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REVIEW

Diagnosing and managing patients with drug hypersensitivity

Javier Fernandez[a] and Inmaculada Doña[b]

[a]Allergy Section, Alicante University Hospital, UMH-ISABIAL, Alicante, Spain; [b]Allergy Service, Carlos Haya Hospital (Pavilion C), Malaga, Spain

ABSTRACT

Introduction: Diagnosing and managing drug hypersensitivity is challenging because there are no clear limits between different types of drug reactions. Distinguishing between type A (predictable) and type B (hypersensitivity) reactions when a drug is introduced on the market is not easy. When many people use a drug, adverse reactions can occur, conditioned by diverse genetic profiles, viral infections or concomitant therapy. Occasionally the only tool clinicians have on which to base the diagnosis is the clinical history. Skins tests or *in vitro* tests sometimes have low sensitivity or are unavailable, and drug provocation tests may be dangerous or strictly forbidden in case of severe cutaneous reactions.

Areas covered: This paper reviews the diagnosis and management of the two main types of immunological reactions: IgE-mediated immediate drug hypersensitivity reactions (IDHRs) and non-immediate drug hypersensitivity reactions (NIDHRs).

Expert commentary: Although Europe and the United States use different diagnostic methods, patients with history of drug hypersensitivity must avoid the suspicious drug, and clinicians must assess tolerance to safe alternatives under medical surveillance. Sometimes desensitization may be required. There is a consensus about the need to perform genetic testing for specific drugs and give patients proper documentation to prevent future exposure to culprit drugs.

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1. Definition

The term 'drug allergy' is widely used in a popular sense to encompass both some type A reactions, which are predictable side effects due to the drug's pharmacological action, and type B reactions, which represent true hypersensitivity due to idiosyncratic and individual predisposition [1,2].

The classification of a drug hypersensitivity reaction (DHR) is important for determining appropriate diagnostic procedures, options for further treatment, and possible cross-reactivity with similar medications, but in practical terms, immunological drug reactions can be divided into two broad types, as recommended by the World Allergy Organization (WAO) [2]. These categories are based on the timing of the symptoms' onset: immediate drug hypersensitivity reactions (IDHRs) occur within one hour of the first administered dose and are usually IgE mediated, while non-immediate drug hypersensitivity reactions (NIDHRs) occur anytime thereafter, but usually more than six hours and occasionally weeks to months after the start of administration; most of these reactions are cell-mediated hypersensitivities and involve several unknown mechanisms, which act simultaneously or even sequentially [1,3–6]. In NIDHRs, reactions can be classified based on systemic symptoms, affected organs, or severity of the reaction in the main organ involved (e.g. skin) [7–10]. In cell-mediated drug hypersensitivity, Pichler has proposed an update of the old Gell and Coombs classification to explain the different T-cell subset and functions involved [8,11].

This paper reviews the diagnosis and management of the two main types of immunological reactions: type I or IgE mediated (IDHRs) and type II, III, and IV (NIDHRs) (Table 1).

2. Diagnosing IDHRs: focus on penicillin and nonsteroidal anti-inflammatory drug hypersensitivity

The diagnostic approach to IDHRs may include a detailed clinical history, followed by skin testing, *in vitro* testing, and drug provocation testing (DPT).

2.1. Clinical history

A detailed clinical history is the most important step toward an accurate diagnosis of drug hypersensitivity. It includes a description of the symptoms, the time interval between the drug administration and the onset of the reaction, the dose of the drug, and the route of administration. It is important to note whether patients were taking other concurrent medications when the reaction occurred, if they required medical treatment or hospitalization because of the reaction, and whether they have received the culprit medication or a related drug since the first reaction occurred [12].

Clinical history taking has limitations, and in most cases, it is not appropriate for establishing a drug hypersensitivity diagnosis, especially as time passes. In fact, fewer than 20% of patients with a history of drug hypersensitivity react in DPT to the culprit drug suspected by clinical history [13]. Moreover, causality can be difficult to ascertain because patient accounts

CONTACT Javier Fernandez fj.fernandez@umh.es

Table 1. Gell and Coombs classification adapted to drug reactions.

	Type I	Type II	Type III	Type IV (a, b, c, d)
Immune mechanism	Immediate (IgE)	Antibody mediated	Immune complex mediated	Cell mediated
Tissue lesion mediation	Chemical mediators from basophils and mastocytes	Complement Recruitment and activation leukocytes Alteration of receptor function	Complement Leukocyte recruitment and activation	Predominant cell: (a) Macrophage (b) Eosinophils (c) T-cells (d) Neutrophils
Start after contact with the drug	Minutes	From 2 to 6 h	From 2 to 6 h	From 24 to 48 h to days
Anatomo-pathological lesion	Edema Vasodilatation Muscle contraction	Necrotizing vasculitis	Necrotizing vasculitis	Cellular perivascular infiltrates Edema
Transfer between animals	Serum	Serum	Serum	Sensitized lymphocytes
Responsible antibody	IgE	IgG, IgM	IgG, IgM	–
Effector cells	Mastocytes and basophils	Neutrophils and monocytes and NK cells	Neutrophils and monocytes	Macrophage Eosinophils T-cells Neutrophils
Secreted mediators Effector molecules	Vasoactive amines Lipid mediators TH2-cytokines (IL4, IL13, and IL5)	Activated complement products Inflammatory cytokines (IL1, IL12, IL18, IFN-ϒ and TNF-α, and CM-CSF)	Activated complement products Inflammatory cytokines (IL1, IL12, IL18, IFN-ϒ and TNF-α)	IFN-ϒ and TNF-α, IL5, IL4/IL13 Perforin/granzyme B CXCL8, GM-CSF

Modified from [8].

are prone to inaccuracies, especially when the reaction occurred a long time ago: the chronology may be imprecise, the clinical manifestations may be heterogeneous, and the patient may not recall the exact name of the culprit drug [12].

