

Spanish Society of Allergology and Clinical Immunology (SEAIC) Vision of Drug Provocation Tests

Audicana MT¹, Ortega N², Lobera T³, Blanca-López N⁴, De la Parte B⁵, García I⁶, Gelis S⁷, Martín J⁸, Barranco R⁹, Vila C¹⁰, Laguna JJ¹¹, on behalf of the Spanish Society of Allergy and Clinical Immunology (Drug Allergy Committee)

¹Servicio de Alergología e Inmunología Clínica, Hospital Universitario Araba, OSI Araba, Vitoria, Spain

²Servicio de Alergología, Hospital Doctor Negrín, Las Palmas de Gran Canaria, Spain

³Sección de Alergología, Hospital Universitario de San Pedro, Logroño, La Rioja, Spain

⁴Servicio de Alergología, Hospital Universitario Infanta Leonor, Madrid, Spain

⁵Servicio de Alergología, Hospital del Tajo, Aranjuez, Spain

⁶Servicio de Alergología, Hospital Quirón Salud Campo de Gibraltar y Hospital Quirón Salud Córdoba, Córdoba, Spain

⁷Unidad de Alergia, Servicio de Neumología, Hospital Clinic, Institut d'investigacions Biomediques August Pi i Sunyer (IDIPAPS), Barcelona, Spain

⁸Servicio de Alergología, Hospital San Rafael, La Coruña, Spain

⁹Servicio de Alergología Hospital Universitario 12 de Octubre, Madrid, Spain

¹⁰Unidad de Alergia, Hospital Universitario Severo Ochoa, Leganés, Madrid, Spain

¹¹Unidad de Alergia, Unidad de Alergoanestesia, Hospital Central de la Cruz Roja, Madrid, Spain

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■ Abstract

The controlled drug provocation test (DPT) is currently considered the gold standard for the diagnosis of drug allergy. Adverse drug reactions (ADRs) are an increasingly common presenting complaint in both primary and specialized care. In Spain, ADRs are usually assessed via the allergology department, which rules out immunological mechanisms in up to 90% of cases. An adequate approach to ADRs clearly impacts the costs and efficacy of the treatments prescribed by other specialists. Consequently, if we did not use DPTs, patients would require more expensive, more toxic, and less effective treatments in many cases.

In recent years, many new drugs have been developed. This document is intended to be a practical guideline for the management of DPTs according to the vision of the Spanish Allergology Society. The diagnostic work-up begins with a detailed clinical history. Skin tests are only useful for some medications, and in most cases the diagnosis can only be confirmed by DPT. Although cross-reactivity is common, DPTs can confirm the diagnosis and help to find an alternative drug. Programmed individualized patient management based on the type of drug to be studied and the patient's comorbidities usually enables a solution to be found in most cases.

Key words: Drug-controlled exposure tests. Adverse drug reaction. Drug allergy diagnosis.

■ Resumen

La prueba de exposición controlada a fármacos (DPT) se considera actualmente el estándar de oro para el diagnóstico de alergia a medicamentos. Las reacciones adversas inducidas por medicamentos (RAM) son un motivo creciente de consulta tanto en atención primaria como especializada. Las consultas de Alergología en España son las que habitualmente estudian estas RAM y descartan mecanismos inmunológicos implicados hasta en el 90% de los casos consultados. Un abordaje adecuado de estos casos repercute de una manera evidente en los costes y la eficacia de los tratamientos requeridos por otros especialistas, de modo que, si no empleáramos los DPT, los pacientes requerirían tratamientos más costosos, más tóxicos y menos eficaces en la mayoría de los casos.

En los últimos años se han desarrollado un gran número de nuevos fármacos y este documento pretende ser una guía práctica en la gestión de las DPT con la visión de la Sociedad Española de Alergología. El trabajo de diagnóstico comienza con un historial detallado del paciente. Las pruebas cutáneas solo son útiles en algunos medicamentos y, en la mayoría de los casos, el diagnóstico solo puede confirmarse mediante el DPT. Aunque suele haber reactividad cruzada, las DPT pueden confirmar el diagnóstico y también contribuir a encontrar un fármaco alternativo tolerable. El manejo individual de los pacientes de forma programada, teniendo en cuenta tanto el tipo de fármaco a estudiar como las comorbilidades del paciente, suele permitir encontrar una solución para la mayoría de los pacientes.

Palabras clave: Pruebas de exposición controlada con fármacos. Reacción adversa medicamentosa. Diagnóstico de alergia a fármacos.

1. Introduction

Drug provocation tests (DPTs) are currently considered the definitive approach or gold standard for the diagnosis of allergy to food and drugs. In the case of drugs, DPT has 3 main advantages:

- Adverse reactions to drugs in the form of rash are not always allergic, and prolonged avoidance of certain drugs has proven to be more toxic and more expensive than a proper allergy study.
- The use of DPT is often crucial since most drugs—because of their low molecular weight—are not complete antigens but behave as haptens and consequently result in false negatives in both skin tests and in vitro tests.
- In the case of a confirmed positive allergy to a pharmacological group, it is often necessary to evaluate whether the patient can tolerate an alternative.

Before we turn to DPT, a clinical history should be taken and testing (skin and/or patch, in vitro) should be performed. However, not all tests are applicable to all drugs.

In daily clinical practice, life-threatening risk demands quick action, and the most sensitive approach is the so-called graded challenge and desensitization, which differs from the DPT.

A DPT is a diagnostic procedure performed when the patient is in good health with no signs of active disease. It serves to identify a well-tolerated drug that could potentially be useful in the future [1]. Graded challenge and drug desensitization, on the other hand, are therapeutic procedures, and are more likely to be performed when the patient requires immediate treatment with the medication in question. As indicated in the recently updated US practice parameter on drug hypersensitivity reaction (HSR), graded challenge should be carried out in patients who are unlikely to be allergic to the drug and with no intention of inducing tolerance [1-3]. Thus, patients who tolerate a graded challenge are considered not to be allergic to the drug. However, when a patient has a relatively high risk of being allergic to a drug, desensitization (or induction of drug tolerance) should be considered. This procedure allows temporary modification of a patient's immune response to safely tolerate the drug providing that the patient continues to take the specific drug.

Many new drugs have been developed in recent years. This paper aims to be a practical guideline in the management of DPTs.

1. 1. Indications and Contraindications

Indications for controlled exposure tests will vary depending on the drug to be studied, its relevance in the patient's condition, and the patient's comorbidities [1,2].

A DPT is considered in 3 basic conditions, as follows:

- To confirm tolerance of a drug with which there is reasonable doubt concerning an allergic or idiopathic reaction associated with a negative test result, concomitant medication, or an inconclusive clinical history.
- To establish a firm diagnosis of drug allergy in case of inconclusive study results in in vivo and in vitro tests.
- To confirm the absence of cross-reactivity with related drugs in order to prescribe alternative medication.

In the case of β -lactams, some authors propose a direct DPT when adverse reactions occurred more than 10 years previously and/or are poorly defined [3,4]. We do not consider this procedure to be sensitive without a prior skin test and in vitro test, except for nonsevere cases in children [4-6].

Contraindications depend on the reaction, the patient, and the drug itself, as follows:

- *Severe reactions*: severe cutaneous syndromes, vasculitis, severe anaphylaxis, especially if the patient has other comorbidities that could interfere in the treatment of the reaction.
- *Patient*: pregnancy, severe comorbidities (infections, poorly controlled asthma, heart disease, liver or kidney disease), human leukocyte antigen associations that increase the susceptibility of adverse reactions to a particular drug.
- *Drug*: currently unused drugs such as streptomycin, drugs with doubtful therapeutic value or alternatives with supporting literature, unpredictable drugs, necessary drugs (anesthetics), drugs that implicitly induce toxicity (iodinated and gadolinium contrast), and drugs requiring complex testing techniques, such as sedation and intubation.

