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Advances and novel developments in drug hypersensitivity diagnosis

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Abstract

A correct diagnosis of drug hypersensitivity reactions (DHRs) is very important for both the patient and health system. However, DHRs diagnosis is complex, time consuming, requires trained personnel, is not standardized for many drugs, involves procedures not exempt of risk, and in most cases lacks standardized in vivo and in vitro tests. Thus, there is an urgent need for improving the different approaches to diagnose patients with suspected DHRs. In this review, we have analyzed the advances performed in immediate and nonimmediate DHRs diagnosis during the last two years and obtained several conclusions: the significant heterogeneity in current practice among centers illustrates the need to re-evaluate, update, and standardize in vivo tests and protocols for the diagnosis and management of patients with suspected drug allergy. Regarding in vitro tests, the latest studies have focused on increasing their sensitivity or on establishing the sensitivity and specificity for the tests performed with new drugs. There seems to be a consensus about combining in vivo and in vitro tests as the best way to increase the diagnostic accuracy.

KEYWORDS

diagnosis, drug hypersensitivity, in vitro tests, In vivo tests

1 | INTRODUCTION

The diagnosis of drug hypersensitivity reactions (DHRs) has important implications for both patients and health system.¹ Mainly because an allergy label, whether true or not, implies the avoidance of medications that may be essential, the performance of unnecessary desensitization procedures, or the use of alternative medications. All these alternatives can lead to a less effective treatment, more

potential adverse effects, and costs for health systems.² Moreover, in the case of antibiotics, it results in bacterial resistance.³

Considering that there are no specific tests to distinguish between a viral infection and DHRs in the acute phase, a diagnostic work-up should be performed to remove a false label of hypersensitivity.⁴ DHRs diagnosis is complex, time consuming, needs to be done by trained staff, and it is not standardized for many drugs. It is mainly based on skin testing (ST) and drug provocation tests (DPTs),

Abbreviations: AX, Amoxicillin; BAT, Basophil activation test; BL, Beta-lactam antibiotics; CBZ, Carbamazepine; CLV, Clavulanic acid; DHRs, Drug hypersensitivity reactions; DPT, Drug provocation test; DRESS, Drug reaction with eosinophilia and systemic symptoms; EAACI, European Academy of Allergy and Clinical Immunology; I-DHRs, Immediate drug hypersensitivity reactions; LTT, Lymphocyte transformation test; NECD, NSAID-exacerbated cutaneous disease; NI-DHRs, Nonimmediate drug hypersensitivity reactions; NIUA, NSAID-induced urticarial/angioedema; NMBA, Neuromuscular blocking agents; NSAIDs, Nonsteroidal anti-inflammatory drugs; RCM, Radiocontrast media; SCARs, Severe cutaneous allergic reactions; sIgE, specific IgE; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; ST, Skin testing.

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not risk-free procedures with still a long way until having a standardized in vitro test available for all laboratories. However, a complete allergy assessment is crucial for allergy delabeling, especially in cystic fibrosis patients with antibiotic hypersensitivity reactions.⁵ All this highlights the need for improving the different approaches for diagnosing patients with suspected DHRs.^{1,6} In this review, we have analyzed the advances performed in DHRs diagnosis during the last 2 years.⁷

From a practical point of view, DHRs diagnosis can be performed by in vivo and in vitro tests (Figure 1) depending on the type of reactions, which can be immediate (I-DHRs) (appearing from 1 to 6 hours after drug intake) and nonimmediate (NI-DHRs) (appearing after 1 hour of drug intake),⁸ and the clinical manifestations, which include very different immunological mechanisms, especially in the latest, with manifestations ranging from maculopapular exanthema or fixed drug eruption to severe cutaneous allergic reactions (SCARs) such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis, drug reaction with eosinophilia, and systemic symptoms (DRESS) or drug-specific reactions such as abacavir hypersensitivity syndrome.^{9,10} I-DHRs are mainly mediated by specific IgE (sIgE), although other off-target mechanisms, such as COX-1

inhibition (pharmacological effect) and MRGPRX2 receptor (direct stimulation), can be involved.¹¹ NI-DHRs are mostly T cell mediated.^{9,10}

