Giornale Italiano di Dermatologia e Venereologia
EDIZIONI MINERVA MEDICA

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Giornale Italiano di Dermatologia e Venereologia 2020 Sep 17
DOI: 10.23736/S0392-0488.20.06698-5

Article type: Review Article

Article first published online: September 17, 2020
Manuscript accepted: June 22, 2020
Manuscript revised: June 15, 2020
Manuscript received: April 30, 2020

Skin tests in the diagnosis of adverse drug reactions: a systematic review

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Word count: 8337

Number of references: 131

Number of tables: 19

Number of figures: 4

Funding sources: None

Conflict of interest: All authors have no interests to report

The article has not been previously published and is not currently submitted elsewhere

ABSTRACT

Adverse Drug Reactions (ADRs) are common and influence negatively the patient's therapeutic options. They recognize multiple pathogenic mechanisms, some of immunological origin, and the clinical manifestations involve several organs and systems, including skin and/or mucous membranes in 25–30% of patients. The identification of the trigger drug remains a medical challenge, mainly in poly-medicated patients. Anamnesis and clinical approach are crucial, but allergy work-up is the essential tool to confirm or exclude the causative role of the culprit drug. Besides *in vitro* tests and drug provocation test, skin tests (ST) represent the cornerstone: patch test in delayed ADR, prick test in immediate ADR, and intradermal test in both. Nevertheless, ST are in continuous evolution and characterized by technical difficulties (concentration and vehicle) that can influence their value and specificity.

In this article we review the indications and the rules in performing patch test, prick test, and intradermal test with the most commonly used drugs in Italy to determine the cause of a cutaneous and/or mucous ADR, precise the involved pathogenic mechanism, and provide a valid therapeutic alternative to the patient.

KEY WORDS: Adverse drug reaction; Patch test; Prick test; Intradermal test; Skin test; Review.

1. Introduction

Adverse drug reaction (ADR) is defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product".[1] Adverse drug reactions are classified into six types: dose-related (Augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure).[1] ADRs are immunologically mediated adverse reaction to medicinal substances and are therefore included among non-dose-related reactions.

According to their chronology, ADRs can be classified in immediate and non-immediate. Immediate ADRs tend to occur within 1 hour (h) after drug administration but may develop after 1-6 h. Exceptionally immediate ADR can arise later, up to 10 h (immediate-delayed ADR). Non-immediate ADRs occur later than 6 h, mostly 24 h, up to days (D) after drug intake (Figure 1).[2] Sometimes the time of onset does not allow differentiating immediate from non-immediate ADR. Moreover, the anamnesis provided by patients could not be clear. In these cases, clinical features can be useful to define immediate and non-immediate ADR. Time intervals between initial drug use and first onset of symptoms can change according to clinical phenotypes of ADR (Table I).[3-5]

2. Cutaneous adverse drug reactions

ADRs can affect any organ and system, but skin and mucous membranes are the most frequently involved.[1] Skin manifestations are manifold and include:

- *Urticaria/angioedema*. Urticaria is characterized by the sudden development of wheals consisting of central swelling of variable size, surrounded by a reflex erythema, itching (or sometimes a burning sensation), and fleeting nature, with the skin returning to its normal appearance, usually within 1-24 h (Figure 2a). Wheals can be localized anywhere on the body. Angioedema is characterized by pronounced whitish or skin-colored swelling of the lower dermis and subcutis with frequent involvement below mucous membranes, pain (rather than itching), and resolution in up to 72 h (Figure 2b). Angioedema often affects the face (cheeks, eyelids, lips, ears) and genitalia, but also oral mucosa, tongue, larynx, and pharynx.[6]
- *Anaphylaxis*. Anaphylaxis is defined as severe, life-threatening, systemic hypersensitivity reaction, which is characterized by life-threatening airway, breathing, or circulatory problems, usually associated with skin and mucosal changes (generalized urticaria, angioedema, erythroderma, and itch).[7]
- *Maculopapular eruption (MPE).* MPEs are characterized by acutely erupting, widespread multiple small, round to oval, erythematous macules and/or papules, with different degrees of confluence (Figure 3a). The individual lesions persist for several days. Drug-induced MPEs typically involve flexural areas, with symmetric centrifugal spreading (sparing palms and plants), and resolution with scaling. They are frequently associated with itch and eosinophilia.
- *Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE).* SDRIFE is a symmetrical erythematous rash on the gluteal and intertriginous areas observed after exposure to systemic drugs (Figure 3b). Previously, it was referred as baboon syndrome, due to the distribution of the lesions which are localized to the buttocks and inner thighs (resembling the red rump of baboons).[8]
- *Erythema multiforme major (EMM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).* EMM (also called EM with mucosal involvement) presents with typical target lesions (Figure 3c) and with or without raised atypical target lesions. The lesions do not show

confluence and are often restricted to the limbs and sometimes disseminated. There is mucous membrane involvement and cutaneous blistering with epidermal detachment of <10% body surface area (BSA) (Figure 3d). EMM is mainly caused by infections and rarely induced by drugs. SJS and TEN are considered as severity variants of the same disease entity. The lesions in SJS/TEN are macules and flat atypical targets that show confluence and on which blisters occur leading to various amounts of skin detachment, associated to haemorrhagic erosions of mucous membranes (oral, nasal, conjunctival, genital, anal) (Figure 3e). The skin may be initially painful. Bullous lesions develop often within 12 h, both on the skin and on mucous membranes. Patients are severely ill and often develop fever. The area of confluent bullae leading to detachment of the skin is <10 % BSA in SJS, 10-30% in SJS/TEN overlap, and >30% in TEN. Nikolsky's sign is positive in TEN. SJS/TEN is usually triggered by a drug, rarely by an infection.[9]

- *Acute generalised exanthematous pustulosis (AGEP*). AGEP is characterized by sudden onset of disseminated non-follicular, small, sterile pustules on an erythematous skin with no or minimal mucous membrane involvement. Intertriginous areas and the trunk are often involved. Pustules may become confluent and form large very superficial detachment with scales and crusts (Figure 3f). AGEP is typically itchy. Patients have fever and leukocytosis with neutrophilia and sometimes mild eosinophilia in the peripheral blood. Systemic involvement with hepatic, renal, or pulmonary insufficiency occurs in approximately 20% of cases.[10]

- *Generalized pustular figurate erythema (GPFE)*. GPFE, the Schwartz-Janniger syndrome, is a distinctive severe cutaneous ADR with widespread urticarial or edematous plaques scattered over the entire body that become topped with non-follicular pustules that evolve into erythematous and sometimes atypical targetoid plaques converging into annular and arcuate patterns prominent on the trunk and extremities.[11] It has been linked with medications, especially hydroxychloroquine, and was delineated in the beginning of the COVID-19 pandemic. GPFE has characteristic varied morphology that is reminiscent of both AGEP with its pustulosis and SJS/TEN with its targetoid component, hence it had been labelled previously as atypical AGEP or AGEP/SJS/TEN overlap. Unlike AGEP, which has an onset usually within 48 hours of ingestion, GPFE is typically characterized by an onset of 2 to 3 weeks.

- *Drug reaction with eosinophilia and systemic symptoms (DRESS).* The disease usually starts abruptly with fever of >38 C. The cutaneous lesions usually appear as a MPE, but pustular, bullous, target-like or eczema-like lesions can be observed. The lesions are symmetrically distributed on the trunk and extremities, with palms and soles usually spared. The most characteristic cutaneous lesion is a facial edema (Figure 3g). Mucosal surfaces can occasionally show a few lesions. Lymphadenopathy can be found favouring the cervical, axillary, or inguinal regions. In the peripheral blood, eosinophilia, leukocytosis, and atypical lymphocytes are often found. Concerning further involvement of internal organs, hepatitis with elevation of liver enzymes, nephritis, pneumonitis, myocarditis, colitis, pancreatitis, or arthritis can be observed. Prolonged courses and flare-ups, even after discontinuation of the culprit drug, are common. A link to reactivation of herpes viruses (Human Herpes Virus 6 and 7, Epstein Barr Virus, Cytomegalovirus), which are commonly detected in DRESS, has been speculated.[12]