These general considerations should be assessed in each case as previously discussed by contextualizing the needs and circumstances of the individual patient. In this sense, treatment with angiotensin-converting enzyme inhibitors (ACEIs) and β -adrenergic blockers increases susceptibility to adverse reactions, and treatments instituted in the case of anaphylactic reactions are less effective [2-7]. In addition, the management of drug reactions in patients with mast cell activation syndrome is difficult and not well researched. Drugs such as antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, neuromuscular blocking agents, and radiocontrast media are known triggers in patients with mast cell activation syndrome [3,8].

1.2. Process

A DPT ensures controlled exposure to a drug through administration in progressively increasing doses, usually at 15- to 30-minute intervals, under careful monitoring.

An exhaustive allergy work-up is mandatory for risk-free practice. Therefore, the patient must sign a consent document. If the patient is unable to sign the document of his/her own accord (eg, because of incapacitation or because he/she is under legal age), then a close relative could do so. According to Spanish legislation, children aged ≥ 12 years must be able to understand the procedure and sign the corresponding consent form themselves, as well as their parents/legal guardians.

Vital signs should be monitored (pulse, blood pressure), and subjective symptoms and skin should be checked periodically, as in all exposure tests. Adrenaline and other indicated anaphylaxis treatments should be readily available, as should all necessary equipment and trained health personnel. The optimal situation is one where the medication to be administered is well labeled and the adrenaline syringe is prefilled at the patient's head. It is also considered advisable to have available antihistamines, parenteral corticosteroids, saline solution, and bronchodilators in solution with an inhalation system.

Patients usually undergo an appropriate, gradual, and personalized exposure protocol.

1.2.1. Initial premises

DPT requires continuous monitoring of the patient undergoing drug administration to recognize possible adverse reactions. A successful procedure is based on stratifying the risk for the individual patient, following a series of steps [3].

- First, the risk-benefit ratio of the allergy study must take into account age and comorbidities, the relevance of the drug to be studied in the context of the patient's condition, and the availability of alternative medication.
- Second, the exposure or exposures should be planned taking into account the condition and the drugs necessary to treat it. Studies of analgesics in a patient with pain compared with an asymptomatic patient or of antibiotics in an elderly patient with severe pneumonia compared with a healthy child do not require the same amount of detail.
- Consider the patient's comorbidities in relation to the risk of adverse effects induced by the drug administered in the DPT and a possible allergic response.
- Monitor the patient by recording the color of skin and mucosa, blood pressure, and pulse before starting the procedure and before each new administration of the drug. Maintain direct control through nursing and medical supervision at all times. Baseline spirometry and peak flow with periodic peak flow and/or spirometry assessments are recommended for asthmatics, as are NSAIDs after each new exposure. Nasal exposure tests should be monitored using rhinomanometry.
- Inform patients and caregivers about possible early manifestations of anaphylaxis (palmoplantar pruritus, tachycardia, dizziness, cough) or if urticaria, angioedema, dyspnea, and other manifestations occur. In this case,

monitoring of changes in vital signs is essential so that the necessary measures can be taken to ensure that the patient is treated immediately by the attending physician.

- Have medication and necessary material ready for the treatment of anaphylaxis or the adverse effects of the drug administered.
- Previous requirements must be confirmed, as follows:
 - Signature of informed consent.
 - The patient must never take drugs that could interfere with the DPT.
 - Suspension of treatment with antihistamines, corticosteroids, β -blockers, ACEIs, and antileukotrienes [2].
 - Ensure that the patient does not have acute disease that may interfere with the DPT.

1.2.2. Placebo/Nocebo Concept

Randomized controlled trials make it possible to verify the occurrence of adverse effects, thus leading to the coining of the term "nocebo" to denote the harmful effects attributable to placebo. The nocebo effect is idiopathic and not dose-dependent. The psychological mechanisms that contribute to it comprise expectations, conditioning, learning, memory, motivation, reward, and anxiety.

Spanish legislation does not explicitly address the use of placebo in clinical practice: it neither authorizes nor prohibits its use, because it conflicts with patient autonomy and shared decision making [9]. The patient should be blind to controlled drug exposure so as not to compromise tolerance. This concept should be included in the terms and accepted by the patient before undergoing DPT.

1.2.3. Preparation of Drugs

In oral exposure, the capsules are usually opaque so that the patient cannot identify the drug or the dose taken. Placebo capsules are filled with sucrose or corn starch. Commercial preparations are generally used for parenteral drugs, and

Table 1. General Protocol Recommended for Drug Provocation Tests, Under Strict Medical Supervision in Hospital

Route	Immediate IgE-mediated reactions		Nonimmediate drug reaction without systemic involvement (eg, delayed rash or exanthemas)[7] ^a
	Low likelihood of drug allergy	High likelihood of drug allergy	
Intravenous administration	Administer 10% of the dose within 30 min, then in 30 min, administer the remainder of the dose (90%) [8,9].	Administer, successively, the doses of 1% - 10% - 50% and 100% of the daily dose of the drug. Doses should be administered over 30 min and the patient should remain under observation for 30 min, before the next dose [1,10,11].	Administer 10% of the dose within 30 min, then in 30 min administer the remainder of the dose (90%) [8,9].
Oral, subcutaneous, or intramuscular administration	Administer 25% of the total daily dose of the drug, observation within 60 min and then administer the remainder (75%) [8,9].	Administer in incremental doses: 1% -10% - 50% - 100% of the usual daily dose, at an interval of about 30 min [1,10,11].	Administer 25% of the total daily dose of the drug, observe for 60 minutes, then administer the remainder (75%) [8,9].

^aIf the drug provocation test is negative, a full course of drug treatment should be extended for 2 to 10 days, or for at least as long as it takes the patient to develop the reaction recorded in the clinical history.

dilutions are made with physiological saline solutions or distilled water.

Lysine acetylsalicylate is prepared in various pipetting solutions to be deposited in the lower nasal turbinate in the case of nasal exposures.

1.2.3.1. Dose

Dosage of test preparations and dosing intervals vary between published studies and depend on the type of drug, the severity of the adverse reaction under investigation and its mechanisms, and the expected latency between application and reaction. A summary protocol table recommended for DPTs performed under strict hospital surveillance can be found in Table 1.

If a patient is at risk of a positive test result and/or there is high suspicion of sensitization, the first dose must be equivalent to 10 or 100 times less than the original dose that triggered the reaction in the first place. If there is low suspicion of reaction or in cases where it is sought to confirm tolerance, a 25% higher dose could be applied. The therapeutic dose is usually reached on the same day, and the patient must remain in observation for 1 to 3 hours after the last dose. In the case of NSAIDs, it is recommended to extend the observation period (Table 1) [10-12].

The volume of administration depends on the guideline chosen. Capsules are generally used to mask the doses in oral drugs. The dose is 0.2 mL for intradermal injection, 0.2-0.6 mL for subcutaneous injection, and 0.6-1.0 mL for intramuscular and intravenous injection. The patient should be monitored continuously during perfusion. In intravenous infusions, the fractional drug is usually administered in progressively increasing boluses until the therapeutic dosage is complete.

Dose increases may vary markedly, although they are usually 2-fold or 3-fold. When starting with very low doses, the increase is 10-fold, depending on the authors and the drugs (Table 1) [10-12].

Administration of the defined daily dose is desirable. The expected latency between application and reaction may be hours, days, or, occasionally, weeks before completion, depending on the type of drug itself, the severity of the ADR under investigation, and the mechanisms involved (Table 1) [2,3].

1.2.3.2. Interval between doses

The standard interval is 20 to 30 minutes between doses for oral administration and 15 to 20 minutes for parenteral administration [1,2,10-12]. A DPT consists of increasing doses of the suspected drug up to the full therapeutic dose or until onset of a drug reaction (Table 1).