2 | IN VIVO DIAGNOSIS

2.1 | Clinical history

The first step in diagnosis is anamnesis (Table 1), which must include detailed information about the reaction and drug involved, as suggested by European Academy of Allergy and Clinical Immunology (EAACI) position papers and consensus recommendations.^{3,9,12} Over last years, predictive models of DHRs and causality assessment tools based on clinical history have been investigated,¹³ including comprehensive risk stratification using the reaction details and current clinical condition. However, these tools have shown limited value¹⁴⁻¹⁶ and must be adapted to the local environment, considering reliability of the interviewer, allergy epidemiology and cross-reactivity, other related drugs, and resources.¹⁵

Despite its limitations, the anamnesis is an important starting point to select the next steps and classify reactions into I-DHRs and

BOX 1. Unmet needs and future research perspectives

- To work on a risk stratification consensus for drug hypersensitivity reactions (DHRs) based on patients' clinical history.
- To incorporate big data and artificial intelligence to diagnosis.
- To standardize protocols for skin testing (ST) including reagents and concentration.
- To standardize drug provocation test (DPT) protocols including the number of steps, doses, time interval between doses, and the duration of DPT.
- To improve the sensitivity of in vitro tests by analyzing the inclusion of new chemical structures (drug metabolites, synthetic determinants, drug-carrier conjugates) in addition to the suspected culprit.
- To deepen the analysis of mediators of the effector response (cytokines and cytotoxic molecule releasing cells) as the optimal approach to increase the sensitivity of in vitro test for nonimmediate drug hypersensitivity reactions (NI-DHRs).
- To confirm genetic variations in HLA and to identify new associations with drug metabolic pathways and susceptibility to hypersensitivity reactions to develop a more accurate diagnosis, treatment, and prediction of DHRs.

BOX 2. Major milestone discoveries.

- There is an important heterogeneity in current practice among different centers; no specific concentrations for ST are available for most drugs and no standardized DPT protocols exist.
- Although controversies exist about the increased sensitivity of performing prolonged DPT with BL for diagnosing nonimmediate reactions, last EAACI position paper considers a one-day DPT to be sufficient to establish a firm diagnosis.
- Direct DPT, without previous STs, has shown to be safe and recommended for penicillin allergy delabeling in low-risk children with mild maculopapular exanthema, but not in low-risk adults with NIR other than palmar exfoliative exanthema.
- High tryptase values (>11.4 ng/mL) are more frequently detected in life-threatening reactions than in non-life-threatening ones in perioperative hypersensitivity patients.
- Basophil activation test is a promising tool to complement ST for the diagnosis of patients allergic to amoxicillin-clavulanic acid and to omeprazole.
- Lymphocyte transformation test is useful to assess cross-reactivity and to confirm drug causality in Stevens-Johnson syndrome/toxic epidermal necrolysis patients taking multiple medications.
- The combination of several tests, in vivo and in vitro, is the best way to perform an accurate diagnostic

NI-DHRs, and also to perform a risk assessment for guiding further investigations. The risk stratification to distinguish high- from low-risk patients allows a patient-tailored management, which will ensure a safe and more effective approach. Once risk stratification is more widely applied and more studies are published, it will be possible to reach consensus and make recommendations.³

2.2 | Skin tests

The main limitation on STs, the most used *in vivo* test, is the lack of information on specific test concentration for most drugs¹⁷ as the only commercial agents are penicillins (minor determinants,

amoxicillin [AX], and clavulanic acid [CLV]), although some of them are not available in all countries.¹⁸ For other drugs, nonirritating concentrations are used, although in many cases they are not standardized.^{17,19} Moreover, factors such as dilution can affect drug stability and therefore the rate of positivity, as demonstrated with neuromuscular blocking agents (NMBA).²⁰ The time interval between the reaction and the study²¹ and the latency for reading the STs²² can also affect the likelihood for obtaining positive results in ST.²¹ This leads to a high heterogeneity in current practice.^{5,18} Moreover, differences in the sensitivity of the tests and the diagnostic approach exist due to different regional consumption patterns and to the introduction of new drugs.^{3,18} This is the reason why testing subjects with DHRs to beta-lactam antibiotics