- *Fixed drug eruption (FDE).* FDE manifests with a characteristic erythematous to violaceous, sometimes oedematous plaque, which may become bullous centrally (Figure 3h). This lesion always arises at the same site after re-exposure to the culprit drug. The lesion characteristically resolves with residual hyperpigmentation. Sometimes multifocal fixed drug eruptions do occur.[13] If they are bullous and widespread over the body, they are called generalized bullous fixed drug eruption (GBFDE). In contrast to patients with SJS/TEN, patients with GBFDE have more rapid onset (in 1-24 h rather than in 1-4 weeks), no systemic symptoms, the lesions are well demarcated

and the mucous membranes are rarely involved.[14,15] In these cases, also a drug-induced bullous pemphigoid should be excluded.[16]
The first clinical approach step when observing a patient with a suspected ADR is a precise characterization of the clinical phenotype and chronology. The next crucial step is the careful evaluation of the possible offending drugs. Algorithms, like the one from French Pharmacovigilance system[17] or the Naranjo[18] score can help finding the most probable culprit. They are based on medical history, selection of drugs introduced within the usual latency period for each pattern of ADR, and identification of those drugs that, according to previous publications, are usually associated with such a reaction pattern. Specific algorithms are proposed for betalactams[19,20] and non-steroidal anti-inflammatory drugs (NSAIDs)[21] induced ADRs. Despite these tools, sometimes the identification of the culprit drug is challenging, and the use of computer-aided diagnosis systems was proposed.[22]
The information that should be documented are reported in Table II.[3]

3. Skin tests

The diagnostic approach in patients with ADR is complex and requires multiple steps. Anamnesis and clinical approach are essential to design a correct workup. Afterwards, especially in case of severe ADR, *in vitro* test should be performed. These are safe, without risks of local and systemic reactions, but sensitivity and specificity vary depending on the drug involved and the clinical phenotype.[19] In case of negative *in vitro* tests, the diagnostic work-up continues with in *vivo test*, starting with ST. Finally, if also ST give negative results, a drug provocation test is often necessary to provide a definite diagnosis.[3]

3.1. Skin tests: which to perform

Immediate ADR are investigated by skin prick test (SPT) and intradermal test (IDT) with immediate reading and in selected cases also by patch test (PT) with immediate reading. Non-immediate ADR are studied by PT and IDT with late readings. Scratch tests with drugs are poorly standardized and are not recommended.[24]
There is no consensus on the safety of ST in patients with severe ADR (anaphylaxis, SJS/TEN, DRESS, AGEP). PT, performed according to the recommendations and with appropriate concentration adjustment, is a safe diagnostic test, even in severe ADR. The risk of ADR reactivation is very low, and the reactions are usually mild. There are very exceptional reports of anaphylaxis when PT is incorrectly performed.[25] Only if PT results negative, the work-up continues with SPT and IDT. These have been recommended in mild ADR, while their application in severe ADR needs to be considered with caution and reserved when suspected drug is needful for the patient.[26-29]

3.2. Skin tests: sensitivity

PT is estimated to provide informative results in less than 50% of cases, but shows great variability related to population tested, drugs, methodology, and type of ADR. The sensitivity of ST appears to be moderate to high for immediate ADR to betalactam antibiotics, perioperative drugs, heparins, platinum salts, radiocontrast media, but low for many other drugs.[24] For example, PT with allopurinol results frequently negative in patients with confirmed severe non-immediate ADR, like DRESS.[30] Moreover, it has been reported that PT may be more useful in AGEP and less useful in SJS/TEN. SPT and IDT may increase the diagnostic value (10–20%) in non-immediate cutaneous ADR.[26]
Sensitivity and specificity of ST will be discussed separately in the session dedicated to single classes of drugs.

3.3. Skin tests: how to perform

ST cannot be performed during the acute phase of the ADR. It is recommended to wait at least 6 weeks after complete resolution of the reaction and perform ST within the following 6-12 months.[31] Moreover, postponing of ST investigations should be considered in patients with systemic immunosuppressive treatment in relevant doses. In case of chronic treatment, when it is difficult or impossible for patients to stop their immunosuppressive drugs, ST may be undertaken. Nevertheless, the clinicians must be aware that false-negative reactions may occur. When chronic immunosuppressive therapy is stopped to avoid false negative results, a period of five drug half-lives is requested. Antihistamines have not been reported to influence the allergic PT reaction, while they seem to affect SPT and IDT with immediate readings. Beta-blockers should be stopped on the day of ST because they reduce the response to some rescue therapies (adrenergic, beta agonists) in case of systemic reactions. Postponing of ST investigations should be considered when ST sites are involved by skin lesions, recently treated with topical corticosteroids (CS) (in this case 7 days of postponing are considered adequate), and recently exposed to ultraviolet rays.[32]

Timing of tests, the choice of tested substances and test concentrations depend on the suspected pathomechanism, the severity of the reaction, and the risks associated with the chosen ST method.[3]

Although rarely, ST with the culprit drug can elicit systemic, sometimes life-threatening, reactions. For this reason, ST have to be performed in protected environment, and the physicians and the nurses must be able to solve potential emergency situations.

An individual risk–benefit assessment is essential in all cases. PT during pregnancy or lactation is not harmful but postponing testing is recommended, while SPT and ID are more invasive and should be avoided. Other contraindications are patients affected by uncontrolled asthma and chronic urticaria-angioedema, severe diseases or in those treated with drugs that carry a considerable increased risk, inadequate compliance, lack of understand of the ST procedure and risk.

De novo sensitization as a result of ST is possible, whereby this risk depends on the substance tested, its concentration, and the test method used. Therefore, ST should only be performed with the drug suspected of triggering the ADR, possible cross-reagents, or relevant alternatives.

Whenever possible, both the pure drug and excipients should be tested. ST should be prepared using the pure active ingredient or, alternatively, the parenteral (preferably intravenous) preparation of the suspected drug. The recommended concentrations for PT, SPT, and IDT are given by literature data. If literature is lacking, the drug concentration must be established in 20 healthy controls, using increasing drug concentration. In these cases, incremental increases of the test substance concentration (1:1000, 1:100, 1:10) can reduce the risk of severe allergic reactions.

When the drug is available only in oral formulation or topical form, only PT and SPT can be performed, because of high risk of irritating reactions on IDT. Despite there are no standardized protocols on the optimal drug concentration available for ST prepared with an oral formulation, the common practice is to dissolve the tablet/capsule content in 0.9% saline solution and to use the maximum concentration achievable, considering that a lot of drugs are poorly soluble in water and saturated suspension is used.[3,23] If possible, the drug for PT should be dissolved in petrolatum (pet), while for SPT and ID the drug needs to be diluted only in saline solution in order to avoid irritant reactions.

ST reactions can occur also later, sometimes also more than 1 week. Flare-up after drug provocation test or drug reintroduction by the patient are also reported.[33] Patients need to be informed that, in such cases, they should immediately inform the treating physician.[3]

3.3.1. Patch test

PT in ADR are performed on the upper back, as for the investigation of allergic contact dermatitis (ACD). PT are removed after 48 h (D2) and readings are performed at D2 and D3 (Figure 4a). In special situations, the PT performing and its readings can be modified. For example, PT must be performed in the pigmented lesion of FDE together with PT on uninvolved skin. In this case, the culprit drug is vehicled in pet but to enhance PT sensitivity, dimethyl sulphoxide (DMSO) is used as vehicle. PT in FDE is left for 6-24 h, usually under occlusion with a PT chamber, and readings are performed at D1 and D2 (possibly also at 6h), as the reaction is usually accelerated.[3,32,34]
In the case of anaphylaxis and high risk of systemic test reactions, an open test or a PT with an early reading at 20-30 min could be performed.[3,32,34] In the case of CS allergy, additional readings at D7 can be helpful (Figure 4b).[35]
PT reactions are valuated as for ACD. Other reaction patterns (pustular, lymphomatoid, or bullous) that reproduce the clinical manifestation of a severe ADR may occur.[32,36-39] In the case of suspected photo-induced reactions, photo-PT should be performed.[32]

3.3.2. Prick test
SPT are performed in case of immediate ADR. If it is possible, especially for severe ADR (anaphylaxis), SPT should follow a negative open test or PT with an early reading. In selected cases, SPT should be performed for non-immediate ADR with late reading after 24 h.[3] SPT are performed on the volar aspect of forearm. It is considered positive when the diameter of the reaction is larger than 3 mm than that observed to negative control (0.9% saline solution) (Figure 4c).[26]

3.3.3. Intradermal test
IDT is useful to study both immediate and not-immediate ADR. IDT needs to be performed after the negative result of PT and SPT. Dilutions should be prepared no longer than 2 h preceding administration. IDT are performed in the same site of SPT, with a solution volume (0.04 ml) that produces a wheal of 4 to 6 mm in diameter. A negative control is performed with saline solution. At 30 mins reading, IDT is considered positive if a wheal of more than 10 mm in diameter is observed (Figure 4d). In case of non-immediate ADR, a late reading after 24 h is needed, and the diameter of the papule is measured.[26]

3.4. Skin Tests: reporting
The report of the ST results must be very exhaustive and understandable. Drug tested, concentrations, and vehicle used for all performed ST must be reported. In case of marketed preparation, the trade name of the drug used must be reported, in order to know the possible excipients contained. The positive reactions must be reported with semi-quantitative (+, ++, +++) valuation.
A sentence explaining the risk of false negative reactions, and the eventual necessity to perform drug provocation test, must be clearly reported.
Especially in case of test with multiple drugs, a “Drug Allergy Passport” in English language should be drawn up.[40]