1.2.4. Interval Between Reaction and DPT

As a rule, DPT should be performed not earlier than 4 weeks after the episode. A booster effect is recommended if the reaction happened more than 1 year earlier, since antibody levels sometimes decrease, for example, with aminopenicillins. Therefore, some authors recommend the repetition of skin test or even a rechallenge 2 to 4 weeks later [2].

In delayed reactions (such as exanthema in children), once immediate tolerance is demonstrated in the allergy department, some authors recommend extra doses at home every 12 hours

for at least 2-3 days [6]. In contrast, authors from northern Europe recommend courses of treatment for 7 days, usually when benzylpenicillins are involved [13].

1.2.5. Concomitant Drugs

In order to guarantee complete elimination of concomitant drugs and accurately calculate their effect, the elimination half-life should be multiplied by 5. Any concomitant medication that might influence the outcome of the DPT should be completely washed out.

1.3. Assessment of Test Results

A DPT can be considered positive if it reproduces the original symptoms. Photographs of previous skin reactions can help confirm the diagnosis. General clinical tests such as complete blood count, eosinophil count, and determination of mediator release (histamine in blood, methylhistamine in urine, eosinophil cationic protein, serum tryptase) can also be helpful.

The predictive value of DPT depends mainly on the type/mechanism of reaction and the drug involved. If the patient is finally labeled as drug-allergic, it is essential to provide adequate documentation for the drugs that should not be taken again and those that were tolerated in the test. A personalized clinical report should be drafted, and allergy warnings should be specified in the clinical history.

1.4. Management of Adverse Reactions

Treatment of adverse events during DPT depends on the type of reaction and its severity. The first action to be taken is to stop further drug testing, followed by adequate general and specific procedures for the treatment of anaphylactic reactions. Drugs should only be introduced to mitigate this reaction when the symptoms point to a conclusive positive test result.

- Reactions such as urticaria, angioedema, and anaphylaxis are treated with antihistamines, corticosteroids, and/or parenteral adrenaline, as in other common allergic reactions.
- Antihistamines and corticosteroids are usually sufficient for management of drug eruptions and monitoring of possible associated infections or progress to more serious conditions.
- In drug-induced serum sickness, removal of the suspected drug and administration of antihistamines and corticosteroids is usually sufficient. In more severe cases, plasmapheresis may be useful.
- High-dose corticosteroids are recommended for the treatment of Stevens-Johnson Syndrome. The usual daily dose for moderate cases is 80 mg of prednisone; more severe cases require hospitalization, supportive measures, and 60 mg of intravenous methylprednisolone for 4-6 hours. It is important to reduce the doses gradually over the course of 2-3 weeks, since sudden withdrawal can cause relapses. Corticosteroids are insufficient to control the process in toxic epidermal necrolysis syndrome, and these patients usually require vigilance in a burn unit.
- Treatment with corticosteroids is usually sufficient to accelerate the resolution of the process in other reactions

such as drug-induced fever, vasculitis, or reactions that affect blood components, even in affected solid organs.

1.5. Limitations of Drug Provocation Testing

1.5.1. Technique

Although DPT is the gold standard for diagnosis, it is subject to limitations [14]. Negative predictive values vary depending on the drugs: 94% to 98% for β -lactams and >96% for NSAIDs [11]. A negative exposure does not completely guarantee subsequent tolerance of the drug for 2 main reasons:

- IgE levels decrease over time
- Cofactors such as food, exercise, and viral infections may be involved

1.5.2. Interpretation by an allergy specialist

DPT results should be evaluated based on objective parameters; however, subjective symptoms must also be recorded. Clinical presentation and progress of a reaction over time should be documented, and quantitative parameters (eg, blood pressure, heart rate, oxygen saturation, and, sometimes, peak flow) should be measured for each new dose of the drug administered.

In open DPTs, nocebo-like responses might lead to misinterpretation of subjective symptoms such as a positive DPT result (reported in up to 27% of patients) [15-18].

Serum tryptase is an objective marker of a true allergic reaction, although it is only positive in 20% of drug exposures [3,19]. In the case of a serious adverse reaction in the context of a DPT, tryptase should always be determined. The window of opportunity for a solid diagnosis is within the first 2 hours [20].

1.5.3. Patient and physician reluctance

The Spanish Society of Allergology and Clinical Immunology (SEAIC) recently studied the quality of life of patients with drug allergy and found that the greatest impact on well-being was having experienced an anaphylaxis episode and having developed more than 1 allergy to various drugs [21].

Bavbek et al [22] reported that not being atopic, high education level, and drug hypersensitivity in older persons were associated with nocebo effect during DPTs. A double-blind placebo-controlled exposure test may be necessary in adults, especially in those with a history of multiple reactions to drugs from different families [16].

- Although the negative predictive value of the DPT is high, approximately one third of patients feel reluctant and do not take the drug again despite their negative result [11,12].

1.5.4. Resensitization

DPT rarely induces resensitization in patients (children and adults) with negative skin test results and a history of penicillin allergy, even after repeated doses [5,23-25]. Nevertheless, a routine repeat DPT is not indicated in standard assessment of drug allergy.

1.6. Benefits of drug provocation testing

Well-defined benefits of DPT include, on the one hand, those derived from ruling out allergies and, on the other, access to safe alternatives [12]. Hospital treatment for patients wrongly labeled “penicillin-allergic” is less cost-effective and more prone to adverse reactions than those treated with β -lactams [3].

Negative results in DPTs decrease anxiety and enable new exposures to be better tolerated [17]. Therefore, it is important to start testing the drug that is the most likely to be tolerated.

A SEAIC multicenter study has confirmed that completing a drug allergy evaluation improves the quality of life of patients who have experienced drug anaphylaxis or more than 1 allergic drug reaction or a musculoskeletal disease [21].

2. β -Lactams

Guidelines, including the European Network of Drug Allergy guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) [2,5,26], consider DPT to be the gold standard for confirming the diagnosis of HSRs to β -lactams.

The chemical structure of β -lactams contributes to the specificity of the immune responses both in immediate and in delayed reactions. In Mediterranean countries, the immune response is directed predominantly against the side chains of aminopenicillins and thus differs from patterns found in northern Europe, where more benzylpenicillins are consumed. In fact, amoxicillin is currently considered the most frequent cause of anaphylaxis among β -lactams in Spain.

During recent years, many studies in pediatric series [6,27-29] and in adult series [30-33] have confirmed the safety and usefulness of DPT in the diagnosis of β -lactam allergy. Many cases can be overdiagnosed if DPT is not carried out, because the sensitivity of skin and in vitro tests is not optimal, varying widely between studies [35-40].

Proposed DPT protocols included in the β -lactam allergy work-up varied widely between studies in terms of doses, steps, interval between doses, incremental doses, and days of dosing. For both immediate reactions (IRs) and nonimmediate reactions (NIRs), the EAACI has validated 2 algorithms, which are now followed by many groups [41,42]. According to these procedures, after taking a detailed clinical history, we must perform in vitro testing and/or skin testing; if the results are negative, DPT can be considered [41,42]. Nevertheless, in recent years, some authors have reported the possibility of performing DPTs without previous skin testing in selected cases of mild NIR, such as maculopapular exanthema and urticaria, especially in children [6,43-46], but also in adults with benign reactions [47,48]. The SEAIC routinely recommends an allergological study consisting of skin tests and in vitro tests prior to exposure. Importantly, the study of allergy to β -lactams in the Mediterranean area has developed considerably over more than 30 years, in contrast with other countries [49], which have not studied patients for as long and now find that they have a pool of patients erroneously labeled as allergic. Figure 1 shows the algorithm recommended by the SEAIC for studies of immediate reactions in which β -lactams are required.