2.2. Skin tests

The procedure generally begins with a skin prick test (SPT) and, if negative, an intradermal test (IDT). Skin tests (STs) are considered the best-validated *in vivo* method for diagnosing immediate reactions to a large range of drugs [3,14]. However, the diagnostic values of ST are not well established in all cases because the right concentrations for STs may be unknown or poorly validated [5,15]. Moreover, for most drugs, the full range of metabolites and intermediate forms of the drug to which patients may be susceptible has not been determined, and testing reagents are not available. Thus, in most cases, testing is undertaken with only the native form of the drug, which may fail to detect hypersensitivity in a large proportion of patients [16]. In addition, some drugs, including opioids, quinolones, and vancomycin, can cause direct mast cell degranulation, making it impossible to study them [5,17]. Furthermore, many drugs are not available in injectable form and hence IDTs are not possible [5].

The loss of test sensitivity over time or negativization rate depends on the drug but ranges from 60% after six months for dipyrone [18,19] to 47% within four years for neuromuscular-blocking agents (NMBAs) [20]. Therefore, ST should be performed soon to avoid false negatives [18,20,21], although at least four weeks after the episode to avoid a possible refractory period when testing may also give a false-negative result [22].

Despite these limitations, STs have proven useful for IDHRs to beta-lactams, pyrazolones, and other drugs like NMBAs [15].

Regarding beta-lactams, patterns of sensitization vary over time depending on intake of antibiotics [23], leading in the last decades to a fall in the ST positivity to previously consumed penicillins [24,25]. Traditionally, STs with major (benzylpenicilloyl-poly-l-lysine [PPL]) and minor benzylpenicillin determinants (minor determinant mixture [MDM]) were used [3]. However, since the advent of semisynthetic penicillins with different side chains such as amoxicillin, ampicillin, and various cephalosporins [26,27], there has been an increase in hypersensitivity reactions to these drugs [24], displacing benzylpenicillin's status as the most relevant hapten in IDHRs to beta-lactams [28]. Indeed, the inclusion of amoxicillin in ST could increase positivity to up to 70% [28]. The increasing consumption of clavulanic acid in recent years has also been accompanied by hypersensitivity reactions to it, prompting the need for its inclusion in the diagnostic evaluation, as well. Including clavulanic acid in ST has increased sensitivity from 9% to 18.7% in SPT and from 63.6% to 81.2% in IDT [29,30]. Therefore, clavulanic acid should be included in addition to amoxicillin in ST for the routine diagnosis of allergic reactions. Otherwise, there are no clear benefits to adding benzylpenicillin to ST that already include PPL (Pre-pen from ALK, USA) and MDM, both reagents commercially available from Diater S.A, Spain, in populations where amoxicillin and amoxicillin–clavulanic acid are the main culprit drugs [31], but it is useful if PPL and MDM are not available. When any other beta-lactam is involved in the reaction and the results of ST for PPL, MDM, and amoxicillin are negative, it is necessary to perform STs with the culprit beta-lactams [3,29,32]. The negative predictive value (NPV) of penicillin STs when performed with the major determinant is very high (97–99%); however, it may be lower for amoxicillin [33–36]. The positive predictive value (PPV) of penicillin STs is approximately 50% (33–100%) [34,37,38]. Notably, systemic symptoms occur in up to 8% of patients with a positive ST result [39], so some authors have recommended reducing the hapten concentration down to 1:1000 dilution and using each determinant separately if the patient has a history of anaphylaxis [32].

With regard to IDHRs to nonsteroidal anti-inflammatory drugs (NSAIDs), most studies have investigated IDHRs to pyrazolones [18,40], which are only used in a few countries. Reported sensitivity ranges widely, from 41% [19] to 85.7%

[18] for dipyrone and 83% for propyphenazone [40], with a specificity of 100% for both drugs [18,40,41]. For other NSAIDs [42], the authors have reported positive ST results in small patient series and single case reports, mainly for paracetamol [43–45] and diclofenac [46].

Regarding IDHRs to NMBAs, STs have a high sensitivity (>95%) and specificity (96–98%) and are considered mandatory for diagnosing suspected NMBA hypersensitivity reactions [47].

2.3. In vitro *tests*

As IDHRs are IgE mediated, *in vitro* tests basically consist of the quantification of the drug-specific IgE (sIgE) in serum by immunoassay or gaging a functional response through a basophil activation test (BAT) [48]. The diagnostic value of *in vitro* tests depends on the drug, although they are generally less sensitive than ST and are mainly used to complement these. The combination of ST and *in vitro* tests increases diagnostic sensitivity; in fact, up to 30% of patients with negative results on ST to dipyrone have positive BAT results [10,18], and this figure can rise up to 40% in the case of beta-lactams [49,50].

Although there is no general consensus, *in vitro* tests are usually recommended in high-risk patients before DPT and even ST due to the potential risk of systemic reaction [51,52]. As with ST, serum IgE levels decrease over time if the patient experiencing an immediate reaction is not reexposed to the drug, leading to a decrease in test sensitivity [18,20,21,53]. Therefore, it is crucial to perform the test as soon as possible following a time interval of 4–6 weeks after the reaction [21].