4. Antibiotics

4.1. Betalactams
BLs are the most common cause of ADR, probably due to their widespread prescription. They can induce both immediate ADR and non-immediate ADR.
Hypersensitivity reactions to BLs can be due to reactivity to the BL ring or the side chain. Among penicillin, benzylpenicillin allergy was mainly attributed to sensitization to the BL ring, especially in

the cases of immediate ADR, while amoxicillin allergy is more frequently related to sensitization to aminopenicillin side chain.[24] To better study the sensitization to BL ring, penicilloyl-poly-L-lysine (PPL) and minor determinant mixture (MDM) can be used. However, in non-immediate ADR ST with PPL and MDM have been demonstrated to be scarcely useful.[24] In order to improve SK sensitivity, penicilloyl-poly-L-lysine (PPL), minor determinant mixture (MDM), benzyl penicillin, amoxicillin and the suspected BL should be tested.[41,42] However, considering the actual low use of benzylpenicillin comparing to amoxicillin, PPL and MDM ST should be reserved to patients with suspected benzylpenicillin allergy and with suspected immediate ADR. Amoxicillin may be used in combination with a betalactamase inhibitors (e.g. clavulanic acid), that could be possible sensitizer.[43] In these cases, ST should be carried out against the original drug and individual component of the antibiotic combination.[24] Regarding cephalosporins, immediate ADR are actually attributed to structural involvement of the R1 and R2 chemical side in causing IgE-mediated reaction. Less studied are non-immediate ADR. The risk of cross-reactions related to side chain is resumed in Table III.[44] Despite the presence of BL ring, both carbapenems and monobactams are well tolerated in patients sensitized to BLs. Only in patients who are allergic to ceftazidime, there have been reports of aztreonam reactions, which are due to a shared R1 side chain.[45,46]

ST remains the most important method for confirming BL allergy. The sensitivity of BL ST may be as high as 70% in immediate ADR and 10-30% in non-immediate ADR.[23] However, in immediate ADR, they should be preceded by *in-vitro* test.

According to these considerations and literature data,[24,41-48] and considering the antimicrobial spectrum of drugs available in Italy, we suggest a wide betalactam series, including penicillin, cephalosporins of all generations, and carbapenems (Table IV).

4.2. Quinolones

Quinolones are the second most common antibiotics associated with allergic reactions, following BLs. Interestingly, a previous diagnosis of ADR to BL antibiotics has been shown to be a strong risk factor for developing quinolone allergy.[49] Quinolones ADR incidence has increased in recent decades, likely due to the extensive utilization and the introduction of moxifloxacin. Despite this, data on quinolone allergy are scarce and real incidence of ADR is not reported. Immediate ADR are more common and severe for 70% of cases. Clinical entities typical for immediate ADR are urticaria with or without angioedema (31.6-85%) and anaphylaxis (32.8-42.1%). The most common trigger is ciprofloxacin (23.2-43.7%), followed by moxifloxacin (15.4-63.2%), and levofloxacin (7.9-38.5%); moxifloxacin is most frequently involved in anaphylaxis. Non-immediate ADR to quinolones are less common. MPE and FDE are the most reported reactions, but also severe ADR, like AGEP, SJS, and TEN have been reported. The most frequently involved quinolone in non-immediate ADR is ciprofloxacin, followed by levofloxacin and moxifloxacin.[49-51]

Quinolones can be classified, according to generation and antibacterial spectra, in 4 groups: first generation includes cinoxacin and nalixidic acid; second generation includes ciprofloxacin, enoxacin, lomefloxacin, norfloxacin, ofloxacin, pefloxacin, and rufloxacin; third generation includes gatifloxacin, levofloxacin, sparfloxacin, and tosufloxacin; fourth generation includes gemifloxacin, moxifloxacin, and trovafloxacin.[52]

ST with quinolones are not well standardized and have displayed low sensitivity and specificity. IDT showed higher sensitivity but have a higher risk for inducing irritant and false-positive reactions. For SPT and IDT, widely divergent non-irritant test concentrations have been recommended.[50-52] For these reasons, drug provocation testing is considered the gold standard to establish diagnosis. Our recommended concentrations are reported in Table V.

Cross-reactivity within the quinolone drug class has been reported in the literature, but the evidences are conflicting. It has been suggested to be associated with the 4-oxo-1,4-

dihydroquinoleine ring core, although the structure of groups bound to the C1, C5, C7, and C8 positions may also play a role.[51] Some reports describe a cross-reactivity among quinolones, with a recommendation to avoid any quinolone among patients who have had a reaction to one of them. Conversely, other studies demonstrated a lack of cross-reactivity among moxifloxacin and ciprofloxacin and levofloxacin, explained by moxifloxacin's unique side chain, and tolerance of ciprofloxacin in some patients sensitized to levofloxacin and viceversa.[51] Moreover, ADR to quinolones has also been associated with neuromuscular blocking agent (NMBA) sensitization.[52]

4.3. Other antibiotics

Sometimes the anamnesis is unclear, because the patient referred multiple reactions to antibiotics belonging to different families or does not remember the culprit antibiotic. Moreover, in many cases antibiotics belonging to multiple classes are used, both in therapy and in prophylaxis. In these cases, a wide series of antibiotics, including all the most used classes, are recommended (Table VI).

5. Azoles

Azole antifungal agents are the largest and the most efficient class of synthetic antimycotics. They are classified into two groups: imidazoles, with two nitrogen atoms in the azole ring, and triazoles, with three nitrogen atoms in the azole ring. Moreover, azoles drugs include a large family of substances with an imidazole ring in their chemical structure (Table VII).[53]

The most frequently reported ADR to azoles are ACD, due to their widespread topical use[54,55], but systemic ADR have also been reported. Azoles immediate ADR are very rare. Among non-immediate ADR, MPE, SDRIFE, FDE, and anecdotal severe ADR (SJS/TEN, DRESS, and AGEP) are reported.[53]

Despite data of literature are poor, in immediate ADR, no allergic cross-reactivity has been evidenced. On the contrary, in cases of non-immediate ADR, the existence of cross-reactivity among the different imidazole compounds has been investigated and demonstrated.[52] It has been suggested that azoles belonging to phenylethyl imidazoles are more likely to cross-react among themselves than with phenylmethyl imidazoles, which show a low degree of cross-sensitivity among themselves.[56]

The diagnostic accuracy of ST for antifungal azoles is not well established. Our antimycotic azoles series is reported in Table VIII.

6. Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a wide class of drugs, including several active ingredients belonging to several classes (Table IX).

They are recognized, together with BL, to be the most common drugs involved in ADR, and skin is the most frequent organ involved.[57] The European Academy of Allergy and Clinical Immunology (EAACI) provided a new classification for NSAID-induced ADR that has been progressively adopted worldwide.[58] This includes five clinical entities, four of them are characterized for immediate reactions (NECD: NSAID-exacerbated cutaneous disease; NERD: NSAID-exacerbated respiratory disease; NIUA: NSAID-induced urticaria angioedema; SNIUAA: single NSAID-induced urticaria, angioedema or anaphylaxis) and one that includes several delayed reactions (SNIADR: single NSAID-induced delayed hypersensitivity reaction). To those five major groups, two additional entities have been added: organ-specific reactions and skin/systemic reactions. Moreover, the

patients who develop these reactions can be classified as selective responders (SR), if react to only one NSAID, or cross-intollerants (CI), if react to more than one NSAID (Table X).[59]
Considering the entities within the CI category (NERD, NECD, NIUA), the pathogenic mechanism seems to be non-immunologically mediated (non-allergic). NSAIDs share similar anti-inflammatory mechanisms, related to the inhibition of cyclooxygenases, enzymes which are responsible for the generation of prostaglandins and thromboxanes.[58] However, a more complex mechanism emerges considering all the by-products released, the enzymes involved, and the receptors through which the mediators signal.[58] In these cases, ST are always negative and not useful to confirm diagnosis.
In other patients, hypersensitivity symptoms occur only after the ingestion of a single, specific, NSAID (or more than one, but belonging to the same chemical group), while other chemically nonrelated drugs are generally well tolerated (SR). These reactions are usually immunologically mediated (allergic) and should be immediate (IgE-SNIUAA) or delayed (Tcells-SNIADR),[58] even if other non-immunologically mediated mechanisms are worth exploring.[58] In those cases, ST can be useful, especially for NIADR. It should be noted that in clinical practice, reactions that are blended or not well fitting into classification reactions may occur. Organ specific reaction can also be immunologically mediated, and ST can be useful also in cases of involvement of other organs, like in cases of NSAID-induces aseptic meningitis.[60]
PT with up to 10% NSAID in pet do not seem to be irritant to the skin. Concentrations up to 30% may be tolerated, although the additional value of using the higher concentration is unclear. The irritating potential of all NSAIDs appears to be low in SPT, and the specificity is thus high ($\gg$ 95%). For IDT, 0.1 mg/ml appears to be not irritating to the skin.[24]