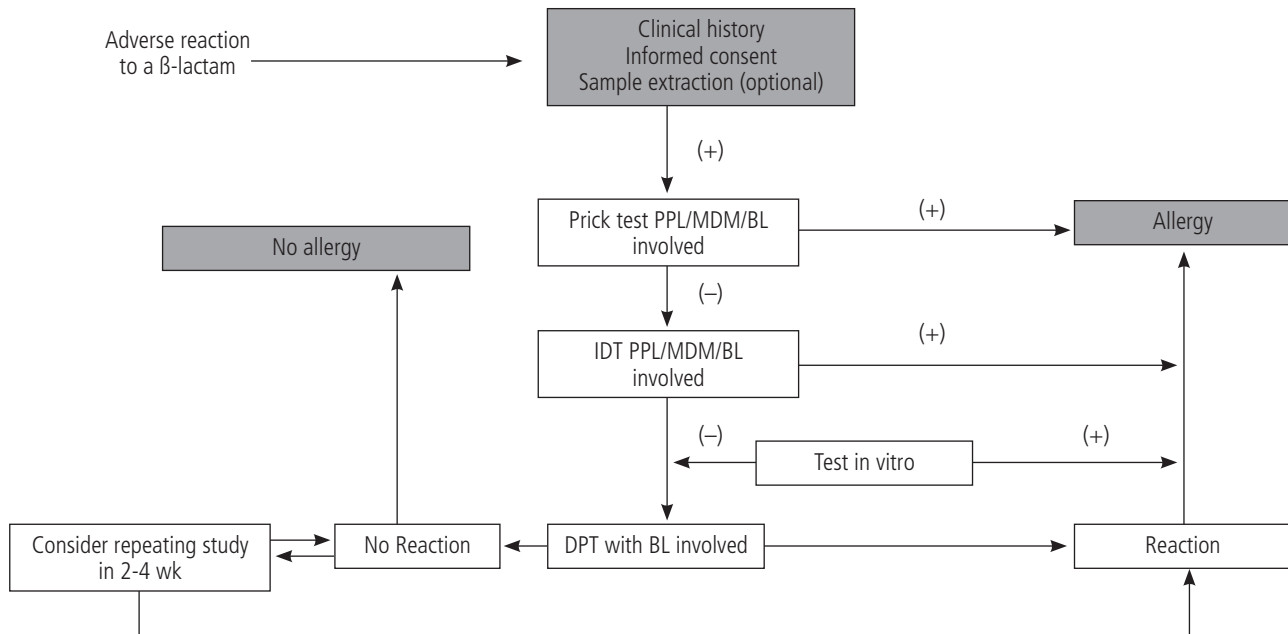


Figure 1. Algorithm for diagnosis of β -lactam allergy diagnosis when immediate treatment with a β -lactam is necessary. PPL indicates penicilloyl poly-L-lysine; MDM, minor determinant mix; BL, β -lactam; IDT, intradermal test; DPT, drug provocation test.

Consensus has not been reached on whether DPT in β -lactam allergy should be performed with escalating doses or a single dose or on whether it should last 1 day or longer. Dosing for DPT ranges from 3 steps or fewer, as in mild IRs and NIRs [30,50,51], to protocols with additional lower-dose steps at the beginning, which may cause severe reactions in high-risk patients [52]. Nevertheless, as published recently, the possibility of challenge without previous skin testing is without risk in mild NIR [6,34,43-48,50,53]. Duration is controversial, with debate over whether DPT performed in a single day would be sufficient to confirm a diagnosis, especially in NIRs. While some groups considered 1 day to be sufficient [50-54], others believe that DPT performed on a single day can generate false-negative results, thus necessitating prolongation of the test for several days to confirm the diagnosis [10,45,47,55,56,57]. A Spanish study on pediatric allergy recommends 2 days [6].

The allergological study of patients labeled with penicillin allergy makes it possible to rule out allergy in our environment in more than 90% of cases and therefore enable this treatment to be administered to most patients. Furthermore, many patients have a selective allergy to aminopenicillins and can tolerate a wide range of other β -lactams [32,35].

When allergy to a β -lactam is confirmed, it is also crucial to confirm whether there is a therapeutic alternative within the group. In vivo cross-reactivity between penicillins and cephalosporins is approximately 10% when the R1 side chain is different, although this increases to >30% when the side chain is identical (Figure 2) [32,35,36,57]. Cross-reactivity between cephalosporins is also based on the similarity of the chemical structure of the same R1 side chain: it can be very high when the side chains are similar or identical. Patients who are allergic to non-monobactam β -lactams usually tolerate aztreonam, although this drug should be avoided in patients

diagnosed with allergy to ceftazidime, which shares the same side chain (Figure 2) [57,58].

Recent Spanish guidelines on the management of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome recommend controlled re-exposure tests with an alternative β -lactam (not the culprit) if the benefit outweighs or at least equals the risk [59]. The graded challenge exposure test recommended by Romano et al [60] for nonimmediate β -lactam allergic reactions is an initial dose of 1/100 of the therapeutic dose. In cases with negative results 3 days to 1 week later, a dose of one tenth is given, and if the result is again negative, a full dose can be given at the previously used interval [49,56,58,60].

3. Nonsteroidal Anti-Inflammatory Drugs: Specific Aspects for Confirmation of Diagnosis

According to the classification proposed by Kowalski et al [61], acute reactions are first divided into 2 groups and then subdivided according to the presence of underlying disease (Table 2).

Diagnosis of hypersensitivity reactions to NSAIDs is based on clinical history, physical examination, and, if possible and appropriate, in vitro or in vivo tests, followed by drug challenge procedures.

3.1. Drug provocation test

Depending on the route of NSAID administration, nasal, bronchial, and oral DPTs can be used. The oral DPT is considered the gold standard for diagnosis of hypersensitivity reactions to

this drug and is indicated to confirm or exclude the diagnosis when there is no other test available and to find an alternative NSAID once the diagnosis is confirmed [62]. These tests should

be single-blind placebo-controlled, although in some cases a double-blind procedure is necessary. According to international guidelines, other medications are withheld before testing [63].