Immunoassays have been developed for a wide variety of drug-sIgE; however, many of them have been commercialized before published validation. Most studies evaluating immunoassays for diagnosing immediate reactions have used beta-lactams [49,54–58], quinolones [53,59], NSAIDs [40,41], and NMBAs [60–63].

In case of beta-lactams, commercial immunoCAP-FEIA is available for benzylpenicillin, penicillin V, amoxicillin, ampicillin, and cefaclor, with an estimated mean sensitivity of 50.1%, specificity of 81.01%, a PPV of 80.4%, and an NPV of 53.3% [64]. The availability of ImmunoCAP, limited to only a few beta-lactams, has led to the use of in-house immunoassays, such as the sepharose-radioimmunoassay (RIA) or the radioallergosorbent test (RAST) [51]. Compared to ImmunoCAP, RAST shows higher sensitivity (42.9–75.0%) and specificity (67.7–83.3%) for both penicillins and cephalosporins [57]. Sepharose-RIA – used for cephalosporins – also shows a good sensitivity (67.1–74.3%) and specificity (100%) [65]. For these antibiotics, the sensitivity of immunoassays generally correlates with the severity of clinical symptoms [51,57].

In case of quinolones, in-house assays have become the only alternative immunoassay. In-house *sepharose-RIA* has shown low sensitivity (31.6–54.5%) but high specificity (100%) [53,59]. Differences in sensitivity may be due to the quinolone involved in each study and the severity of the reactions, with better results when ciprofloxacin is the culprit and reactions are less severe (e.g. urticaria) [53,59].

Regarding NSAIDs, immunoassays (mainly ELISA) based on experimental or commercially available prototypes may be applicable [40,41] with a sensitivity of 58% for propyphenazone [40]. With other NSAIDs such as acetylsalicylic acid (aspirin), sIgE has only been detected for a small number of patients [66]. A panel of monoclonal antibodies to diclofenac have been developed; however, sIgE antibodies in humans were not detected [67,68].

For NMBAs, immunoassay studies show in general a sensitivity of 79.3%, a specificity of 92.2%, a PPV of 91.3%, and an NPV of 83.3% [65]. RIA shows higher sensitivity (62–96%) and specificity (97.2–100%) than InmunoCAP sensitivity (44–92%) and specificity (68–100%) [61]

BAT has proven to be a useful additional test for diagnosing immediate reactions [56,69,70]. However, basophils can be activated through a non-IgE-mediated mechanism, so the involvement of the FcεRI-mediated pathway should be confirmed by inhibition with PI3 kinase inhibitors such as wortmannin [71].

Most BAT studies have been performed for beta-lactams [49,50,56,72], NMBAs [20,61,73,74], fluoroquinolones [59,75,76], and pyrazolones [18,19,77].

The highest sensitivity and NPVs have been found for fluoroquinolones [59,65,76,78]. Sensitivity ranges from 36% to 71%, depending on the drug tested [59,78]. This variability could be partly due to the chemical structure and photodegradation of the molecules. Moxifloxacin has a higher rate of photodegradation than ciprofloxacin [75], so laboratory light conditions may affect moxifloxacin BAT results, reducing the positivity of the test from 35.7% when carried out in dark conditions to 17.9% in settings with more illumination [75]. Moreover, using additional fluoroquinolones can affect the results; in moxifloxacin-allergic patients, BAT sensitivity increased to 79.2% when both moxifloxacin and ciprofloxacin were included in the test, compared with 41.7% when using only the culprit [59]. A higher rate of positive cases has also been reported for severe reactions (69%) [59].

For their part, beta-lactams show the lowest sensitivity and NPV [65]. Sensitivity ranges from 50% to 77.7% and specificity from 89% to 97%, while NPV stands at approximately 49.9% [40,56]. Differences between studies are due in part to the characteristics of the patients and drugs involved [29]. The combination of immunoassay and BAT results showed an increase of around 20% in sensitivity compared to using only one test [65], while the combination of *in vivo* and *in vitro* testing increases sensitivity by around 15% compared to *in vivo* testing alone [28,49,50,55,57,79]. A decrease in serum sIgE can affect the results of both BAT and RAST. However, BAT in amoxicillin-allergic patients becomes negative after a shorter period than with RAST (more than 50% of tests became negative at 18 months or more after the reaction) [21].

Concerning pyrazolones [19,68,80,81], studies have reported a sensitivity of around 55% and a specificity of 85%, with higher values in ST-positive patients [18].

2.4. Drug provocation test

Since clinical history can be unreliable and the sensitivity of STs and *in vitro* tests may be suboptimal, a definitive diagnosis of drug hypersensitivity frequently relies on DPT [82]. In the United States, this test is known as the graded challenge and test doses [15] and is widely considered the gold standard for establishing or ruling out drug hypersensitivity. Moreover, it

may also serve for assessing tolerance to potentially cross-reactive drugs and for providing alternative drugs [22,82].

The DPT is time-consuming and costly, and given the possibility of reproducing the allergic reaction, it is not risk free. Therefore, patients should undergo a risk–benefit analysis prior to the procedure, and only trained personnel should perform it, in a clinical setting where resuscitation facilities are available [82]. DPT should not be performed in pregnant women or in patients at increased risk due to previous severe life-threatening reactions such as anaphylaxis; acute infections; uncontrolled asthma; underlying cardiac, hepatic, or renal conditions; or other relevant comorbidities, as drug exposure might provoke reactions that are hard control [82]. However, exceptions can be made if the drug under suspicion is essential for the patient [82]. Likewise, patients should not be pretreated with antihistamines or glucocorticoids, as these can mask the early signs of an allergic reaction; antihistamines should be withheld for five days and glucocorticoids from three days to three weeks, depending on doses and potency [82]. Beta-blockers should be withheld for 24 h before DPT, as they can interfere with adrenaline treatment for anaphylaxis [82].