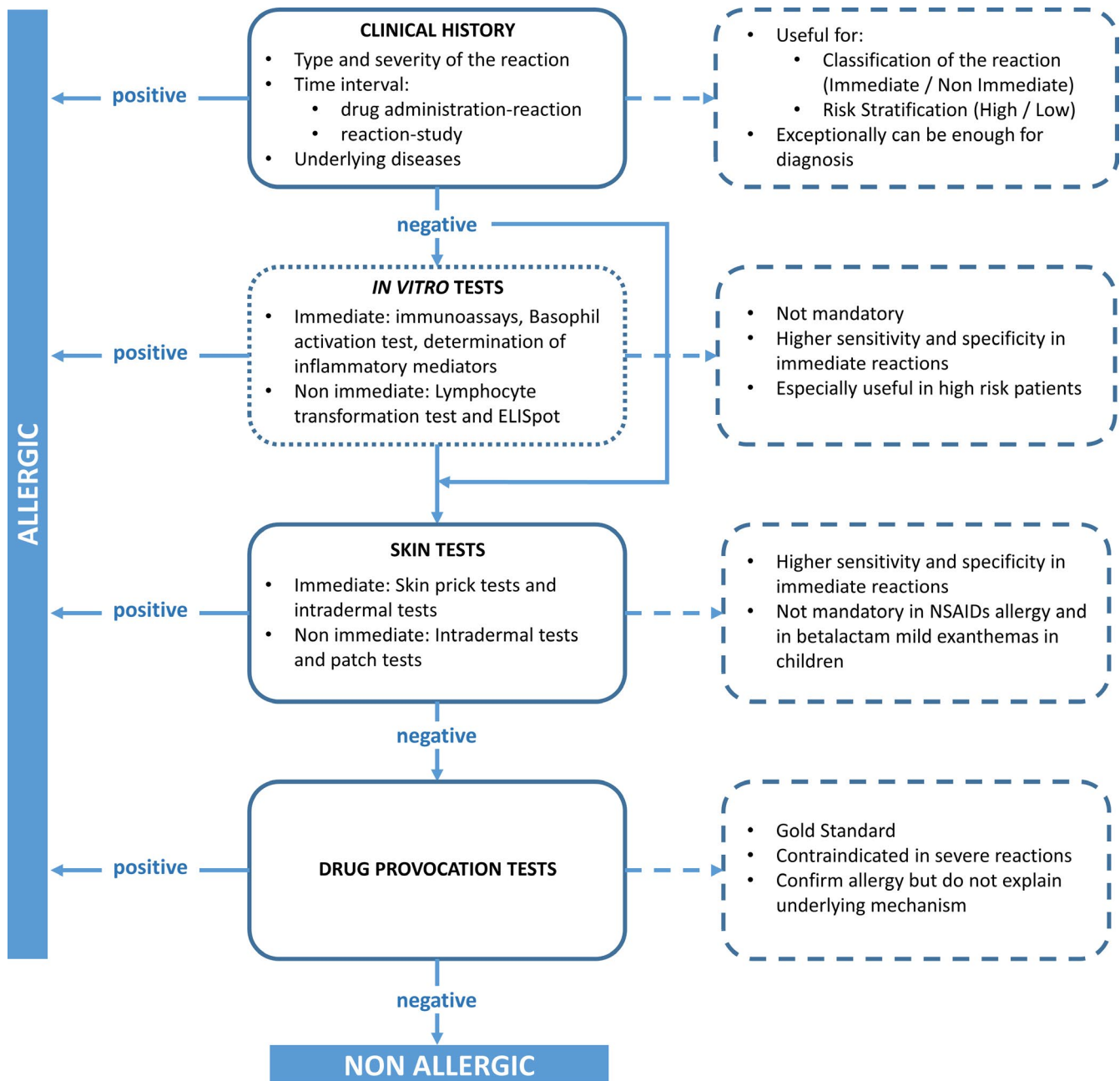


FIGURE 1 General diagnostic approach for drug hypersensitivity reactions

In vivo test	Type of reaction	Future direction	Ref
Clinical History	I-DHR and NI-DHR	Risk stratification	3
		Mathematical models	14–16
Skin tests	I-DHR and NI-DHR	Standardization of concentrations	3,18,19
	I-DHR	Not testing not exposed drugs	19
	NI-DHR	Consensus about protocols in SCAR	24–26
Drug provocation tests	I-DHR and NI-DHR	Contraindicated in severe reactions	16,24,43,44
	I-DHR	1 d/1 dose protocols	48–50,55,56
	NI-DHR	Without previous STs in BL and children	3,57–60

TABLE 1 In vivo diagnosis of I-DHRs and NI-DHRs. Studies published during the last 2 y showing controversies about in vivo diagnosis and future directions are summarized in the last column

Abbreviations: BL, beta-lactams; I-DHR, immediate reactions; NI-DHR, nonimmediate reactions; Ref, references; SCAR, severe cutaneous adverse reactions; STs, skin tests.