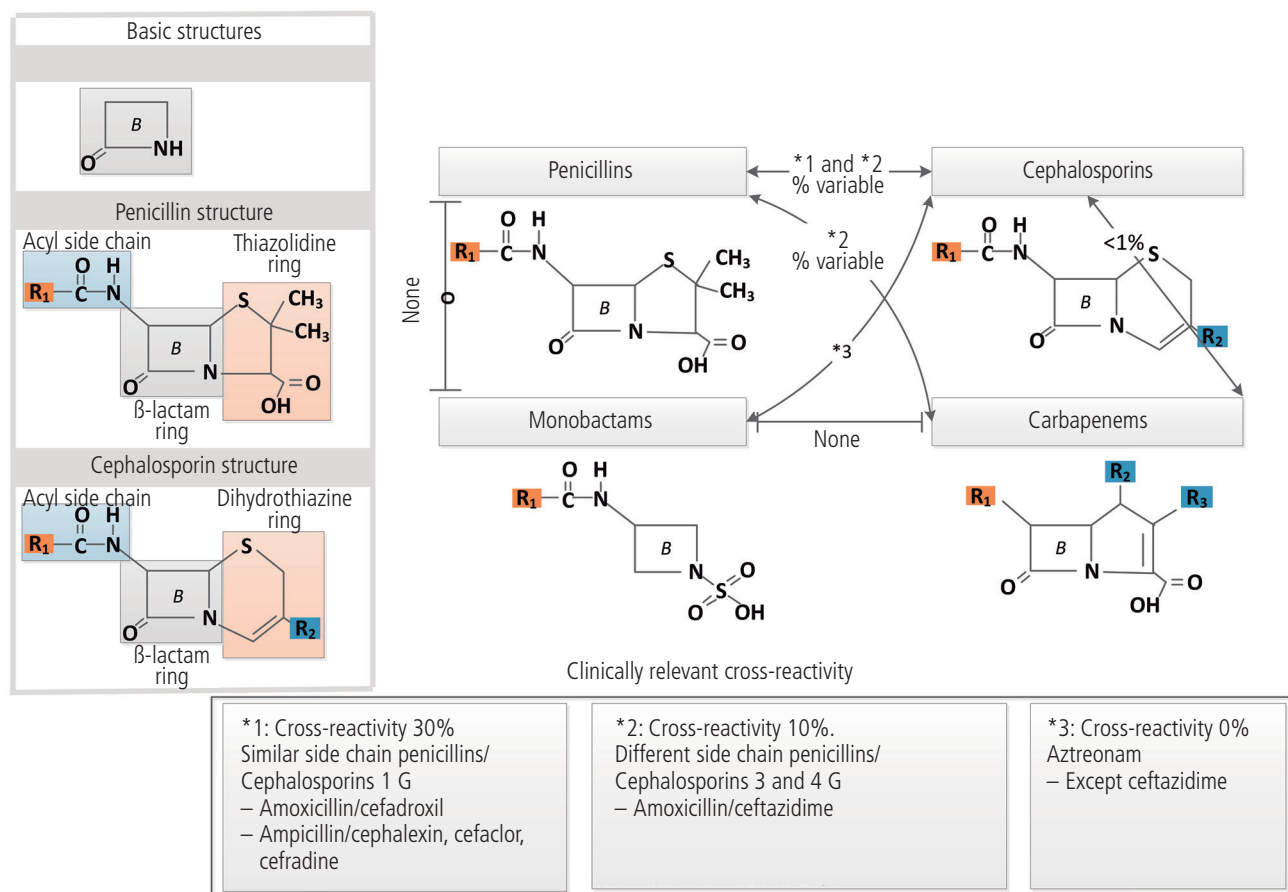


Figure 2. β -Lactam structures and rates of cross-reactivity.

Table 2. Classification of Hypersensitivity Acute Reactions Induced by Nonsteroidal Anti-inflammatory Drugs^a

Type of Reaction	Clinical Manifestation	Underlying Disease	Cross-reactivity	Putative Mechanism
NSAID-exacerbated respiratory disease (NERD)	Bronchial obstruction, dyspnea and/ rhinorrhea or nasal congestion/	Asthma and/or rhinosinusitis	Cross-reactive	COX-1 inhibition
NSAID-exacerbated cutaneous disease (NECD)	Wheals and/or angioedema	Chronic urticaria	Cross-reactive	COX-1 inhibition
NSAID-induced urticaria/angioedema (NIUA)	Wheals and/or angioedema	No	Cross-reactive	Unknown, probably COX-1 inhibition
Single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA)	Wheals/angioedema/anaphylaxis	No	Non-cross-reactive (selective)	IgE-mediated

Abbreviations: COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; NERD, NSAID-exacerbated respiratory disease; NECD, NSAID-exacerbated cutaneous disease; NIUA, NSAID-induced urticaria/angioedema; SNIUAA, single NSAID-induced urticaria/angioedema or anaphylaxis.
^aSource: Kowalski et al. Allergy. 2013;68(10):1219-32.

Nasal lysine acetylsalicylate challenge is recommended for patients who experience upper respiratory tract symptoms and severe asthma. The test may also be performed in an outpatient clinic [63-67]. The sensitivity of this test is 73% and the specificity 94% [66,67].

Table 3. Interval of Administration and Dose of the Drugs Used in the Oral Drug Provocation Test

Drug	Dose, mg ^a
Etoricoxib	60 - 90*
Celecoxib	100 - 200*
Paracetamol (Acetaminophen)	100 - 250 - 500 - 1000*
Meloxicam	7.5 - 15**
Nabumetone	500 - 1000**
Diclofenac	25 - 50**
Metamizole (dipyrone)	First day: 50 - 100 - 250** Second day: 575***
Ibuprofen	First day: 50 - 100 - 200 - 400** Second day: 600***
Acetylsalicylic Acid	First day: 50 - 100*** Second day: 250 - 500***

Source: Ortega et al, J Investig Allergol Clin Immunol. 2014;24(5): 308-23.

^aAdministration interval of each dose: *60 min, **120 min, ***180 min.

The bronchial provocation test (BPT) is indicated in patients with bronchial symptoms with NSAIDs [68,69]. The specificity of the BPT is 100%, with a sensitivity of 62%, although it is less dangerous and time-consuming than oral DPTs [69].

The oral provocation test (OPT) is the only available test for diagnosing patients with nonimmunological reactions and skin symptoms [61,62].

Protocols vary according to the drugs used, administration interval, and total cumulative dose. The most recommended are shown in Table 3 [62,70].

A 1-week interval is needed if various NSAIDs are studied using OPTs. In patients with respiratory symptoms, testing is not usually performed using NSAIDs with strong COX-1 inhibitory activity owing to the possibility of severe bronchospasm [62].

3.2. Diagnostic algorithm

Figure 3 shows a practical diagnostic algorithm to determine the type of NSAID hypersensitivity and enable proper patient management. In most cases of NSAID hypersensitivity, however, the information acquired from the history is not sufficient to confirm the diagnosis, thus necessitating further steps, including OPTs.

An acute reaction may be suspected if the reaction starts to develop within hours after drug intake (up to 24 hours, but usually 1-2 hours). The next step depends on the symptoms reported by the patient.

- Respiratory symptoms. Testing should begin with an NPT or BPT with lysine acetylsalicylate, if possible, in

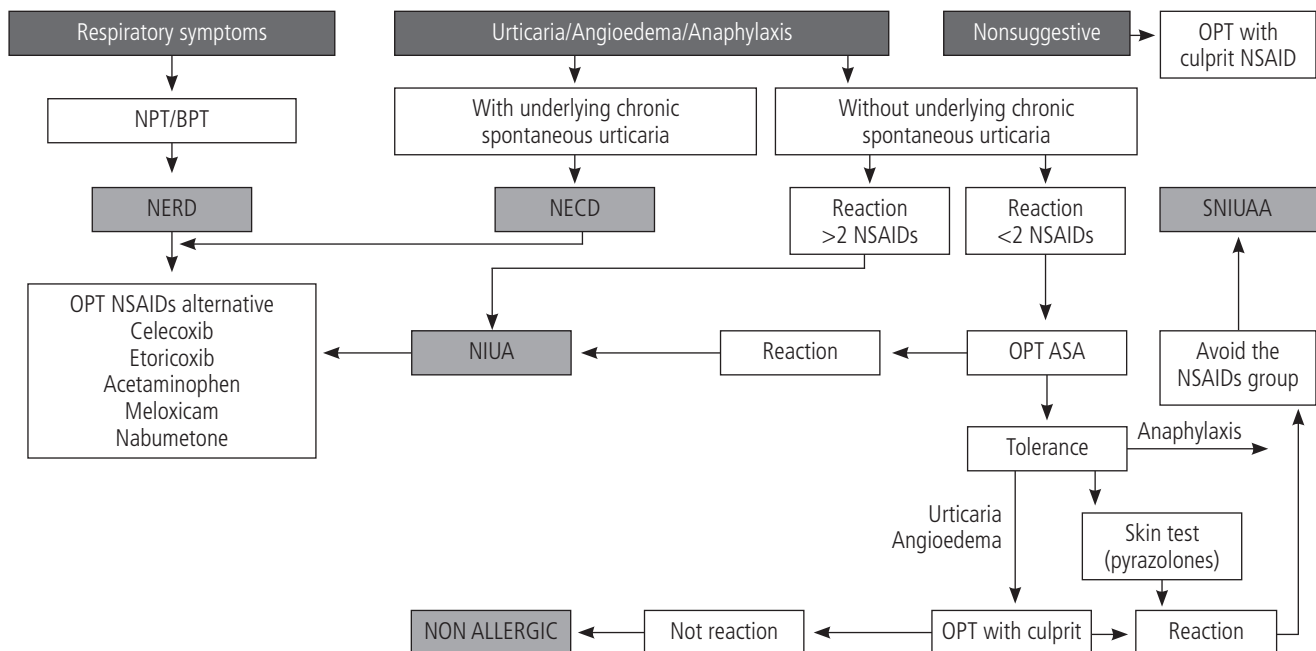


Figure 3. Clinical history of hypersensitivity acute reactions to NSAIDs (<24 hours). BPT, indicates bronchial provocation test; COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; NTP, nasal provocation test; NERD, NSAID-exacerbated respiratory disease; NECD, NSAID-exacerbated cutaneous disease; NIUA, NSAID-induced urticaria/angioedema; OPT, oral provocation test; SNIUAA, single NSAID-induced urticaria/angioedema or anaphylaxis; ASA, acetylsalicylic acid.

the allergy department. A positive response will confirm the diagnosis of NSAID-exacerbated respiratory disease. The patient is prompted to avoid all NSAIDs with strong COX-1 inhibitory activity. Tolerance to alternative analgesics, such as paracetamol (acetaminophen), selective COX-2 inhibitors, and preferential COX-2 inhibitors (eg, meloxicam) should be tested. If there no response, these drugs can be recommended.