Ideally, people should undergo DPT after inconclusive or negative STs and/or *in vitro* tests performed following a 4–6-week interval after the initial reaction [52]. It should be performed in a single-blind, placebo-controlled manner, although in some cases a double-blind procedure may be necessary [82]. Although the traditional DPT consists of stepwise graduations, with increasing doses of the drug administered every 30–60 min until the full therapeutic dose is reached, some authors have recently suggested one-step and two-step test dose strategies [83].

It is important to note that DPT does not prevent recurrent reactions. Patients' tolerance to a drug in DPT does not rule out the possibility of an allergic reaction if they take the drug again in the future. In fact, one study reported that up to 8% of patients developed reactions to antibiotics and NSAIDs despite tolerating them in DPT [84].

3. Diagnosing NIDHRs: focus on organ-specific and systemic cutaneous drug reactions

In IDHRs, there are few clinical entities, and these are usually confined to urticaria, other known allergic symptoms, or anaphylaxis. By contrast, in NIDHRs, there are numerous clinical entities and drugs involved, including antimicrobial drugs (penicillins, cephalosporins, trimethoprim–sulfamethoxazole, vancomycin, quinolones, etc.), NSAIDs, antimalarial drugs, antiretroviral drugs, sulfonamides, several antiepileptic drugs (carbamazepine, phenytoin, lamotrigine, or phenobarbital), gold compounds, heparins, and others (allopurinol, dapsone, minocycline, etc.). Symptoms are mainly cutaneous but may also derive from organ involvement, sometimes at different levels or times or in diverse combinations, with different immunological or even unknown pathophysiologic mechanisms. Thus, these reactions are classified according to the syndrome or organ involved (Box 1).

Box 1. Classification of hypersensitivity drug reactions by systemic or organ-specific reactions.

Systemic reactions
- Anaphylaxis
- Serum sickness
- Drug-induced vasculitis
- Drug-induced autoimmune diseases
- Complex multisystem reactions (DRESS/DiHS)
- Nonallergic hypersensitivity reactions (nonimmune mechanism)
- Drug fever

Organ-specific reactions
- Cutaneous reactions
  - Urticaria y angioedema
  - Maculopapular eruption/exanthemas
  - Drug-induced vasculitis
  - Fixed drug eruption
  - Toxic epidermal necrolysis[a]
  - Stevens–Johnson syndrome[a]
  - Photodermatitis
- Hematological reactions
  - Eosinophilia
  - Cytopenia
- Lung reactions
  - Inflammatory reactions
  - Pulmonary fibrosis
- Liver reactions
  - Cholestasis
  - Hepatocellular damage
- Kidney reactions
  - Interstitial nephritis
  - Vasculitis

[a]Most with systemic symptoms.
DRESS: Drug reaction with eosinophilia and systemic symptoms; DiHS: drug-induced hypersensitivity syndrome.

3.1. Clinical history and risk factors

3.1.1. Clinical history

As in IDHRs, for NIDHRs, it is essential to take a detailed clinical history [12], which includes a description of the symptoms, the time interval between the drug administration and the onset of the reaction, the dose of the drug, and the route of administration. However, as the different signs and symptoms do not happen simultaneously or in a short period of time after the start of administration, these symptoms often go unnoticed until the organs involved are severely damaged. As drug reactions can occur during all types of medical treatment, administration of the suspected drug should be suspended immediately, particularly in the presence of dangerous signs such as bullous or hemorrhagic lesions of mucosal affectations or the involvement of internal organs [85] (Box 2).

Although there are systemic NIDHRs, such as drug fever, serum disease, drug-induced vasculitis, or systemic lupus, most are organ specific, especially those affecting the skin. Box 3 presents a classification of cutaneous drug reactions by frequency.

Although dermatologists can easily recognize the morphological presentation of cutaneous hypersensitivity reactions, general practitioners or other specialists may find it more difficult, as they could encounter a wide spectrum of inflammatory patterns such as pruritus; erythema; erythroderma; urticaria; angioedema; and maculopapular, vesicular, bullous, vasculitic, and hemorrhagic exanthemas [86,87]. However, all physicians should be alert to the danger signs.

Box 2. Danger signs for severe cutaneous reactions.

DRESS/DiHS
- Facial edema
- Extensive edematous erythema (confluent lesions)
- Involvement of extended body surface (erythroderma)
- High fever (>39°C)
- Lymphadenopathy, arthralgia, or arthritis
- Hepatic or renal impairment
- Eosinophilia (>1000 mm^3), cytopenia, or atypical lymphocytes

SJS/TEN
- Painful skin (initial symptom)
- Nikolsky's sign positive
- Epidermolysis (advanced stadium)
- Vesicle, bullous lesions (advanced stadium)
- Mucosal erosions or aphthous lesions
- Atypical target lesions
- Lymphadenopathy, arthralgia, or arthritis
- High fever (>39°C)
- Hepatic or renal impairment

Hypersensitivity vasculitis
- Hemorrhagic lesions
- Bullous lesions and later necrotic lesions
- Mucosal erosions or aphthous lesions

AGEP
- High fever (>39°C)
- Lymphadenopathy
- Neutrophilia

Serum sickness and autoimmune diseases
- High fever (>39°C)
- Lymphadenopathy, arthralgia, or arthritis

Modified from [85].
DRESS: Drug reaction with eosinophilia and systemic symptoms; DiHS: drug-induced hypersensitivity syndrome; SJS: Stevens–Johnson syndrome; TEN: toxic epidermal necrolysis; AGEP: acute generalized exanthematous pustulosis.