7. Perioperative drugs

In most cases, patients undergoing surgery are exposed to multiple different drugs, mainly administered intravenously. These drugs can be responsible for anaphylactic reactions, with an estimated incidence that varies between 1:6,000 and 1:20,000.[61] Although the most common culprits are NMBA, followed by antibiotics, chlorhexidine, and latex, many other agents such as colloids, hypnotics, opioids, and dyes may be implicated. In 90% of cases, these reactions occur during induction of anesthesia.
Perioperative anaphylaxis may depend on a mast cell IgE-mediated degranulation, which requires previous sensitization to the culprit drug, or on a release of mediators determined by the direct stimulation (pharmacological or toxic) of the mast cells by the drugs. These two pathogenic mechanisms are the basis of clinical pictures usually indistinguishable.
The most common clinical manifestations are hypotension, bronchospasm, tachycardia, cyanosis, and bradycardia, while skin lesions (urticaria and angioedema) are less reported.[62]
The allergy diagnostic work-up of these reactions can be challenging because many different drugs are administered almost concurrently. In addition, the alterations of the vital parameters of the patients can be caused by the surgery itself and not by the drugs administered. Finally, the clinical skin manifestations, especially when modest, could not be detected in a fully draped patient and the anesthetized patient cannot refer itch.
The purpose of the dermatologists is to confirm the causal agent for the reaction and consequently to propose other drugs that are reasonably safe for any subsequent anaesthesia.
A perioperative test series (Table XI), edit on the base of literature data is suggested.[63-71] However, on the basis of an accurate anamnesis of the patient integration with other drugs is recommended. In particular, local anaesthetics, antibiotics and analgesic are frequently used in the premedication of patients undergoing surgery. For these drugs, we remand to the specific sections (see local anaesthetics, antibiotics, NSAIDs, and opioids).

8. Opioids

There is no universal agreement on the optimal vehicle (aqua, petrolatum, ethanol) or test concentration to perform PT with opioids. However, NIADR confirmed by positive PT have been described. Natural opioids (like morphine) induce nonspecific direct histamine release, probably due to off-target occupancy of MRGPRX2 receptors on the mast cells and basophils, leading to nonallergic reactions (itch, urticaria, angioedema, anaphylaxis) and false-positive SPT and IDT. Instead, syntetic opioids (like tramadole, fentanyl and derivates) seem not bind these receptors; consequently, SPT and IDT with these opioids seem more specific. To minimize erroneous reading due to histamine release or irritant reaction, it is proposed that increasing dilutions of the suspect opioid should be used. Despite this, the value of ST with opioids remains unproven, and optimal ST concentrations are unknown.[20,65-66,72-75] In Table XII possible concentrations for the more widely used opioids are suggested.
Codeine seems always cross-react with morphine, while fentanyl is usually well tolerated in codeine/tramadole sensitized patients.[76]

9. Local anaesthetics

Local anaesthetic (LA) molecules contain a lipophilic aromatic ring, connected to a hydrophilic amine group by a linking chain, that is used to classify the agents as esters or amides. Esters are used in topical preparations, while amides are used mainly in injectable form.
ADR to LA are rare; adverse events are reported in 0.1-1% of procedures in which LA are used and less than 1% of all adverse reactions are due to hypersensitivity. Non-immediate ADR are more frequent, but also immediate ADR have been reported.[77,78] Amides have a lower allergenic potential, because esters are metabolized by pseudocholinesterase to *p*-aminobenzoic acid (PABA), which is responsible for their stronger allergenic potential[77]. Cross-reactivity are common inside the ester and amide group molecules, while cross-reactivity between esters and amides should not occur, because the drugs chemical structures and their metabolites are different. Nevertheless, some cases of allergic reactions to both esters and amides have been described; it is unknown whether this was a consequence of co-sensitization or cross-reactivity.[77,78] Cross-reactivity between amide compounds is not well defined, but the meta-xylene aromatic ring (which is shared by mepivacaine, lidocaine, and bupivacaine) has been identified as a possible antigenic determinant.[79] It has been suggested that articaine is a reliable substitute in case of sensitization to amide LA,[80,81] because of the presence of a thiophen ring instead of meta-xylene ring, despite cross-reaction between articaine and lidocaine/bupivacaine has been reported.[82]
LA formulations frequently contain methylparaben and propylparaben as preservatives; these compounds have breakdown products that are chemically similar in structure to PABA. Additional potential allergens are sodium metabisulphite and sodium bisulphite, antioxidants present in epinephrine-containing LA.[83]
ST are useful in diagnosis of non-immediate ADR; negative results have a significantly predictive value of up to 97%.[77] They are less useful in immediate ADR, so that some Authors advise against the use of IDT, suggesting the use of SPT before subcutaneous challenge test.[78]
Undiluted LA appears non-irritant in PT and SPT, and 1/10 diluted LA has been shown to be non-irritant for IDT. PT could be performed also with concentrations higher than those used in clinical practice, especially for amides, while it is recommended that neat LA is used for SPT, and 1/10 dilution LA for IDT.[26] In case of severe ADR, SPT and IDT should be started with diluted (up to 1:10000) LA.[78] SPT and IDT should not be performed with LA containing vasoconstrictors like

adrenaline, as they mask a local wheal and flare reaction.[26,78] Ideally, patients suspected allergy to LA should be tested with amides and esters. The choice should mainly rely on local prescription habits and may change over time. Excipients should also be tested. The recommended LA series is reported in Table XIII.

10. Contrast media

10.1. Iodinated contrast media (ICM)

The molecular structure of ICM is characterized by a 2,4,6-triiodinated benzene ring. ICM can be classified as having a monomeric structure (if they have a benzene ring) or a dimeric structure (if the benzoic nucleus is covalently bound). ICM can be ionic, if they transform into ions or charged particles in aqueous solution, or nonionic, if they does not form ions, remaining electrically neutral in solution. Moreover, ICM can also be classified according to osmolality into high-osmolality ICM (≥1400 mOsm/kg H_2O), low-osmolality ICM (500-900 mOsm/kg H_2O), and iso-osmolalality ICM (290 mOsm/kg H_2O).[84] The ionization capacity and the osmolality are directly related to the frequency and severity of the adverse reaction to ICM.[85] For these reasons, ICM actually used are more frequently non ionic and low-osmolar.

ICM immediate reactions can be non-allergic or IgE-mediated. Allergic immediate hypersensitivity accounted for less than 10% of cutaneous ICM reactions, but more than 50% of life-threatening ICM reactions.[86] Unfortunately, only half of immediate allergic ICM reactions will potentially be identified using ST, and IDT seems to be the most sensitive test. Specificity, on the contrary, is very high (> 95%).[87]

ICM non-immediate ADR occur in 0.5-23% of patients receiving ICM.[88] They usually present as MPE, but also SDRIFE, FDE, AGEP, DRESS, or SJS/TEN have been reported.[89] Also in delayed allergy, about half of reactions can be documented by ST,[84] and IDT shows the best sensitivity, with very high specificity.[87]

Interestingly, both immediate and non-immediate ICM hypersensitivity reactions may occur at the first exposure to ICM.[87]

ST may have a role not only in confirming the pathogenic role of culprit ICM, but also in identifying an alternative ICM in patients with prior hypersensitivity who need further contrast imaging.[87,88]

The ICM used for ST need to be carefully chosen because of common cross-reactivity between different products. Iodixanol, iohexol, iopentol, ioversol, and iomeprol present frequent cross-reactivities (especially iodixanol and iohexol), while ioxaglate, iopamidol, iopromide, and iobitridol show limited cross-reactivity.[84-87]

ST are performed with the ICM involved in the reaction if known. If the result is positive, or if the culprit ICM is unknown, ST should be performed with the broadest possible panel of ICM.[84] PT and SPT with a wide ICM test panel is recommended (Table XIV), performing IDT with alternative ICM separately, until finding a not-reacting ICM. However, a negative ST result to an alternative ICM does not necessarily mean that the patient will tolerate its administration, and premedication and controlled administration are recommended.

PT and SPT are performed with undiluted ICM,[24,86] while IDT with progressive dilution of ICM (1:1000, 1:100, 1:10) is recommended. For non-immediate reactions, IDT with undiluted ICM can be performed, but the risk of irritating reactions needs to be considered.