- Cutaneous symptoms. Up to one third of patients with chronic urticaria experience exacerbations when exposed to NSAIDs that inhibit COX-1, but not to COX-2 inhibitors [71,72].

NSAID-exacerbated cutaneous disease should be sought in the clinical history. Tolerance to alternative analgesics should be verified.

In patients with urticaria and/or angioedema without underlying chronic urticaria, there are 2 possibilities:

- If the patient reports reactions with >2 NSAIDs from unrelated chemical groups, then he/she is diagnosed with multiple hypersensitivity to NSAIDs according to the clinical history (NSAID-induced urticaria/angioedema) [61,62]. In this case, tolerance to alternative analgesics should be assessed.
- If the patient reacted with <2 NSAIDs from unrelated chemical groups, then an OPT with ASA or a potent COX-1 inhibitor (if acetylsalicylic acid is involved) should be carried out. If the result is positive, the patient should be diagnosed with NSAID-induced urticaria/angioedema, and an OPT to alternative analgesics should be performed.
- If a patient tolerates acetylsalicylic acid, an OPT with the culprit drug should be performed; if positive, the diagnosis is acute selective reaction (single NSAID-induced urticaria/angioedema). Administration of the culprit drug in this group of patients depends on the type of reactions and is contraindicated in patients with anaphylaxis.
- If the patient tolerates acetylsalicylic acid and the culprit NSAID, then he/she should be diagnosed as nonallergic.

4. Macrolide, Quinolone, and Aminoglycoside Antibiotics

4.1. Macrolides

Macrolides are amongst the safest antibiotics, accounting for very few cases of drug hypersensitivity [73]. Skin tests with suspicious macrolide antibiotics have usually yielded negative results, except for a few reports in immediate or delayed reactions, in the form of as fixed drug eruptions. Basing assessment on the clinical history alone leads to an overestimation of macrolide hypersensitivity, and skin/laboratory tests do not seem to be useful for confirming diagnosis. Oral challenge tests are considered the gold standard for confirming or ruling out drug hypersensitivity [74]. Based on the low frequency of hypersensitivity to these agents and low likelihood of drug allergy, a graded challenge is recommended [74,75]. Several studies on cross-reactivity in this drug group have suggested that the overall risk is low given

the differences in size of the lactone ring [76]. Findings have also been reported for macrolide immunosuppressants [77]. In conclusion, when an allergic reaction to a macrolide is detected, an exposure to an alternative macrolide is recommended to confirm its tolerance [78,79].

4.2. Quinolones

There is considerable cross-reactivity between quinolones, although no predictive pattern has been established [80]. Sensitization to one quinolone does not predict sensitization to another. Furthermore, as skin tests provide little information, it is necessary to carry out challenge tests to confirm sensitivity or tolerability [81]. However, it is considered advisable to perform skin tests with several quinolones to guide the diagnostic study before the oral provocation challenge [82]. The basophil activation test and determination of specific IgE to quinolones are also recommended if available [83]. Levofloxacin is usually the safest alternative quinolone [80].

4.3. Aminoglycosides

Aminoglycosides rarely cause allergic drug reactions, including IgE-mediated systemic reactions; in fact, the most frequent reactions are delayed by neomycin [5]. In cases of previous reaction to an aminoglycoside, controlled administration of an alternative aminoglycoside from another group is recommended. Cross-reactivity between gentamicin, tobramycin, and neomycin has been reported, as has cross-reactivity between streptomycin and kanamycin [77].

5. Other Antimicrobial and Tuberculostatic Drugs

5.1. Tuberculostatic Agents

Challenge tests with tuberculostatic agents are usually performed orally, except for gentamicin and tobramycin, which can only be administered by injection or topically. Depending on the severity of the previous reactions and in the case of positive test results and multiple diseases, it is recommended to start with an alternative member of the group at 1/10 of the therapeutic dose [74,80,84]. Challenge tests with gentamicin and tobramycin follow the same rules as oral antibiotics.

In Spain, some adverse reactions (paresthesia) attributed to penicillins in the 1970s and 1980s occurred after joint administration with streptomycin. In these cases, it would be interesting to confirm tolerance to penicillin (rule out allergy), although assessment of streptomycin is unnecessary, since it is no longer in use.

Rifampicin and pyrazinamide are the most frequently involved drugs in this group [85-89].

Skin tests (prick and intradermal) with tuberculostatic agents are not very useful, although positive intradermal test results have been reported [89,90-92]. In NIRs, intradermal tests with delayed readings and patch tests are helpful [93-96].

Concerning in vitro tests, IgE antibodies in IRs and the lymphocyte transformation test in NIRs can be positive and can help diagnosis [90,97].

Drug provocation protocols have been published with rifampicin, isoniazid, pyrazinamide, and ethambutol, as have desensitization protocols [87,98-101].

5.2. Sulfamides

Skin tests can help to confirm the diagnosis and to look for alternative drugs in IRs. In NIRs, patch tests do not seem to be useful [102], except in some cases of fixed drug eruption [103].

IgE against sulfamethoxazole has been shown to be positive in IRs [104,105].

While cross-reactivity between antimicrobial sulfonamides has been reported [103], it is not yet clear between antimicrobial and non-antimicrobial sulfonamides [106-108], except with sulfasalazine, which cross-reacts with antimicrobial sulfamides [109].

5.3. Tetracyclines

Together with minocycline and tetracycline, doxycycline may have the best overall safety profile regarding the potential for the allergic reactions compared [110].

Cross-reactivity varies in tetracyclines taken for dermatological manifestations. Some studies show cross-reactivity between the tetracycline class in FDE, whereas others do not [111-113].

5.4. Glycopeptides

Except in the case of red man syndrome, which is an infusion-related reaction, skin tests aid diagnosis and the search for alternative drugs in HSRs.

Positive skin test results have been reported in allergic reactions to vancomycin and teicoplanin [114-116]. Cross-reactivity is variable [117-122], and vancomycin challenge protocols have been published [123].

5.5. Nitroimidazoles

In the case of nitroimidazoles, some authors consider skin and in vitro testing to be useful, while others do not [124,125].

The cross-reactivity of imidazoles is variable [126,127].

5.6. Lincosamides

Skin tests with clindamycin have limited diagnostic potential [128], although positive results have been reported in patch tests [129-131]. PubMed contains no cross-reactivity studies or desensitization protocols [77].

Leprostatic Sulfones

HSRs have been reported to dapsone, although PubMed contains no cross-reactivity studies or desensitization protocols [132-135].

5.7. Antiparasitics

Skin tests (prick and intradermal testing) with antimalarial drugs are of little use, although patch tests are useful in NIRs [136-141]. IRs and NIRs to paromomycin have been reported [142-143].

Hypersensitivity reactions to praziquantel, benzimidazole, albendazole, and pentamidine have been described, although

PubMed contains no cross-reactivity studies or desensitization protocols [144-152].