Box 3. Cutaneous drug reactions by frequency.

Frequent
- Maculopapular eruption/exanthemas
- Urticaria and angioedema

Less frequent
- Acute generalized exanthematous pustulosis
- Drug reaction with eosinophilia and systemic symptoms
- Fixed drug eruption
- Photosensitivity

Infrequent
- Severe cutaneous reactions
  Stevens–Johnson syndrome/toxic epidermal necrolysis

The time interval between drug administration and the onset of the reaction is at least an hour but usually more than six hours and occasionally weeks to months after the start of administration, depending on the type of reaction. However, a significant clinical overlap occurs in the different reactions because apart from T-cells, other cell types and cytokines are also involved [1] (Table 1).

Clinically, the different types of reactions have characteristic cutaneous signs and symptoms (Box 3). But organ involvement may occur in the absence of skin findings, or where skin findings are minor and overlooked. Presentations include isolated, drug-induced hepatitis, isolated interstitial nephritis, and isolated pneumonitis [1]. Nevertheless, there may be involvement of any other organ – whether in isolation or in association with others (cardiac, neurological, and hematological reactions or autoimmune diseases) [88].

Two severe cutaneous reactions deserve special attention:

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening NIDHR that includes skin eruption, hematologic abnormalities (eosinophilia and atypical lymphocytosis), lymphadenopathy, and internal organ involvement (liver, kidney, and lung) [89–91] and is frequently associated with the reactivation of latent human herpesvirus infections [92,93].

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe mucocutaneous reactions; they are most commonly triggered by drugs and characterized by extensive necrosis and detachment of the epidermis. Both are considered variants of the same disease, with an overlap syndrome between them. The percentage of body surface involved (SJS <10% and TEN >30%) with blister and erosions differentiate the two reactions [94].

An algorithm for ascertaining drug causality (ALDEN) has been developed for patients presenting epidermal necrolysis exposed to multiple drugs [95], while a prognostic scoring system called SCORTEN, based on seven clinical and laboratory variables, may also be used to evaluate the prognosis of patients with SJS/TEN [96].

In the differential diagnosis of these severe cutaneous reactions, clinicians should also consider another entity, acute generalized exanthematous pustulosis (AGEP) [97], as well as defined dermatological entities such as erythema multiforme, erythroderma and erythematous drug eruptions, generalized bullous fixed drug eruption (FDE), phototoxic eruptions, staphylococcal scalded skin syndrome, paraneoplastic pemphigus, and linear IgA bullous dermatosis.

3.1.2. Risk factors

Viral infections and human leukocyte antigen (HLA) associations are risk factors for NIDHRs. Epstein–Barr virus and cytomegalovirus are associated with reactions to antibiotics, and human herpesvirus 6 with anticonvulsants, in defined syndromes. But some severe cutaneous reactions occur more frequently in patients with certain HLA types, since the drugs have been shown to bind predominantly to the HLA alleles [98]. Some authors have recommended screening patients for specific alleles prior to administering carbamazepine (HLA-B*15:02) [99], dapsone (HLA-B*13:01) [100], abacavir (HLAB*57:01) [101,102], and allopurinol (HLA-B*58:01) [103–106]. However, HLA associations do not explain all cases, and screening has a low PPV, suggesting the involvement of additional factors in the mechanisms of DHRs [106,107].

3.2. Skin and *in vitro* tests

3.2.1. Patch and intradermal tests

The approach to diagnosing DHRs differs significantly between the United States and Europe [108,109]. In the United States, neither *in vitro* (e.g. lymphocyte activation tests) nor skin testing (intradermal testing with delayed reading or patch testing) is widely utilized to diagnose NIDHRs. These techniques are more commonly employed in European countries, where patients with NIDHRs are evaluated by both patch and delayed-reading intradermal testing [15], including those with severe NIDHRs, such as TEN/SJS, DRESS/drug-

induced hypersensitivity syndrome, and AGEP [15]. In these patients, if SPTs are negative, IDTs are performed using higher drug dilutions [15].

ST sensitivity appears to be moderate to high for immediate reactions but low for NIDHRs; however, a position paper of the European Academy of Hypersensitivity and Clinical Immunology (EAACI) [14] describes ST concentrations for systematically administered drugs. A Spanish version also exists with details on more drugs, but the original is easily understandable in English [110].

3.2.2. *Skin biopsy and* in vitro *tests*

A skin biopsy for histologic examination may be warranted if the diagnosis is uncertain or if there is concern about a severe cutaneous reaction that may confirm the diagnosis and exclude other conditions that simulate SJS/TEN. Although the paradigm of SJS/TEN is the keratinocyte necrosis with a sparse perivascular lymphohistiocytic inflammatory infiltrate, more than one pattern is frequently observed in a single biopsy [93].

For suspected drug-induced exanthema, a routine laboratory evaluation of patients is generally not necessary, but the presence of any danger signals makes it mandatory. This should cover at least a complete blood cell count with differential (looking for eosinophilia), liver and kidney function tests, and antinuclear autoantibody tests. A few small studies have evaluated other investigational tests in SJS/TEN, such as soluble Fas ligand, soluble CD40 ligand, granulysin, and high-mobility group box 1 protein (a nonhistone nuclear protein released by necrotic and apoptotic cells) [111–113].