10.2. Paramagnetic contrast media (PCM)

PCM are widely used in magnetic resonance imaging (MRI). PCM are based on paramagnetic ion gadolinium and consist of complex molecules, resulting in chemical bonds between a gadolinium ion and a chelating agent. The chelating agents prevent the toxicity of gadolinium while

maintaining its contrast properties. The different chelating agents give to the molecule a cyclic or linear structure. Moreover, they can be ionic or non-ionic. PCM can be classified as linear ionic (gadopentetate dimeglumine, gadobenate dimeglumine, gadoxetate disodium, gadofoveset trisodium), linear non-ionic (gadodiamide, gadoversetamide), cyclic ionic (gadoterate meglumine), and cyclic non-ionic (gadobutrol, gadoteridol).[84,90]

Immediate ADR to PCM are more frequently described than non-immediate ADR, but their incidence is lower than 0.1%.[91] The most common clinical manifestation is urticaria (50-90% of cases), while anaphylaxis occurs with an incidence of 0.004% to 0.01%.[84] Cyclic and ionic molecules seem to be more sentitizing.[92] Rarely, anaphylaxis after first exposure have been reported; in these cases, latent sensitization induced by previous exposure to other macrocyclic structures (such as macrolide antibiotics) or to other gadolinium sources (magnet manufactures, metallurgical plants, fluorescent lamps, or television sets) have been suggested.[93]

Only one case of PCM-induced non-immediate ADR characterized by MPE has been reported.[94]

Cross-reactivity between gadolinium-based PCM is still unclear, although it appears less frequent between macrocyclic and linear substances.[90,93]

ST are useful for etiological diagnosis. Among these, the IDT seems to have the greatest sensitivity.[90] ST are quite safe, even if systemic reaction can be observed.[93] Commercial compounds of offending agents can be used. PT and SPT are performed using undiluted PCM, while for IDT it is recommended to use increasing concentrations (from 1:1000 to 1:10), and undiluted commercial compound should be avoided because of the risk of irritant reactions.[24,90,93]

As for ICM, ST are performed with the PCM involved in the reaction. If the result is positive or if the culprit PCM is unknown, ST should be performed with the broadest possible panel of ICM.[90] PT and SPT with a wide PCM panel is recommended (Table XV), performing separately IDT with alternative PCM tested, until finding a not-reacting ICM.

10.3. Fluorescein

Intravenous fluorescein can be responsible for ADR, including hypersensitivity reactions. The incidence of these events is not clear, changing considerably among different reports.[95]

Literature on ST to fluorescein is poor. Fluorescein has been used neat for SPT and 1:10 for IDT.[24,95]

10.4. Blue dyes

Experience with blue dyes is limited. SPT should be performed with undiluted solutions, while for IDT is recommended 1:10 dilution for patent blue dye and 1:100 for methylene blue dye. Cross-sensitivity has been described, and we therefore recommend testing other dyes.[24,96]

11. Antiepileptic drugs

Antiepileptic drugs (AED) are classified as aromatic (carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, primidone, zonisamide) and nonaromatic (clobazam, ethosuximide, gabapentin, levetiracetam, pregabalin, topiramate, valproic acid, vigabatrin).

Immediate ADR to AED are not reported. Instead, AED are frequently responsible for non-immediate ADR, both MPE, that occurs in 2-16% of patients who receive them, and severe cutaneous ADR, like SJS/TEN, DRESS, and AGEP. Aromatic AED are more frequently involved in severe reactions, especially phenytoin, lamotrigine, and carbamazepine in adults, and phenobarbital, carbamazepine, and lamotrigine in children. Children younger than 5 years have 3 to 5 times higher risk for AED-induced ADR. Other risk factors are immune system disorders,

systemic lupus erythematous, infectious diseases, and CS treatment. Moreover, high starting dose and rapid dose escalation were identified as risk factors.[97]

Clinical cross-reactivity has been reported mainly between the traditional aromatic AED, including carbamazepine, phenobarbital, and phenytoin, but also with newer aromatic AED, like lamotrigine and oxcarbazepine, between 15% and 70%, in different studies. More rarely, it was shown that sodium valproate may show PT cross-reactivity with aromatic AED, but clinical cross-reactivity is not determined. Cross-reactivity between nonaromatic AED has not been reported.

ST are useful for the diagnosis; it has been shown that the rate of positive PT ranges between 19.7% and 100%.[96] The diagnostic value of PT varies according to the incriminated drug, with a reported higher sensitivity for carbamazepine. Although there are limited data regarding the optimal concentration for PT, the maximum recommended concentrations have been found to be 10% in pet for pure substances and 30% in pet for commercialized forms of AED. In patients with suspicion of severe non-immediate ADR, such as DRESS or SJS/TEN, it is recommended to start at a concentration of at least 1%.[98,99] The sensitivity of PT seems unaffected by the vehicle used (pet, saline solution, water or ethanol).[24] SPT and IDT are less standardized. Concentrations of 0.1% and 0.01% have been suggested.[100]

Test with the culprit drug and a personalized series of alternatives, on the basis of the risk of cross-reactions and the therapeutics needs of the single patient, are recommended.

12. Heparins

Heparins are a complex mixture of polysaccharide chains and, based on their diverse lengths and molecular weights, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and ultra-LMWH (ULMWH) can be distinguished.[101]

Heparins are known to provoke all types of hypersensitivity reactions.[101] Non-immediate ADR are common, especially eczematous patches localized on the injection sites, after a latency of 2-10 days to 3 weeks;[101-102] however, if heparin treatment is continued, there is a risk of a generalized eruption.[26] Only rarely generalized MPE and exceptionally TEN have been described.[104] Conversely, only a few cases of immediate ADR have been reported, as urticaria, angioedema, palmoplantar itch, dyspnoea, and anaphylaxis.[101-102] Risk factors for hypersensitivity include obesity, female sex, pregnancy, and prolonged treatment.[102-105]

LMWH were the most frequent culprit heparins, probably because of their widespread use.[104] Cross-reactivity among heparins is frequently reported, both for non-immediate ADR and immediate ADR. The distribution of cross-reactions is independent of the heparin molecular weight[106,107], while fondaparinux, which is a fully synthetic pentasaccharide inactivating activated factor X, is considered a safe and effective alternative,[101,102] even though cases of cross-reactivity between fondaparinux and other heparins have been described, with different incidence rate (from 0.4%[101] to 10.4%,[107] up to 25% in small case series[108]). In case of non-immediate ADR to subcutaneously injected heparin, intravenous administration of the drug should be tolerated, may be because of differential processing on presentation of antigens depending on the route of administration. Furthermore, in case of therapeutic necessity, the shift from subcutaneous to intravenous heparin administration without prior ST may be justified.[103]

ST show high sensitivity in demonstrating the role of the suspected eliciting agent (83.3% in immediate ADR[101]), particularly PT for non-immediate ADR and ID for immediate ADR.[100,101] It is mandatory to perform a correct allergy work-up, not only to identify the incriminated heparin, but also to find a safe alternative, including UFH, LMWHs, and fondaparinux.[102]

Neat heparins appear non-irritant and can be used as such for PT and SPT, while can be irritant for IDT. IDT should be started with 1/10 dilution, and further tests 1/100 and 1/1000 dilution should

be conducted in the suspect of irritant reaction.[24] The recommended heparins series is reported in Table XVI.[102]
Heparin ST are contraindicated in patients with heparin-induced thrombocytopenia.[24]

13. **Corticosteroids**

CS are widely used to treat allergic diseases but may themselves give rise to ADR. Immediate ADR are very rare, with the prevalence estimated to be 0.1-0.3%. However, it is very important to suspect and to diagnose them, because of their life-threatening risk. These are more frequent after IV administration. The clinical features are classic, including urticaria, angioedema, and anaphylaxis appearing within a few minutes after exposure to the culprit molecule. Hydrocortisone 21-sodium hemisuccinate and methylprednisolone sodium succinate are the systemic CS molecules more frequently implicated, probably because of their widespread use. It is also important to exclude allergic reactions to additives/preservatives, such as carboxymethylcellulose or macrogol.[109-111] Non-immediate ADR are more frequent. ACD is the most frequent presentation, and patients previously sensitized by topical use of a CS may also react upon systemic administration. Non-immediate ADR induced by systemic CS have also rarely been described. Clinical features are unusual, with atypical and frequently minor clinical signs and delayed time of onset. ACD caused by CS may present as classic eczema, with the eruption often being more pronounced at the periphery of the treated zone (the so called “edge effect”) or with erythematous ad edematous plaques. Systemic reaction are more frequently characterized by MPE or erythematous ad edematous, urticarial, eruption. Severe ADR, like AGEP, have also been described.[112] Allergy to CS can be suspected also in cases of CS-sensitive diseases that do not respond or worse following the use of CS.[109-111] Budesonide and CS molecules without C16-methyl substitution or halogenation, such as hydrocortisone and methylprednisolone, are the stronger sensitizers.[113]
Management of CS hypersensitivity is not easy, and the choice of an alternative CS is difficult, owing to the high frequency of cross-reactions. Different CS classifications have been purposed with the aim of identifying class of cross-reacting CS. The most recent was published by Baeck *et al* on the basis of PT results and molecular modelling of CS, and classify CS into three different groups: group 1, the non-methylated, most often non-halogenated molecules which produce most of the allergic reactions; group 2, the halogenated molecules with a C16/C17 cis-ketal/diol structure (acetonide group B); group 3, the halogenated and C16-methylated which only rarely produce allergy. Moreover, two subgroups of patients have been identified: patients who react to molecules from one unique group, and patients who may react to the entire spectrum of CS. The latter probably present with a powerful enzymatic hydrolysis system or recognize the global skeleton of the steroid molecules rather than particular substitutions.[114] Deflazacort is not included in this classification; it has been reported to be a safe alternative in subjects with CS hypersensitivity, and reports of deflazacort hypersensitivity are rare. Despite this, deflazacort can cross-react with other CS, and that this risk is higher in patients with positive reactions to CS belonging to cluster 1 of Baeck, probably because of structural similarities with methylprednisolone.[115]
None classification has been demonstrated to have high predictive value in predict cross-reactions and systematic, individualized, evaluation of the sensitization profile is necessary. For this reason, a wide CS series is suggested (Table XVII). Higher drug concentration can result in false negative reaction, because of anti-inflammatory effect of CS. It is important to perform late readings (D7 for PT and D1 for SPT and IDT) and to inform the patient about possible even later reactions. The reading is sometimes not easy, because of the risk of atypical positive reactions (erythematous