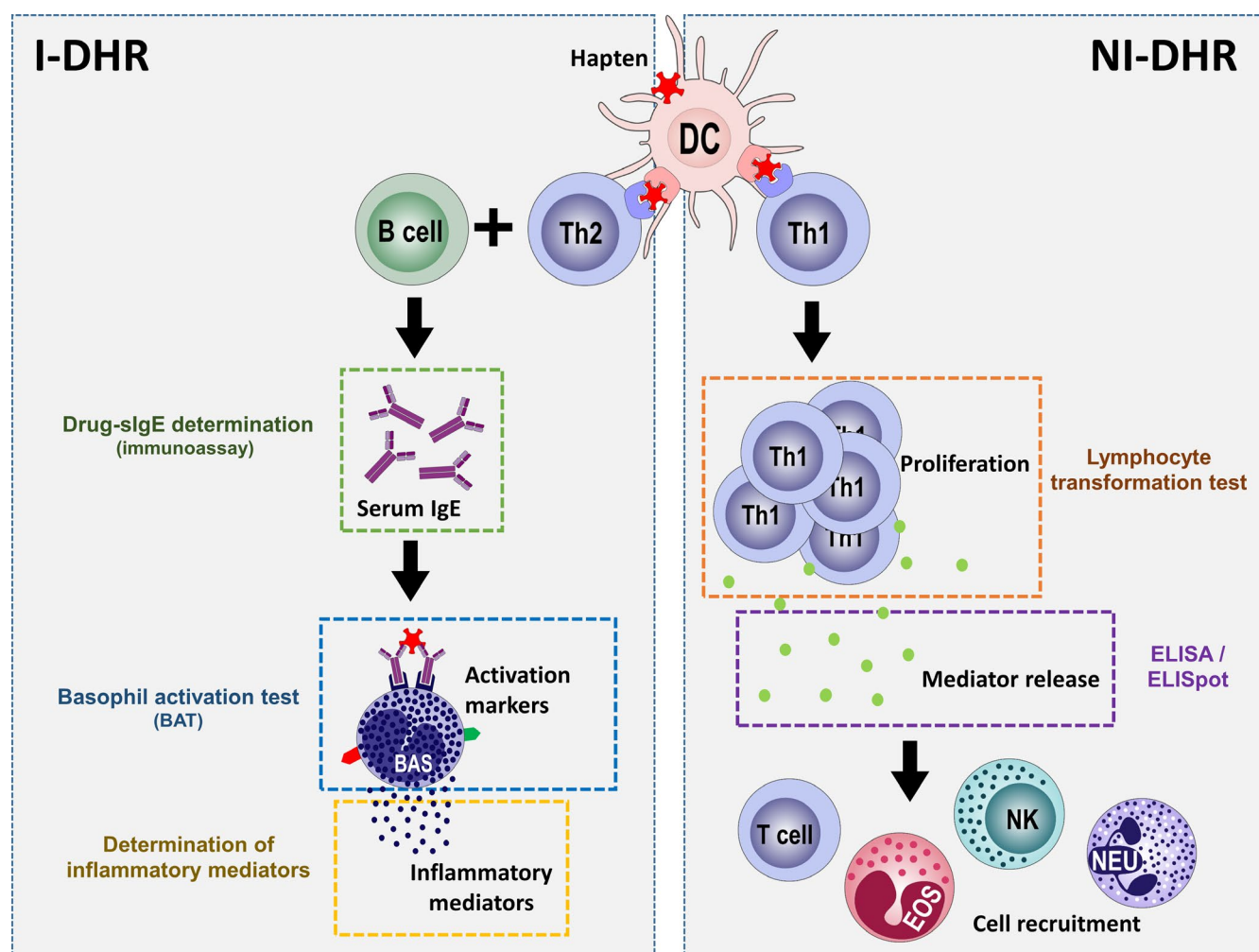


FIGURE 2 Representation of the general mechanisms drug hypersensitivity reactions indicating the most used in vitro tests used for diagnosis

(BL) may include not only penicillin and its minor determinants, but also amoxicillin, and any suspected BL, to detect side chain-specific sensitizations.^{3,18,23} Moreover, there are still concerns regarding the safety of STs in SCARs^{24–26}; therefore, it is recommended to

perform patch test first, and if negative, to continue with skin prick test and intradermal test.²⁴

Furthermore, STs are useful to assess cross-reactivity and find safe alternatives, which is essential in the evaluation of irreplaceable

drugs such as cytostatic agents. In this sense, low cross-reactivity has been demonstrated between cisplatin and other platinum salts.²⁷ However, for the evaluation of radiocontrast media (RCM) it has been recommended to perform DPT to alternative RCM to which the patient has had a negative result in ST for confirming tolerance, especially in cases with positive ST with the culprit.^{28,29} Nevertheless, testing drugs to which the patient has not been exposed¹⁹ as well as routinely screening of STs with cephalosporins for the prevention of anaphylaxis²³ are not recommended due to an unfavorable cost-effectiveness balance. It is important to improve the adherence of patients to perform STs by informing patients better about the reaction and its consequences in order to reduce the recurrent DHRs.³⁰ Further studies are necessary to provide data regarding the standardization of protocols for ST, including reagents and concentration.

2.3 | Drug provocation test

DPT is the gold standard in DHRs diagnosis and in searching safe alternative treatments,^{3,13,31,32} even in non-IgE-mediated reactions like drug-induced enterocolitis syndrome.^{33,34} It is considered a tool to diagnose multiple drug hypersensitivity syndrome,³⁵ although it cannot discriminate between immune- and non-immune-mediated hypersensitivity.³⁶ DPT can be performed by oral, nasal, inhaled, or intravenous route depending on the delivery mode of the culprit drug. In the case of DHRs to nonsteroidal anti-inflammatory drugs (NSAIDs), intranasal and bronchial DPTs with aspirin/ketorolac are safer and faster procedures than oral DPT, although with less sensitivity.³⁷⁻⁴¹

Nevertheless, DPT is a risky procedure, with 30% of patients tested with cytostatic agents experiencing severe reactions.⁴² Therefore, it is contraindicated in life-threatening reactions^{16,24,43,44} and only recommended when the benefit outweighs the risk.^{19,24,45,46} Due to this contraindication, the real predictive value of STs is unknown in severe reactions.⁴⁷