Although drug-specific immune response has been demonstrated in many cases of DRESS by positive patch test reactions and/or *in vitro* lymphocyte proliferation assays (lymphocyte transformation test [LTT]) [114,115], LTT sensitivity also depends on the type of reaction; it is quite high in maculopapular eruptions (MPE), FDE, AGEP, and DRESS, but low in SJS/TEN [116,117]. In any case, these assays are not available in most centers.

Recently, studies have shown the usefulness of enzyme-linked immunosorbent spot assay (ELISpot), especially in severe cases, but at present, neither American nor European guidelines recommend this testing [51,117].

3.3. Drug provocation tests

For non-severe NIDHRs, any drug may be attempted if required, although only beta-lactam challenge protocols are used, and with great variations in terms of initial doses and length [109]. Except for rare exceptions due to extreme medical necessity, patients with clear histories of severe NIDHRs should not receive any culprit drugs again under any circumstances because reexposure can trigger recurrent symptoms [108].

4. Managing and diagnosing DHRs

4.1. Managing the acute phase in IDHRs

The main symptoms of IDHRs can range from a mild flushing or pruritus to moderate urticaria (intensely pruritic, raised, red plaques that appear and resolve within hours) with or without angioedema. More severe reactions include bronchospasms (wheezing, chest tightness, difficulty breathing, or repetitive dry cough), laryngeal edema (throat tightness or change in voice quality), abdominal distress (cramping, nausea, vomiting, or diarrhea), or hypotension in the context of anaphylaxis or even anaphylactic shock. All these symptoms have to be treated immediately with adrenaline, antihistamines, corticosteroids, and other drugs, depending on the symptoms and following standardized protocols [118,119].

Serum tryptase level can be helpful to confirm a diagnosis of anaphylaxis in these IDHRs, especially if blood is drawn 60–90 min after the onset of still-ongoing symptoms, and at least 24 h after resolution to compare [4].

4.2. Management of symptoms in NIDHRs

NIDHRs resolve once the culprit drug is discontinued, usually within one to two weeks, although symptoms may worsen for a few days even after the drug is stopped [120].

Fluid and electrolyte management, nutritional support, temperature management, pain control, and monitoring or treatment of superinfections [121] are the main measures available in supportive care units for severe cutaneous reactions such as burns or wounds. But different treatments without high-quality evidence have been used together, such as systemic corticosteroids and/or intravenous immunoglobulins [122–124], plasmapheresis [125], and others [126–130].

4.3. Diagnosis and management following a DHR

Patients with a history of drug hypersensitivity must avoid the medication suspected to have caused the reaction (see Figure 1). If there is a continued need for drug therapy, structural similarities between the culprit and the newly given drug should be avoided and a non-cross-reactive alternative drug given [131]. With the exception of DRESS, where immune deviation may lead to a broadening of sensitivity to other less similar drugs [132], switching to a totally different drug class does not carry a considerably increased risk for a reaction.

However, alternatives may confer their own risks, such as toxicities and higher cost, and in some cases, they can be less efficacious, potentially leading to a suboptimal or failed therapeutic outcome [133,134]. Moreover, in the case of antibiotics, the use of broad-spectrum antibiotics contributes to the development of bacterial resistance [135,136].

If other drugs from the same group are needed, clinicians should assess tolerance. Cross-reactivity is based on the drug structure within one drug group and exists especially among beta-lactams, NSAIDs, and NMBAs [137–139].

Even in patients with hypersensitivity to beta-lactams, the allergic reaction is mostly directed against a specific side chain of the drug and not to the central beta-lactam ring. Therefore, patients with an allergic reaction to an aminopenicillin (ampicillin or amoxicillin) mostly tolerate all other non-aminopenicillins and cephalosporins except first-generation preparations with an amino group (i.e. cefaclor, cefadroxil, and cefalexin) [137].

The likelihood of cross-reactivity among similar drugs also depends in part on the type of allergic reaction in question. For example, a patient with a T-cellmediated exanthema to amoxicillin