and edematous, with edge effects, to PT; edematous with slight erythema, to SPT and IDT). Finally, IDT should be performed carefully, because of an important risk of atrophy.

14. **Biological agents**

BA are increasing used to treat a variety of inflammatory diseases, autoimmune diseases, and malignancies. They can be grouped into 3 main categories, including cytokines, antibodies (murine, chimeric, humanized, or fully humanized) directed to soluble proteins (like cytokines), cell surface molecules, immunoglobulins, tumor antigens, or receptors, and fusion proteins. They differ from traditional drugs, because are larger sized proteins structurally similar to autologous proteins, with molecular weights much greater than 1 kDa. Biologics are produced with molecular genetic technique and purified from engineered cells, processed but not metabolized, with inherent immune-mediated effects.[116] Their dosage is usually standardized and fixed and not weight-related, even if in selected cases dose tapering is performed.[117]

These agents become more widespread in their use, with consequent increasing amount of related ADR. However, as monoclonal antibodies have evolved from murine-derived monoclonal antibodies to humanized and fully human monoclonal antibodies, their immunogenicity has decreased due to the decreasing amount of foreign antigens they contain. Among immediate ADR, urticaria, angioedema, and anaphylaxis are reported.[116,118-120] BA administered intravenously can induce acute infusion reactions that may occur also with the first dose. Typical symptoms include fevers, rigors, back pain, abdominal pain, nausea, vomiting, diarrhoea, dyspnea, flushing, pruritus, or changes in heart rate and blood pressure. These reactions can be consequent to type 1 (IgE-mediated) hypersensitivity, cytokine-release, or mixed (type 1 hypersensitivity/cytokine-release) pathogenetic mechanisms.[120] BA can be also responsible for NIADR. Among these, type 3 (complement-mediated) reactions, responsible for vasculitis and serum sickness, are reported.[119] Also type 4 (T helper-mediated) reactions are described, both eczematous or MPE and severe ADR, like SJS, TEN, or AGEP[121]. BA administered subcutaneously are frequently responsible for injection site reactions. These can be irritant or, less frequently, immune-mediated (type 1, cytokine-release, mixed, type 3, type 4 reactions).[120,122] Rarely multiple hypersensitivity to BA are described.[123] Excipients also should be considered.[124]

The literature on ST for BA is poor. However, there are satisfactory data on non-irritant test concentrations for PT and SPT, which should be conducted using the drugs as is[24]. Instead, the ideal concentration to perform IDT is not established for some BA. Moreover, it can be extremely variable among the different drugs (e.g. tocilizumab should be tested as is while omalizumab needs to be diluted 1:100000[125]). The recommended concentrations to perform ST with the most used BA are reported in Table XVIII.

15. **Proton pump inhibitors**

Proton pumps inhibitors (PPIs) are rarely responsible for ADR. Data regarding the most culprit PPIs varies among countries, suggesting that the prevalence rate is influenced by the prescription pattern. Immediate ADR account for the majority of hypersensitivity reactions to PPIs, and anaphylaxis is the most common clinical pattern. There are reported cases of delayed anaphylaxis to PPIs that begin up to 24 hours after drug intake. This may be explained by the enteric coating of the PPIs, which may cause a delay in the onset of the reaction.[126] Non-immediate ADR are less frequent; the clinical patterns range from mild (MPE, SDRIFE, and FDE), to severe ADR (SJS, TEN, AGEP, and DRESS).[127]

With regard to PPIs-induced immediate ADR, ST are useful for the diagnosis (sensitivity 50-67%, specificity 100%,) and non-irritating concentrations for SPT and IDT are defined.[24,126-128] Less defined data are available regarding non-immediate ADR and PT.
Cross-reactivity exists among the various PPIs; however, the patterns of cross-reactivity were quite variable and not consistent across the studies. PPIs consist of a benzimidazole and a pyridine ring but vary in the specific side-ring substitution. Omeprazole, esomeprazole, and pantoprazole are substituted on the benzimidazole ring, whereas rabeprazole and lansoprazole are not substituted. Four general patterns of cross-reactivity have been identified: whole-group hypersensitivity, omeprazole-esomeprazole-pantoprazole hypersensitivity, lansoprazole-rabeprazole hypersensitivity, and selective sensitization to a single PPI.[129] However, not all cross-reactivities observed in some previous studies can be explained by these patterns. Although general conclusions cannot be drawn, an exhaustive allergy workup can lead to find a safe alternative. In this perspective, we recommended an extended PPIs series (Table XIX).

16. **Antihypertensive drugs**

Antihypertensive drugs are rarely responsible for ADR, but both immediate ADR and non-immediate ADR are reported.
ST seem not useful in the diagnosis of IADR, while have demonstrated higher sensitivity in NIADR, especially MPE.[24] They can be useful also in the study of cross-reactions. Among angiotensin II receptor blocker (ARB) it does not seem to exist a class-allergy,[130] while calcium channels blockers (CCB) can cross-react.[131]
ST are not well standardized. For ARB, PT performed at 5% in pet are reported to be sensitive and non-irritant.[130] PT with CCB and beta-blockers of 1-30% drug in pet appear non-irritant.[24]

17. Conclusions

ST are able to locally reproduce clinical manifestations of both IgE-mediated or T-cell-mediated drug allergy. If correctly performed and when the relevance of the positive reactions is confirmed, ST contribute, together with *in vitro tests* and drug provocation test, to confirm or exclude the causative role of the drug involved in ADR. ST sensitivity and specificity depend on drug tested and type of ADR. In some cases, ST are well standardized and reliable, while in other cases they need to be improved regarding concentrations and vehicles utilized. The latter issue represents a real ST limitation to their use due to the lack of literature data, increasing the risk of irritant reaction or nonspecific direct histamine release. Moreover, the possibility that excipients or drug metabolism products are responsible for ADR is well known. For these reasons, more studies on ST in ADR need to be performed to improve their sensitivity and specificity. ST need to be carried out by highly specialized healthcare workers in order to perform a correct procedure, to rightly interpret the relevance of positive results, and to be able to manage any adverse reactions. All these items are mandatory to provide to the patient an exhaustive response for future therapeutic necessities.

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TABLE I. - *Intervals between initial drug use and onset of symptoms.*

Hypersensitivity reaction	**Time interval from intake to reaction**
Urticaria/angioedema, anaphylaxis	≤ 1 hour
MPE	4 - 14 days
SDRIFE	up to 7 days
SJS/TEN	4 - 28 days
AGEP	1 - 12 days
GPFE	2 - 3 weeks
DRESS	14 - 56 days
FDE	30 minutes - 8 hours

MPE: maculo-papular eruption; SDRIFE: symmetrical drug-related intertriginous and flexural exanthema; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; AGEP: acute generalised exanthematous pustulosis; GPFE: generalized pustular figurate erythema; DRESS: drug reaction with eosinophilia and systemic symptoms; FDE: fixed drug eruption.