Regarding DPT protocols, heterogeneity exists among centers in terms of dose steps, time intervals between incremental doses, and dosing days, as well as diagnostic criteria for a positive result.¹⁸ It is particularly relevant regarding assessment of perioperative reactions as DPT is used neither routinely in most centers⁴⁶ nor in BL-induced NI-DHRs, for which there is no consensus.³

The main controversy is DPT duration, and the sensitivity of a several-day protocol with BL compared with a one-day protocol^{22,48-50} especially due to the current concern regarding bacterial resistance. The last EAACI position paper considers one-day DPT to be sufficient to confirm diagnosis,³ although prolonged DPT in NI-DHRs in children seems to be safe and may improve the diagnosis.²² To avoid prolonged DPT, it was also proposed a wash-out period after the initial DPT in which the patient is under observation at home. If no reaction occurs, DPT is resumed at home with therapeutic doses for several days.⁵⁰⁻⁵³ Regarding NSAIDs, it was suggested to consider their absorption speed to determine steps for DPT.⁵⁴

The optimal total cumulative dose for DPT is also under debate. In that sense, in RCM hypersensitivity the use of half of the dose employed in a radiologic examination has shown to be useful.⁵⁵ Considering NSAIDs, it has been reported that a dose of 500 mg of aspirin is sufficient to differentiate between cross-intolerance and selective responders.⁵⁶

Finally, controversies exist about the reported safety and cost-effectiveness of direct DPT without previous STs for penicillin allergy de-labeling in low-risk patients,⁵⁷⁻⁶⁰ while others recommend to perform it with the culprit in all children with suspected BL hypersensitivity.⁶¹ Importantly, the last position paper from the EAACI, in patients with BL allergy, recommends this procedure in children with mild maculopapular exanthema, although it is not recommended in adults experiencing low-risk NI-DHRs other than palmar exfoliative exanthema.³

Further studies are necessary to provide data regarding the standardization of protocols for DPT, especially of those regarding NI-DHRs, for which there is currently no consensus.

3 | IN VITRO TESTS

Different in vitro tests are available for characterizing DHRs depending on the underlying mechanism and reaction phase (Figure 2); however, few of them are commercialized. At the active phase of the reaction, tests focus on determining inflammatory mediators whereas at the resolution phase, tests identify responsible drugs by determining drug-sIgE antibodies, besides activation and proliferation of drug-specific effector cells as basophils, T-lymphocytes, etc. Additionally, due to genetic association to some DHRs, there are other methods to determine the risk of suffering reactions for specific drugs.⁶² Although there are many in vitro tests that can help in the diagnosis and identification of the culprit drug, only a few of them show enough evidence for recommendation and further studies are necessary to improve their sensitivity^{13,62} (Table 2).

3.1 | Inflammatory mediators

Serum tryptase is the most used in vitro test to confirm anaphylaxis, often when detecting high levels (>11.4 ng/mL).^{62,63} A recent study of perioperative hypersensitivity showed that high tryptase values were detected more frequently in life-threatening reactions than in non-life-threatening ones. Furthermore, mast cell activation determined using the formula $\text{tryptase} > 1.2 \times \text{baseline-tryptase} + 2 \mu\text{g/L}$ was more frequent in life-threatening reactions and in adults compared with children.^{64,65}

Histamine is the most abundant and important inflammatory mediator for acute anaphylaxis, with plasma sensitivity ranging from 61%-92% and specificity from 51%-91%.⁶² However, it is difficult to assess due to its short half-life in serum (20 minutes). Therefore, detection of the histamine metabolites N-methylhistamine and N-methylimidazole acetic acid in urine samples (detectable up to 24 hours) has been proposed as an alternative method.⁶³