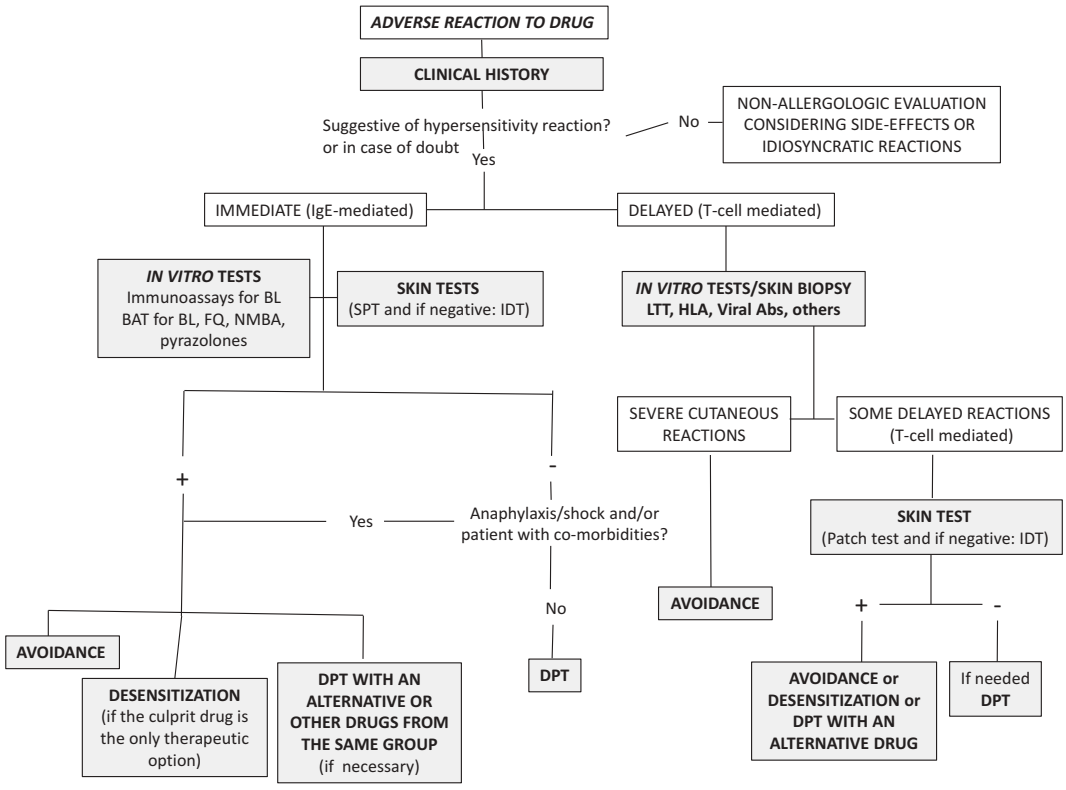

Figure 1. Algorithm for diagnosing and managing a hypersensitivity drug reaction.

is at low risk for reacting to a cephalosporin, but this risk increases for patients with IgEmediated anaphylaxis to amoxicillin [140].

However, cross-reactivity between penicillins and third- or fourth-generation cephalosporins or carbapenems is very rare [140]. The same holds true for carbapenems and aztreonam, which rarely react with other penicillins and cephalosporins. Therefore, patients with a history of immediate penicillin reactions can undergo an urgent IDT for cephalosporin, carbapenems, or aztreonam, and if negative, physicians can administer it in consecutive increasing doses [4]. A similar approach can be taken for a patient with a history of a cephalosporin hypersensitivity, where an ST-negative cephalosporin with different side chain can be selected for therapy with only minimal risk for a severe reaction [141]. Ultimately, clinicians should always undertake a risk–benefit analysis and be prepared for an emergency.

With regard to NSAIDs, functional cross-reactivity exists, mostly with COX-1-inhibitory drugs [138]. Although beyond the scope of this paper, clinicians should bear this possibility in mind when performing a DPT with any NSAID, closely supervising the assessment of this effect before prescribing these drugs to patients [142]. In addition, opioids and corticosteroids are the analgesic and anti-inflammatory alternatives because of their very different structure. If selective hypersensitivity to NSAIDs is confirmed, patients must avoid the culprit drug and those from the same chemical group, and if necessary, they can generally take the rest of NSAIDs [136]. Notably, there have been reactions reported to one specific propionic derivative, with good tolerance to the rest of the drugs from the same chemical group [143].

Cross-reactivity between other drugs is not well known, and published reports on drugs in the same group are not entirely consistent. This is due to the small number of patients included in the scarce studies published. Therefore, cross-reactivity is difficult to predict, and tolerance must be assessed under medical surveillance [144–147].

4.4. Desensitization and prevention

When the drug inducing the reaction is the only therapeutic option available, clinical induction may be required. Desensitization to induce temporary drug tolerance is an established practice only in the management of IDHRs [148].

There is little evidence for the efficacy of desensitization in NIDHRs [149] except for allopurinol [150], and multiple case reports have documented recurrent SJS/TEN with re-administration of the culprit drug or closely related chemical agents [151–154].

Desensitization is used only in certain specific situations and should normally be indicated and supervised by an allergist experienced with drug-allergic reactions through different protocols [148].

It is crucial for clinicians to provide patients with proper drug hypersensitivity documentation to prevent accidental exposures to culprit drugs in the future [131]. Patients should know which drugs or drug classes to avoid and present written information to any prescribing doctor or pharmacist before getting a drug. Lack of proper drug hypersensitivity documentation is the main reason for prescription errors.

5. Conclusions

A precise diagnosis can be difficult in drug allergy, and the diagnostic and managing procedure can be complex, time consuming, expensive, and dangerous. But a detailed clinical

history, followed by STs and/or *in vitro* tests, can be helpful in identifying the culprit agent and in increasing the sensitivity of the diagnostic procedure. Drug provocation test and desensitization under medical surveillance may help for diagnosis and assessment of tolerance, respectively.

The main treatment of DHRs consists of withdrawing the offending drug, providing appropriate treatment, and implementing supportive measures, if needed.

In order to prevent future reactions, patients should receive accurate information about their drug allergies and the need to perform genetic testing prior to administration of specific drugs.

6. Expert commentary

Although the immunological mechanism of drug reactions is often difficult to recognize, clinicians must make efforts to diagnose antibody and cell-mediated reactions in drug allergies.

From the practical point of view, classifying DHRs based on the timing of the symptom onset is useful. IDHRs occur within one hour of the first administered dose and are usually IgE mediated. This prompts the use of STs or *in vitro* tests, whether in the acute phase (assessing tryptase levels) or after the reaction (drug-sIgE or BAT), to identify the culprit agent. The combination of ST and *in vitro* tests increases diagnostic sensitivity.

As IDHRs are the most frequent drug reactions, many papers about their diagnosis and management have been published in the last years. Despite their limitations, STs have proven useful for IDHRs to beta-lactams, pyrazolones, and other drugs like NMBAs, especially when the clinical history is unreliable or a long time has elapsed since exposure. The changing consumption of different side-chain penicillins or new cephalosporins is decreasing the rate of positivity to the old penicillin reagents. Even worse, these reagents are only distributed in a few countries.