TABLE II. - *Patient history and clinical manifestations adapted from Brockow K,* et al.[3]

A. *Clinical manifestations*	Precise description of clinical findings of skin and mucosal Photo-documentation Documentation of clinical manifestations and/or organ systems involved General symptoms: fever, fatigue, … Course of the reaction (duration, morphological change, resolution) Laboratory findings (CBC, liver and kidney function, serum tryptase level, serologies) Histological findings
B. *Additional factors associated with the reaction*	Acute diseases at the time of the reaction (e.g. intercurrent infections) Patient whereabouts and activities Cofactors for allergic reactions: stress, exertion, food and alcohol intake, UV exposure
C. *Documentation of drugs used*	Indication for drug use Trade name Mode of application/subministration Ingredients (active substance, excipients) Duration of use Dosage Tolerance in the case of repeated, earlier, or subsequent use
D. *General patient history and clinical findings*	Basic data (sex, age, profession) Known hypersensitivity reactions Similar reactions in the absence of drug use Predisposing diseases (e.g. atopy, chronic urticaria, mastocytosis, HIV, neoplasm) Current concomitant medications
E. *Chronology of the ADR*	Timing in relation to drug use First onset Course and resolution Therapeutic measures and response in terms of the clinical course

TABLE III. - *Risk of cross-reactions among betalactams according to side chain structure.*

R1 identical in C7	- *Amoxicillin*, Cefadroxil, Cefatrizine, Cefprozil - *Ampicillin*, Cephalexin, Cefaclor - Cefixime, Ceftriaxone, Cefotaxime, Cefditoren, Cefodizime, Cefpodoxime, Cefepime, Cefpirome - Cefamandole, Cefonicid - Cephalotin, Cefoxitin - Ceftazidime, Cefiderocol, Aztreonam
R1 similar in C7	- *Oxacillin, Dicloxacillin* - *Penicillin G/V*, Cefadroxil, Cefatrizine, Cephalexin, Cefprozil, Cefaclor, Cefonicid, Cefamandole - *Ampicillin*, Cefadroxil, Cefatrizine, Cefprozil, Cefonicid, Cefamandole - *Amoxicillin*, Cephalexin, Cefaclor, Cefonicid, Cefamandole - *Penicillin G/V, Piperacillin, Ampicillin,* Cefadroxil, Cephalexin, Cefaclor, Cefonicid, Cefamandole - *Penicillin G/V, Ampicillin,* Cefatrizine, Cephalexin, Cefaclor, Cefonicid, Cefamandole - Cefepime, Ceftaroline fosamil, Ceftolozane - Cefpirome, Ceftaroline fosamil - Ceftaroline fosamil, Cefixime, Ceftriaxone, Cefditoren, Cefodizime, Cefotaxime, Cefpodoxime, Ceftazidime, Cefepime, Cefpirome, Cefiderocol
R2 identical in C3	- Cephalothin, Cephapirine, Cefotaxime - Cefoxitin, Cefuroxime - Cefotetan, Cefamandole, Cefoperazone
R2 similar in C3	- Cefuroxime, Cefotaxime, Cephalotin, Cephapirin - Cefonicid, Cefotetan, Cefoperazone - Ceftazidime, Cefpirome - Cefepime, Cefiderocol

TABLE IV. - *Betalactams series.*

Antibiotic	**PT***	**SPT§**	**IDT§°**
Penicillins			
Benzylpenicillin	5%	10^5 UI	10^5 UI
Amoxicillin	5%	2%	2%
Amoxicillin + Clavulanic acid	5%	2%	2%
Cephalosporins			
Cefazolin (I generation)	5%	2%	0.2%
Cefuroxime (II generation)	5%	2%	0.2%
Ceftriaxone (III generation)	5%	2%	0.2%
Cefepime (IV generation)	5%	2%	0.2%
Ceftaroline (V generation)	5%	2%	0.2%
Carbapenems			
Meropenem	5%	1%	0.1%
Antigenic determinants			
Penicilloyl-poly-L-lysine (PPL)^	5×10^{-5} mM	5×10^{-5} mM	5×10^{-5} mM
Minor determinant mixture (MDM)^	2×10^{-2} mM	2×10^{-2} mM	2×10^{-2} mM

* in pet; § in saline solution

^ Test in selected patients

° In case of suspected severe immediate ADR, starting with 1:100 dilution is recommended

Table V. - *Quinolones series.*

Quinolones	**PT***	**SPT§**	**IDT§**
Ciprofloxacin (I generation)	10%	0.5%	0.0005% - 0.005%
Levofloxacin (II generation)	10%	0.5%	0.0005% - 0.005%
Moxifloxacin (III generation)	10%	0.5%	0.0005% - 0.005%

* in pet; § in saline solution

Table VI. - *Antibiotics series.*

Antibiotic	**PT***	**SPT§**	**IDT§**
Amoxicillin *(betalactam)*	5%	2%	2%
Claritromicin *(macrolide)*	10%	2%	0.05%
Gentamicin *(amynoglicoside)*	25%	4%	0.1%
Ciprofloxacin *(quinolone)*	10%	0.5%	0.0005% - 0.005%
Trimethoprim	8%	1%	1%
Sulphamethoxazole *(sulphamidic)*	10%	1%	1%
Meropenem *(carbapenem)*	5%	1%	0.1%
Teicoplanine *(glycopeptide)*	4%	1%	0.1%
Tigecycline *(tetracycline)*	5%	1%	0.1%

* in pet; § in saline solution

Table VII. - *Azoles actually available in Italy.*

Antifungals: *Phenethyl Imidazoles:* econazole, enilconazole, ketoconazole, isoconazole, miconazole, oxiconazole, tioconazole, sertaconazole, sulconazole *Phenmethyl Imidazoles:* bifonazole, clotrimazole, croconazole *Triazoles:* fluconazole, isavuconazole, itraconazole, posaconazole, voriconazole (systemic use); eficonazole (topical use)
Antiprotozoal: benznidazole, metronidazole, secnidazole, tinidazole
Antihelmintic: albendazole, mebendazole, thiabendazole
Antihistamine (H2): cimetidine
Proton Pump Inhibitors: esomeprazole, lansoprazole, omeprazole, rabeprazole
Antiplatelet: ticagrelor

Table VIII. - *Azoles series.*

Azoles	**PT***	**SPT§**	**IDT§**
Fluconazole	2%	0.2%	0.2%
Itraconazole	2%	0.2%	0.2%
Posaconazole	2%	0.2%	0.2%
Voriconazole	2%	0.2%	0.2%

* in pet; § in saline solution

Table IX. - *NSAIDS classification.*

Acetic acid derivates: *Carbo and heterocyclic acetic acids***:** Etodolac, Ketorolac, Indomethacin, Sulindac, Tolmetin *Phenylacetic acids:* Aceclofenac, Diclofenac
Diaryl heterocyclic acids: Celecoxib, Etoricoxib, Lumiracoxib, Paracoxib, Rofecoxib, Valdecoxib,
Enolic acids derivates: *Oxicams:* Lornoxicam, Meloxicam, Piroxicam, Tenoxicam *Pyrazolones:* Azapropazone, Dipyrone, Oxyphenylbutazone, Propifenazone, Phenylbutazone
Fenamic acid derivates: Flufenamic acid, Mefenamic acid, Meclofenamic acid, Tolfenamic acid
Naphthyl alkanone: Nabumetone
Para-aminophenol derivative: Acetaminophen
Propionic acid derivates: Dexketoprofen, Fenoprofen, Flurbiprofen, Ketoprofen, Ibuprofen, Indoprofen, Loxoprofen, Naproxen, Oxaprozin, Tiaprofenic acid
Pyridinic sulfonamide: Nimesulide
Salicylic acid derivates: Acetyl salicylic acid (ASA), Diflunisal, Salsalates, Sodium salicilate, Sulfasalazine

Table X. - *Classification of NSAID-induced ADR.*

SR/CI	Entity	Mechanism	Clinical faetures
CI	NERD	Inhibition PG-LEK	Asthma, rhinitis/sinusitis, nasal polyposis
CI	NECD	Unknown	Urticaria/angioedema
CI	NIUA	Unknown	Anaphylaxis, urticaria/angioedema
SR	SNIUAA	IgEAb/others	Anaphylaxis, urticaria/angioedema, asthma, rhinitis
SR	SNIADR	T cells	CD Photo-CD Isolated mucosal involvement Bullous erupstions MPE DRESS TEN AGEP FDE NI urticaria Serum sickness Nicolau syndrome
SR	Organ specific	T cells + direct toxicity	Hepatitis Bile duct syndrome Meningitis
SR	Skin/Systemic	Unknown	Vasculitis

AGEP, acute generalized exanthematic pustulosis; CI, cross-intolerant; CSU, chronic spontaneous urticarial; CD, contact dermatitis; DRESS, drug rash with eosinophilia and systemic symptoms; FDE, fixed drug eruption; NECD, NSAID-exacerbated cutaneous disease; NERD, NSAID-exacerbated respiratory disease; NIUA, NSAID-induced urticaria angioedema; NSAID, nonsteroidal anti-inflammatory drug; SNIADR, single NSAID-induced delayed hypersensitivity reaction; SNIUAA, single NSAID-induced urticaria, angioedema or anaphylaxis; SR, selective responders; TEN, toxic epidermal necrolysis.