Mechanism	Biomarker	Drug reported in the last 2 y
Immediate hypersensitivity reactions (I-DHR)		
IgE-mediated and off-target	Inflammatory mediators: • Serum tryptase • Serum histamine • Urine histamine metabolites • Urine eicosanoids	• Perioperative hypersensitivity⁶⁴ • Nonsteroidal anti-inflammatory drugs⁶⁶
IgE-mediated	Serum sIgE	• Cefazolin⁶⁹
IgE-mediated	Basophil activation	• Neuromuscular blocking agents^{73,78} • Amoxicillin-Clavulanic acid⁷⁶ and clavulanic acid metabolites⁷⁹ • Omeprazole⁷⁷ • Sugammadex-Rocuronium complex⁸¹ • Macrogol⁸²
Nonimmediate hypersensitivity reactions (NI-DHR)		
T-cell mediated	Lymphocyte proliferation	• Benznidazole⁸⁷ • Etoricoxib⁸⁹ • Anticonvulsants, anti-tuberculosis drugs, beta-lactam antibiotics⁸⁶
T-cell mediated	Cytokines and cytolytic molecules: • IFN-γ • Granulysin	• Antibiotics⁹⁰; oxypurinol, phenytoin, amoxicillin, carbamazepine, co-trimoxazole⁹¹ • Proton-pump inhibitors⁹²
T-cell mediated	Clonal diversity of T-cell repertoire	• Antibiotics, metoprolol, diltiazem, allopurinol, hydroxyurea⁹⁵
T-cell mediated	Genetic susceptibility: • HLA-B*13:01 (Thai and Han Chinese) • HLA-B*57:01 • HLA-B*57:01 and HLA-A*31:01 (European) • HLA-B*15:02 (Han Chinese, Thai, and Malaysian) • HLA-B*58:01 • HLA-A*32:01 (European) • Variants of GNAI2 gene	• Dapsone⁹⁷ • Abacavir⁹⁸ • Carbamazepine⁹⁹ • Carbamazepine¹⁰¹ • Allopurinol^{103,105} • Vancomycin¹⁰⁶ • Nonsteroidal anti-inflammatory drugs¹⁰⁸

TABLE 2 In vitro diagnosis of I-DHRs and NI-DHRs. Studies published during the last 2 y showing the potential utility of different biomarkers for a given drug are summarized in the last column

The analysis of other inflammatory mediators in certain reactions is being used to confirm the underlying mechanism involved. Recently, eicosanoids measurement (LTE4 and $9\alpha,11\beta$ PGF2) in urine samples has shown a similar pattern of eicosanoid levels following

aspirin challenge in patients with NSAID-exacerbated cutaneous disease and NSAID-induced urticarial/angioedema (NIUA), data confirming the involvement of COX-1 inhibition and the generation of eicosanoid mediators in NIUA.⁶⁶

3.2 | Drug-sIgE determination

Immunoassays are the most common *in vitro* method for determining sIgE in DHRs, although their sensitivity is lower than for STs.^{62,67} The most used commercial method is fluoroimmunoassay, only available for limited drugs. For BLs, it shows a low and variable sensitivity (0%-50%) depending on the clinical symptoms.⁶⁸ The detection of sIgE by fluoroimmunoassay is useful for diagnosing cefazolin allergy (currently for research use only), with a sensitivity and specificity of 49% and 94%, respectively.⁶⁹ Sensitivity is also heterogeneous for NMBA depending on the specific drug: 83%-92% for rocuronium; 78%-84% for morphine; and 44% for suxamethonium.^{62,70} The high sensitivity (84%-97%) of this method for chlorhexidine should be highlighted.⁷¹

In-house radioimmunoassay is used as alternative for drugs not available in commercial assays. It is essential for research purposes in order to analyze the immunological recognition of new chemical structures. A recent study has shown that the pyrazinone determinants of cefaclor mimic better the real antigenic determinant than others previously reported, indicating that they could be good candidates to improve cefaclor sIgE determination.⁷²

3.3 | Basophil activation test (BAT)