The combination of ST and *in vitro* tests increases diagnostic sensitivity up to 40% in the case of beta-lactams. *In vitro* tests are usually recommended in high-risk patients before DPT and even ST due to the potential risk of systemic reaction. Even with BAT, a higher rate of positive cases has also been reported for severe reactions (69%). But only the extended use of DPT has been able to clear up cross-reactivity and to assess tolerance. In fact, fewer than 20% of patients with a history of drug hypersensitivity react in DPT to the culprit drug suspected by clinical history. However, DPT is time consuming, costly, and not risk free, so its use is reserved for hospitals.

It is also essential to take a detailed clinical history in NIDHRs. However, as the different signs and symptoms do not appear simultaneously or shortly after drug administration, they often go unnoticed until the organs involved are severely damaged. But as symptoms are mainly cutaneous, clinicians should look for the presence of dangerous signs such as bullous or hemorrhagic lesions of mucosal affectations or the involvement of internal organs. A dermatologist should be consulted in case of unexplained skin symptoms in the course of a treatment, especially with some specific drugs. Unlike IDHRs, in NIHDRs organ involvement may occur frequently. Viral infections and HLA associations are also risk factors, and in some populations, genetic studies are recommended prior to taking certain drugs.

Desensitization is on the rise, especially in chemotherapeutic and biological treatments. But it should be indicated through different protocols and supervised by an allergist with experience in drug-allergic reactions.

The increasing consumption of biological agents and new drugs like clavulanic acid has been accompanied by hypersensitivity reactions to them, prompting the need for their inclusion in diagnostic research.

The full range of metabolites and intermediate forms of the drug to which patients may be susceptible has not been determined. Testing new adducts with new metabolites and spacers holds promise for detecting hypersensitivity in a large proportion of patients.

The availability of ImmunoCAP (quantification of the drug-sIgE in serum by immunoassay), limited to only a few beta-lactams and other drugs, has led to the use of in-house immunoassays, which need to be evaluated in large populations to validate them as accurate diagnostic tools for DHRs.

BAT has proven to be a useful additional test for diagnosing immediate reactions. But most BAT studies have only assessed a few drugs (beta-lactams, NMBAs, fluoroquinolones, and pyrazolones). Much remains to be done with this technique in the near future.

Although HLA associations do not explain all cases, and screening has a low PPV (suggesting the involvement of additional factors in the mechanisms of DHRs), pharmacogenomic studies are needed to evaluate the role of the genome. In any severe cutaneous drug reaction, a genetic study is advisable.

Although the sensitivity of LTT is higher than that of STs for diagnosing NIDHRs, LTT sensitivity also depends on the type of reaction. This assay is not available in most centers. Changing the measure of stimulation with the suspected drug, from a radioactive isotope of hydrogen to carboxyfluorescein diacetate succinimidyl ester using flow cytometry, may increase its technical application, but more research and evaluation are needed.

Research in drug hypersensitivity diagnosis is open in the search for both new metabolites and adducts and new or renovated *in vitro* techniques that avoid the risk provocation test.

7. Five-year view

It is difficult to predict future advances in DHR diagnosis, but recent history in the field suggests that only large-scale studies, such as the European Network of Drug Allergy (ENDA)/EAACI trial, will achieve dramatic breakthroughs for this growing problem. New drugs will displace the focus on severe drug reactions to present therapies. New metabolites or adducts will be identified, and the extension of BAT and flow cytometry-LTT will give clues in the diagnostic procedure. A new mast cell receptor, MRGPRX2, has been discovered for which medications with tetrahydroisoquinoline-motifs, such as general anesthetics, quinolones, or icatibant, can bind and activate mast cells without IgE [155]. Since then, activation of mast cells through this MRGPRX2 receptor is mentioned as one of the possible IgE-independent mechanisms through which IDHR might occur [156]. But the most promising line of

research is in pharmacogenomics. As the cost of genotyping decreases, it will become increasingly available, including for testing any DHR.

Key issues

- The diagnostic procedure includes a detailed clinical history (often unreliable), followed by skin tests that sometimes have low sensitivity or are unavailable.
- Although insufficient by themselves, in vitro tests can be helpful in identifying the culprit agent and have been shown to increase the overall sensitivity of the diagnostic procedure when combined with in vivo testing. Therefore, these tests improve drug hypersensitivity reactions diagnosis, helping the physician to find safe alternatives and reducing the need to perform a drug provocation test.
- While the drug provocation test is considered the gold standard for establishing or ruling out a drug hypersensitivity reaction, it is time-consuming, expensive, and risky. Moreover, it is strictly forbidden in severe cutaneous drug reactions.
- There are differences between Europe and the United States in applying different diagnostic methods, although serum tryptase level in the acute phase is used in both settings to confirm a diagnosis of anaphylaxis.
- Patients with a history of drug hypersensitivity must avoid the medication suspected to have caused the reaction. Cross-reactivity is difficult to predict in many cases, so if other drugs from the same group are needed, clinicians must assess tolerance under medical surveillance.
- The diagnosis of severe cutaneous reactions, such as SJS/TEN, is based on clinical and histologic findings in patients with a history of antecedent drug exposure or febrile illness. Histologic findings on skin biopsy can support diagnosis but are not independently conclusive. The main treatment consists of withdrawing the offending drug and implementing supportive measures.
- There is a consensus about the need to perform genetic testing for specific drugs associated with severe cutaneous reactions, although their predictive values need to be improved.
- Patients should receive proper documentation about their drug allergies in order to prevent future exposure to culprit drugs.
- When the only therapeutic option is a drug inducing a reaction, desensitization may be required.

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