Table XI. - *Perioperative drugs series.*

Perioperative drugs	**PT***	**SPT§**	**IDT§**
Neuromuscular blockers			
cis-Atracurium	-	0.2%	0.0002% - 0.002%
Rocuronium	-	1%	0.001% - 0.01%
Vecuronium	-	0.4%	0.0004% - 0.004%
Succinilcoline	-	5%	0.0005% - 0.005% - 0.05%
Hypnotics			
Ketamine	-	1% -10%	0.01% - 0.1%
Midazolam	-	0.5%	0.005% - 0.05%
Propofol	-	1%	0.01% - 0.1%
Thiopental	-	2.5%	0.025% - 0.25%
Other drugs			
Atropine	-	0.06%	0.00006% - 0.0006% - 0.006%
Metoclopramide	-	0.5%	0.0005% - 0.005%
Ondansetron	-	0.2%	0.0002% - 0.002%
Neostigmine	-	0.25%	0.00025% - 0.0025%
Plasma expanders	-	3.5%	0.035 - 0.35% %
Sugammadex	-	10%	0.01% - 0.1%
Tranexamic acid	-	10%	0.01% - 0.1%
Antiseptics			
Clorexidine digluconate	1%	0.5%	0.00002 %
Iodopovidone	10%	1%	-
Latex	-	1%	-

* in pet; § in saline solution

Table XII. - *Opioids series.*

Opioids	**PT**	**SPT[§]**	**IDT[§]**
Codeine	5%*	0.1% - 1%	-
Fentanyl	0.005%^	0.00005% - 0.0005% - 0.005%	0.0000005% - 0.000005% - 0.00005%
Morphine	5%*	0.01% - 0.1%	0.00001% - 0.0001% - 0.001%
Sufentanyl	0.005%^	0.0005%	0.000005%
Tramadole	5%*	5%	0.05% - 0.5%

* in pet; [§] in saline solution; ^ in water

Table XIII. - *Local anestetics series.*

Local anestetic	**PT**	**SPT**	**IDT[§]**
Esters			
Benzocaine	5%*	-	-
Procaine	2%*	1%	1%
Tetracaine	2%*	n.p.	n.p.
Amides			
Short acting			
Lidocaine	10%*	1%	0.1%
Medium acting			
Articaine	2%	1%	0.1%
Mepivacaine	10%	1%	0.1%
Prilocaine	3%	1%	0.1%
Long acting			
Bupivacaine	0.5%	0.5%	0.05%
Ropivacaine	1%	1%	0.1%
Excipients			
p-Aminobenzoic acid (PABA)	10%*	-	-
Paraben mix°	16%*	-	-
p-Hydroxybenzoate	-	0.1%	0.1%
Sodium metabisulphite	1%*	0.05%	0.05%

* in pet; [§] in saline solution

° methyl *p*-hydroxybenzoate 4%, ethyl *p*-hydroxybenzoate 4%, propyl *p*- hydroxybenzoate 4%, butyl *p*-hydroxybenzoate 4%

Table XIV. - *Iodinated contrast media series.*

Iodinated contrast media	PT	SPT	IDT[§]
Iobitridol	30%	30%	0.03% - 0.3% - 3%
Iodixanol	32%	32%	0.032% - 0.32% - 3.2%
Iomeprol	40%	40%	0.04% - 0.4% - 4%
Iopamidol	30%	30%	0.03% - 0.3% - 3%
Iopromide	30%	30%	0.03% - 0.3% - 3%

[§] in saline solution

Table XV. - *Paramagnetic contrast media series.*

Paramagnetic contrast media	**PT**	**SPT**	**IDT[§]**
Gadobenate dimeglumine *(linear ionic)*	52.9%	52.9%	0.0529% - 0.529% - 5.29%
Gadodiamide *(linear non-ionic)*	28.7%	28.7%	0.0287% - 0.287% - 2.87%
Gadoterate meglumine *(cyclic ionic)*	37%	37%	0.037% - 0.37% - 3.7%
Gadoteridol *(cyclic non-ionic)*	27.93%	27.93%	0.02793% - 0.2793% - 2.793%

[§] in saline solution

Table XVI. - *Heparins series.*

Heparin	PT	SPT	IDT[§]
Unfractionated heparins			
Heparin calcium (5000 UI/0.2 mL)	as is	as is	1:10
Heparin sodium (5000 UI/mL)	as is	as is	1:10
Low-molecular-weight heparins	as is	as is	1:10
Bemiparin sodium (2500 UI/0.2 mL)	as is	as is	1:10
Dalteparin sodium (5000 UI/0.2 mL)	as is	as is	1:10
Enoxaparin sodium (4000 UI/0.4 mL)	as is	as is	1:10
Nadroparin calcium (3800 UI/0.4 mL)	as is	as is	1:10
Ultra-low-molecular-weight pentasaccharide	as is	as is	1:10
Fondaparinux (2.5 mg/0.5 mL)	as is	as is	1:10

[§] in saline solution

Table XVII. - *Corticosteroids series.*

Corticosteroid	**PT**	**SPT[§]**	**IDT[§]**
Topical			
Budesonide[^]	0.01%*	0.01%	
Desoximethasone	1%°	1%	
Hydrocortisone 17-butyrate	1%°	1%	
Hydrocortisone 21-acetate	1%°	1%	
Systemic			
Betamethasone sodium phosphate	1%°	1%	0.1%
Deflazacort	1%*	1%	
Dexamethasone	1%°	1%	
Dexamethasone 21-disodium phosphate	1%°	1%	0.1%
Fluocortolone[^]	1%°	1%	
Hydrocortisone 21-sodium hemisuccinate	1%°	1%	0.1%
Methylprednisolone	1%°	1%	
Methylprednisolone sodium succinate	1%°	1%	0.1%
Prednisone	1%°	1%	
Triamcinolone[^]	1%°	1%	
Triamcinolone acetonide	1%°	1%	

* in pet; ° in ethanol; [§] all in saline solution

[^] available for both topical and systemic use

Table XVIII. - *Biological agents series.*

Biological agent	**PT**	**SPT**	**IDT[§]**
Anti-TNFalpha			
Adalimumab	4%	4%	0.004% 0.04% 0.4%
Etanercept	5%	5%	0.005% 0.05% 0.5%
Infliximab	1%	1%	0.01% 0.1% 1%
Anti-CD20			
Rituximab	1%	1%	0.001% 0.01% 0.1%
Anti-tumor antigens			
Bevacizumab	2.5%	2.5%	0.025% 0.25% 2.5%
Cetuximab	2%	2%	0.02% 0.2% 2%
Pertuzumab	0.16%	0.16%%	0.0016% 0.016% 0.16%
Trastuzumab	2.1%	2.1%	0.0021% 0.021% 0.21%
Anti-IL6			
Tocilizumab	2%	2%	0.02% 0.2% 2%
Anti-IgE			
Omalizumab	12.5%	12.5%	0.0000125%

[§]In saline solution

Table XIX. - *Proton pump inhibitors series.*

Proton pump inhibitor	PT*	SPT§	IDT§
Esomeprazole	10%	4%	0.04% - 0.4%
Lansoprazole	10%	3%	0.015% - 0.15%
Omeprazole	10%	4%	0.04% - 0.4%
Pantoprazole	10%	4%	0.04% - 0.4%
Rabeprazole	10%	2%	0.02% - 0.2%

* in pet; § in saline solution

Figure Legends

Figure 1. Typical time of onset of immediate and non-immediate ADR.

Figure 2. Immediate ADR: drug-induced urticaria by amoxicillin, with typical wheals, characterized by central swelling surrounded by a reflex erythema (a); angioedema by ibuprofen, with pronounced whitish swelling interesting lips and lower face (b).

Figure 3. Non-immediate ADR: MPE by amoxicillin with widespread multiple small erythematous macules and papules, different degrees of confluence, and symmetric centrifugal spreading (a); SDRIFE by fluconazol with symmetrical erythematous rash on intertriginous areas (b); EMM by sulphamethoxazole with typical target lesions (c); EMM by carbamazepine with mucous membrane involvement, cutaneous blistering, and epidermal detachment (d); TEN by ceftriaxone with confluent macules and flat atypical targets, associated to skin detachment (e); AGEP by amoxicillin with disseminated non-follicular, small, pustules on erythematous skin, confluent in superficial detachment with scales and crusts (f); DRESS by allopurinol with MPE and typical facial edema (g); FDE by acetaminophen with erythematous-violaceous plaque (h).

Figure 4. Positive ST: positive PT to amoxicillin (5% pet) with typical eczematous reaction (a); positive PT to deflazacort (1% pet), with erythematous and edematous reaction and characteristic edge-effect (b); positive SPT to ciprofloxacin (0.5% saline solution) (c); positive IDT to mepivacain (0.1% saline solution) (d).