6. Corticosteroids

Corticosteroids are anti-inflammatory medications that are widely used to treat allergic inflammation. Although the endocrine and gastrointestinal adverse effects of corticosteroids have been described, the occurrence of immediate hypersensitivity reactions and delayed contact dermatitis due to corticosteroids remains underrecognized. Hypersensitivity reactions may be due to the corticosteroid itself or to the excipients in corticosteroid preparations.

Skin testing and DPT can help us to confirm the suspected culprit agent in immediate reactions and therefore to identify an alternative tolerated corticosteroid. Regarding the reading of the skin prick and intradermal tests, we have to perform an immediate reading (after 20-30 minutes) and a nonimmediate reading (after 24, 48, and/or 72 hours) (153).

Patch testing and DPT can help to identify the culprit agents in contact dermatitis and nonimmediate reactions. Cross-reactivity patterns found in contact dermatitis studies are not applicable to immediate hypersensitivity reactions [154-158] (see references [159,160] in tables). Sensitization in contact dermatitis exhibits cross-reactivity patterns based on corticosteroid structure. A DPT should be performed in the case of nonsevere cutaneous reactions with negative skin tests results in order to find an alternative corticosteroid [161]. A succinate-free alternative is recommended [162,163]. Cross-reactivity is well-documented, and the 2 main groups are budesonide with group B and group D members and methylprednisolone with hydrocortisone or prednisolone [163-165].

In the rare cases where a safe alternative cannot be identified and corticosteroids are necessary, desensitization can be performed, as reported for methylprednisolone and hydrocortisone [166-168].

7. Antifungal Drugs

Available antifungals to treat systemic mycosis can be classified into 2 main groups, ie, those that act against the cell wall (caspofungin) and those that act against the cytoplasmic membrane (amphotericin B, bifonazole, clotrimazole, clotrimazole, croconazole, econazole, fenticonazole, ketoconazole, isoconazole, miconazole, neticonazole, oxiconazole, sertaconazole, sulconazole, tioconazole, and antiparasitic agents).

As fixed drug eruption is the most frequently reported symptom, patch tests must be performed not only with the culprit drug to confirm the diagnosis, but also with other family members to rule out cross-reactivity before the DPT [169-175]. Cross-reactivity is not clear in the antifungal group, and several clinical studies report different results for members of the same family [169-176].

Desensitization can be performed in the rare cases in which a safe alternative cannot be identified and antifungals are necessary, as reported for amphotericin B and voriconazole [177,178].

8. Heparins, Anticoagulant Drugs, Insulin, and Antidiabetic Drugs

8.1. Heparins and Anticoagulant Drugs

This anticoagulant group includes heparins, hirudins, and cumarins [179]. Heparins and hirudins can cause different types of allergic reactions, such as cell-mediated type IV reactions, followed by, albeit less frequently, antibody-mediated type II reactions, and, very rarely, type I reactions [180,181].

Depending on the result of the allergological tests, 2 situations can unfold.

- If ADR is highly suspected with skin prick tests or patch test results are positive to heparin or hirudin, a DPT based on alternative heparin with a negative test result can be carried out.
- If the skin prick test or patch test result is negative to all heparins tested, the 2 possible options are as follows:
 - A heparinoid, synthetic pentasaccharide (fondaparinux), or a hirudin is recommended if the allergic reaction is induced by an unfractionated heparin or low-molecular-weight or fractionated heparin because the likelihood of cross-reactivity between these 2 agents is very high [182-185].
 - Another anticoagulant from any group can be tested if the anticoagulant involved in the ADR was a heparinoid, fondaparinux, or a hirudin,

In the case of low suspicion of allergy in the clinical history and positive allergy test results, the approach is the same as in the previous case. However, with negative test results, a DPT can be performed with the suspected heparin. DPT is not recommended in the case of cutaneous necrosis or antibody-mediated reactions.

Drug administration guidelines vary according to the type of reaction [2,186-188]. In type I reactions, 1/10, 3/10, and 6/10 of the total heparin dose should be administered, with 30 minutes between doses. The total dose dispensed must be adapted to the needs of the patient and the condition to be treated. The route of administration can be subcutaneous, preferably in the abdominal area, or intravenous, depending on the heparin class. It is especially important to perform the test using the same route of administration in which the patient presented the reaction. Allergy has been reported to a subcutaneously administered drug, which was subsequently tolerated intravenously [189].

In NIRs, 1/10 of the subcutaneous dose can be injected, and, if there are no reactions in the following 7 days, the rest of the 9/10 dose could be administered. The result is considered negative 7 days after this second DPT. In an emergency, the dose can be administered intravenously in a slow regimen. The most widely used protocol is the one proposed by Gaigl et al [189]: 2500 IU of heparin on the first day, followed by 5000 IU on the second day and 7500 IU every 6 hours for 3 days.

8.2. Insulin and Oral Diabetics

Allergic reactions to insulin are rare, with an estimated prevalence of 0.1%-2% [190,191]. Type I, type III (localized Arthus reaction), and type IV reactions have been reported. The insulin molecule, neutral protamine Hagedorn, or various additives (zinc, cresol, glycerol) can act as allergens [192-194].

A DPT is indicated when there is suspicion that the allergic reaction is due to the neutral protamine Hagedorn molecule or an additive and another class of insulin without them is available.

DPT to demonstrate allergy or tolerance can also be performed in cases in which the skin prick test is negative and the determination of IgE and IgG are also negative.

Desensitization is the only option in cases of life-threatening anaphylaxis and in cases of allergy to insulin itself, because DPT is not recommended [195].

In the case of IRs, the procedure should be performed as described above: 1/10 of the total dose, followed by 3/10 and finally 6/10, with 30 minutes between doses. If an NIR occurs (generalized or local), a single dose can be administered, and the reading can be carried out in the following days. This insulin could be administered if no reaction is observed in the following 5 to 7 days. As with heparin, there have been reports of allergy involving subcutaneous insulin in which the drug was subsequently tolerated intravenously [196].

In addition to the standard monitoring, serial monitoring of blood glucose should be performed.

9. Biological and Cytostatic Drugs

Only a few series report data on DPT with antineoplastic and biological agents [197-204].

A risk assessment based on the severity of the initial reaction, comorbidities, and the indication from the referring physician is mandatory before DPT [197-199,201]. Patients with severe HSR and positive skin tests/specific IgE and/or comorbidities should be excluded. β -Adrenergic blocking agents and ACEIs should be discontinued 24 hours prior to the DPT. Testing should be performed in the medical intensive care unit and involve the desired full dose of the culprit drug according to the manufacturer's instructions, including infusion rates for standard regimens [197-199,201]. Madrigal-Burgaleta et al [199] reported negative results in 229 DPTs out of the 341 performed (67%) and therefore administered the scheduled treatments with the standard regimens. Of the 112 positive DPTs (33%), 17 involved severe HSR (15%). Forty-three percent (48/112) were mild, and 42% (47/112) were moderate according to the Brown classification. The authors concluded that DPT is a vital diagnostic tool that helps to exclude HSR and avoid unnecessary desensitization.

Regarding taxanes, Picard et al [205] reported on 49 DPTs in patients with mild/moderate IR and NIR and negative skin test results. The decision to perform DPT was based on the severity of the initial reactions, skin test results, and the individual patient's comorbidities (FEV₁ values, coronary heart disease), need for treatment, and patient consent [204]. DPT involved administering the culprit drug diluted in 250 mL of normal saline starting at 10 mL/h and increasing progressively up to 160 mL/h without an adverse reaction; all patients tolerated the drug for at least 1 infusion. In 2013, the protocol was modified using 3 steps every 15 minutes, with approximately 10-fold increments for each step until the manufacturer's recommended dose was reached. This change

was made to ensure that the procedure could register HSRs that might appear with a regular infusion [205]. Two patients (4%) had a mild IR and 1 (2%) had a delayed reaction. Premedication with antihistamines, H2 blockers, antileukotrienes, and/or acetylsalicylic acid can be used in DPT, although the authors do not make specific recommendations.

