performed in the context of a research investigation or clinical study.

### General Framework

*Is there a diagnostic network for drug allergy? How many drug allergy consultation centers exist in your country?*

The centers visited work in a stand-alone manner. In some instances, efforts are made to contact other centers from the same region. Most of those in charge do not know about other existing drug allergy consultation institutions in their country or region. In France, three different groups are working on the organization of networks, one connecting departments of internal medicine dealing with drug allergy, another dealing with dermatology/drug allergy consultations, and a third involving the

French Society of Allergology and Clinical Immunology. In Germany, an organized network exists only for bullous skin diseases and bullous skin reactions to drugs [10].

In some countries, national pharmacovigilance organizations collect reported information on untoward drug reactions from drug-specific and nonspecific consultation facilities.

The urgent need for networks, presumably for research but also to improve standards, was expressed in all centers visited.

## Conclusion

The present investigation clearly demonstrates heterogeneity among the different centers evaluating drug hypersensitivity reactions. ENDA is a valuable effort to improve this but it still has some way to go in defining appropriate recommendations which have a proper evidence base. Several of the current position papers might best be described as research agendas and expert opinions rather than position papers fulfilling the criteria of evidence-based medicine. Collaboration and coordination are desirable goals which do not depend on the existence of dedicated clinics. Even in respect of issues which have been debated and agreed upon within ENDA (for instance, the way of collecting data through the ENDA questionnaire) [2], the recommendations have not been effectively put into practice. Thus, protocols and guidelines must be concise and practical in order to be applied in clinical routine.

Consensus or position papers are of limited value in the absence of a mechanism to enforce them. It is reasonable to assume that the existence of specific drug allergy consultation facilities would enhance the diagnostic efficiency and encourage patients to make use of such services.

The choice of how to proceed with skin tests [3] is not always dependent on purely clinical factors, it is sometimes dictated by economic and logistic conditions, or mere habit. The materials used, and especially the drug reagents employed for skin testing differ widely from center to center. This is partly explained by the lack of commercialized drug diagnostic reagents to study these reactions. Indeed, the only standardized tests are the commercial penicillin skin tests reagents (BPO-PLL and MDM-PLL from Allergopharma). In most instances, investigators have to prepare their own reagents and use drugs primarily conditioned for therapeutic purposes and not for drug allergy diagnosis. Most centers use drugs provided in different forms (syrup, pills, capsules, powder, preparations for topical use and, preferentially, IV preparations). This poses some problems, particularly when ID testing is performed, since the preparations for IV use vary considerably from country to country. Moreover, commercial preparations may contain dyes, antioxidants, preservatives etc., some of which may be responsible for allergic or pseudo-allergic reactions. The concentrations of the active substance in these commercial drug prepara-

tions also vary in different countries. The centers use them in various dilutions and vehicles, based on the published literature, but usually according to experience at each center. Data concerning these tests in healthy controls and/or drug-exposed individuals are still scarce. Some centers prepare their own reagents for ID skin test use (sterile solutions) using the pure molecule furnished by pharmaceutical companies. However, this is not always feasible, being expensive and time-consuming. Data concerning the stability of such home-made reagents are also scarce. The pharmaceutical industry is called upon to take note of this problem and to provide commercial test reagents for those drugs which cause allergies most frequently. Regulatory problems in the individual countries pose a further problem, since the respective drugs are not approved for specific use (skin tests).

The positivity criteria for skin tests vary from center to center. This renders comparisons of the results impossible. The fact that a universal definition of a positive reaction can be achieved is illustrated by the rather good acceptance of the ICDRG criteria for patch test interpretation [5].

Adverse reactions to skin tests are not considered to be a problem in most centers. The procedures in use are quite safe if performed cautiously. However, the records are usually poor. They should be evaluated in relation to the total number of confirmed positive drug-allergic patients and should also be related to the type of reaction experienced by the patients, not only to the overall response to the skin tests performed.

Although many laboratory techniques are being applied to study drug allergy patients, most of them are still experimental in nature and mainly used as research tools in specialized centers. Therefore, skin testing and provocation tests [4] remain an important means of studying drug hypersensitivity reactions.

Ethical considerations have been widely debated within the ENDA group, as the procedures are not standardized and many of them lack consensual guidelines. In most cases the choice is between two equally unsatisfactory options for the doctor as well as the patient, namely either do something to study a patient and try to make a diagnosis with imperfect techniques, or do nothing. It is also important to involve the patient in decisions regarding the investigative procedures.

The achievement of a standardized drug allergy diagnosis in Europe still requires considerable efforts. Practical details such as the material used for skin testing (needles or lancets) or the mode of performing tests (e.g., ID in the forearm or back, reading at 15 or 30 min) can be easily standardized. An even more important objective, which appears to be a long-term goal at the present time, is the wide availability and distribution of standardized drug reagents for skin and laboratory tests as well as agreement on detailed test protocols. But standardization, despite its necessity, must never represent a goal in itself but rather be something that is very important to enable proper research to take place and also, through this, to achieve a better degree of precision, allowing us to advise this important group of patients on the basis of proper evidence.

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