Recently, Pagani et al [204] reported a multicenter study that enrolled 84 patients with IRs due to taxanes. Sixteen patients with no alternative treatment, negative skin test results, and mild reactions that involved the skin or a single organ (usually back pain) underwent graded challenges successfully. The offending drug was administered at 10 mL/h for the first hour, and, if tolerated, the remainder was administered according to the manufacturer's instructions [204].

DPT can be performed in patients with mild reactions to biologics, negative skin test results, and normal tryptase levels obtained during IRs [202-203]. The offending drug can

be administered in 2 steps, at 1/10 of the total dose, and, if tolerated, the remainder can be administered until the target dose is achieved [202-203].

9.1. Specific considerations

DPTs with antineoplastic and biological drugs differ from testing in other drugs in many ways:

- The timing of DPT is essential, since it must be performed together with the next scheduled treatment. For this reason, multidisciplinary collaboration is needed between allergists, referring physicians, nurses, and clinical pharmacologists.
- Following the manufacturer's recommendations on the infusion rate and premedication is mandatory for these drugs. Therefore, many DPTs with antineoplastic and biological agents should be performed with additional premedication [197-199,201,204].

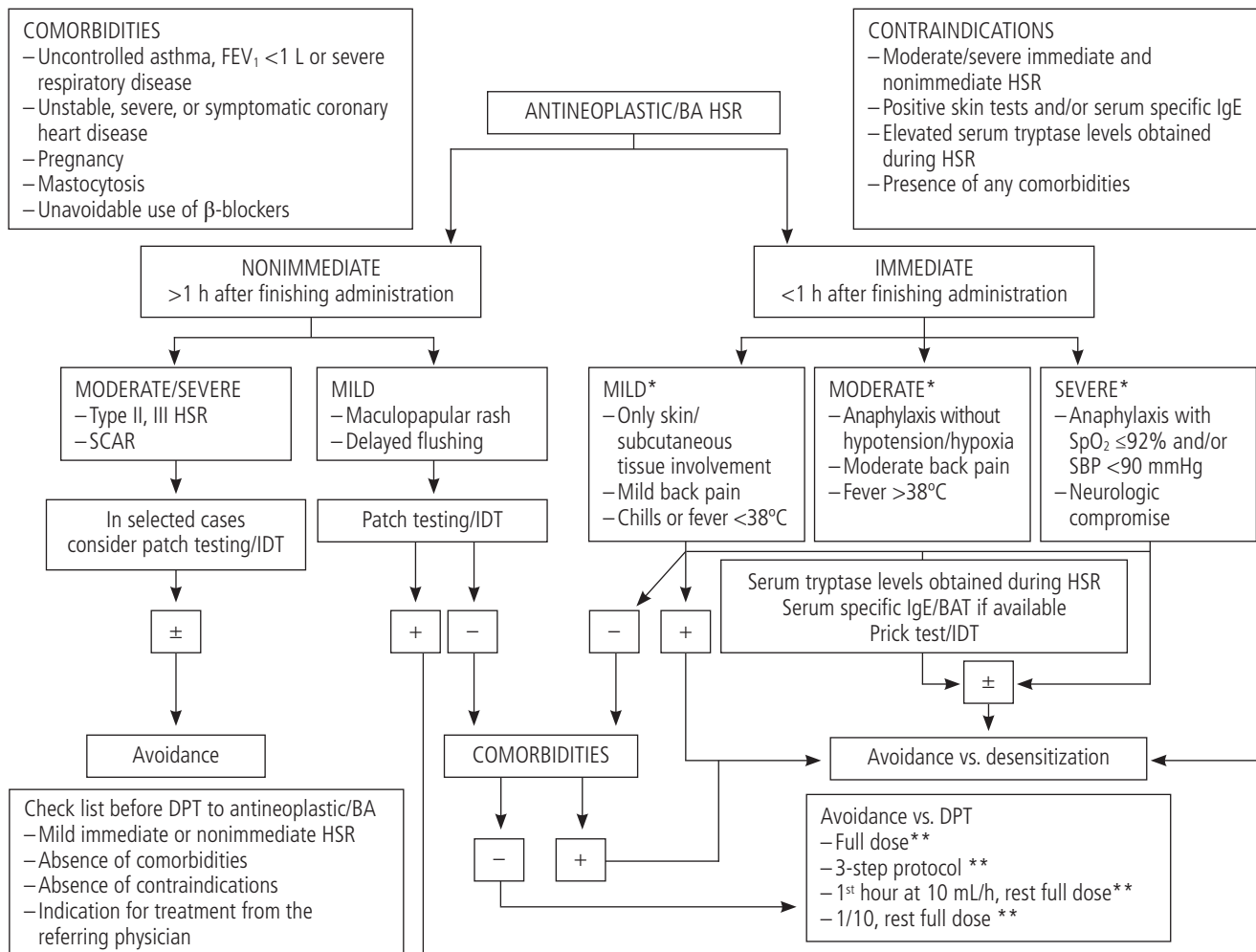


Figure 4. Proposed algorithm for DPT with antineoplastic and biological agents. SCAR indicates severe cutaneous adverse reactions; IDT, intradermal test; SBP, systolic blood pressure; SpO₂, peripheral oxygen saturation; FEV₁, forced expiratory volume in the first second; biological agent; HSR, hypersensitivity reaction; IDT, intradermal test; BAT, basophil activation tests; DPT, drug provocation test.

*Adapted from the classification of Brown (Brown 2004).

**According to the manufacturer's instructions.

- The involvement of premedication in the HSR must also be ruled out before the procedure, as with other concomitant drugs [197,199-201].
- The target dose must be prescribed by the referring physician based on previous laboratory findings. Pharmacists then prepare it according to manufacturer's/institutional safety recommendations.
- The safety of the procedure requires allergists with experience in the drugs involved, specially trained nurses, and one-on-one nursing care. The procedure must be performed in the ICU/desensitization unit [197-199,201,204,205].

An algorithm designed to illustrate the recommended protocol for DPT with antineoplastic and biological agents can be found in Figure 4.

10. Miscellaneous: Iron, Antiretroviral Drugs, Cyclosporine, Interferon, and Growth Factors

In the absence of standardized controlled DPT protocols for the group of drugs indicated, we have developed a unified "graded challenge" proposal for drugs from the various pharmacological groups. The protocol recommended for DPTs should always be performed under strict hospital surveillance (Table 1).

After a series of fatal anaphylactic/anaphylactoid reactions that occurred in 2013 after parenterally administered iron preparations, the European Medicines Agency published a series of recommendations for successive re-exposures. These recommendations are an exception to the usual indications for re-exposures and/or desensitizations because the products are not indicated for patients with known serious hypersensitivity to other parenteral iron products [206].

The risk is enhanced in patients with known allergies including drug allergies and patients with a history of severe asthma, eczema, or other atopic allergies. There is also an increased risk of hypersensitivity reaction to parenteral iron complexes in patients with immune or inflammatory conditions (eg, systemic lupus erythematosus, rheumatoid arthritis).

11. Conclusions

Diagnosis should begin with a detailed clinical history. Skin tests are only useful for specific drugs, and in most cases, the diagnosis can only be confirmed by DPT. Although cross-reactivity is usually present, DPT confirms the diagnosis and helps to find an alternative drug. Individual patient management considering comorbidities normally enables a solution to be found in most cases. Finally, in most urgent or life-threatening cases, we can resort to desensitization or cautious administration of drugs, always under extremely thorough medical supervision.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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■ **María Teresa Audicana Berasategui**

Servicio de Alergología e Inmunología Clínica
Hospital Universitario Araba
Organización Sanitaria Integrada Araba
Edificio de Consultas Externas, 1º planta
Calle Francisco Leandro de Viana, 1
01009 Vitoria-Gasteiz, Spain
E-mail: mariateresa.audicanaberasategui@osakidetza.eus
maiteaudi@telefonica.net