BAT is based on flow cytometry detection of basophil activation in the presence of a stimulus. It is recommended as complementary tool for diagnosing IgE-mediated reactions, especially when no alternative *in vitro* tests is available or sensitivity issues remain, as for CLV, fluoroquinolones, RCM, or chemotherapeutic agents.^{62,73-75} Two recent studies have demonstrated that BAT is a promising technique, complementary to STs, for diagnosing allergy to AX-CLV⁷⁶ and to omeprazole.⁷⁷ Moreover, there are some discrepancies about the utility of BAT for NMBAs, with a retrospective study suggesting that it does not increase the accuracy of ST,⁷⁸ while other studies show an increase in ST combined with BAT up to 77%.⁷³

Moreover, the inclusion of drug metabolites with the parent drug might improve BAT sensitivity. This happens using one synthetic CLV determinant besides the CLV to increase sensitivity significantly: from 41% to 69% in the evaluation of AX-CLV hypersensitivity.⁷⁹ Additionally, the use of nanostructures bound to BLs has proved the relevance of the carrier molecule and the drug distribution for immunological recognition. A novel study showed that nanostructures with higher diameter and number of determinants induced higher basophil activation in allergic patients.⁸⁰

Selective relaxant-binding agents, such as Sugammadex, form high affinity complexes with steroidal NMBAs, particularly rocuronium, generating the complex S-R-Cx. The use of BAT has confirmed in a clinical case the existence of IgE that recognizes the complex regardless of the individual steroidal NMBA.⁸¹ Moreover, BAT has demonstrated positive results for the evaluation of anaphylaxis due to macrogol.⁸²

Interestingly, BAT has been applied for evaluating potential capacity of some drugs as anti-tumor IgE therapeutic candidate (MOv18) for inducing hypersensitivity. BAT showed no reactivity with MOv18 or control IgE in ovarian cancer patients' samples. These results suggest that BAT combined with other clinical and biological parameters could help monitor and predict the safety of anti-tumor IgE therapy.⁸³

3.4 | Lymphocyte transformation tests (LTT) and mediator release determination

LTT, which determines the proliferative response of T-lymphocytes after drug stimulation, has been widely used for evaluating T cell-mediated DHRs or NI-DHRs.⁶² This test can be performed with many drugs and can be used in reactions with different pathomechanisms.⁸⁴ However, the great heterogeneity of DHRs, the controversies regarding the best moment for performing it, the unavailability of commercial tests, and the limited sensitivity hamper its routine use.⁸⁵

As with STs, predictive values of this test for SCAR diagnosis have not been established as DPT is not possible for ethical reasons. A recent study including 41 patients diagnosed with DRESS has shown better results when the tests were performed during the recovery phase, with an overall sensitivity of 80% and a specificity of 82%, greater than ST values.⁸⁶ In patients with benznidazole allergy, it also provided better values of sensitivity and specificity (75.9% and 100%, respectively) than ST.⁸⁷ Moreover, the test was particularly useful to assess cross-reactivity⁸⁷ and to confirm drug causality in SJS/TEN patients taking multiple medications,⁸⁸ and in fixed drug eruption induced by Etoricoxib.⁸⁹

One approach to increase the sensitivity of *in vitro* tests for NI-DHRs could be evaluating the effector mechanism. The results of IFN- γ -releasing cells by ELISpot showed a sensitivity of 52% and a specificity of 100% in SCARs during the acute phase. When these results were combined with ST, the sensitivity increased to 79%.⁹⁰ Moreover, drug-specific IFN- γ -releasing cells are detectable in almost half of SCAR patients, representing a good complement for diagnosis.⁹¹

The determination of other markers such as granulysin after lymphocyte activation with proton-pump inhibitors in NI-DHRs is useful to identify the culprit and cross-reactivity to structurally similar drugs. Higher levels of this cytotoxic molecule were found in DRESS and SJS/TEN patients, with a better sensitivity and specificity than the determination of IFN- γ and a great correlation with patch test results.⁹²

3.5 | T-CELL CLONALITY

Some studies have shown that graft-versus-host disease (GVHD) is characterized by the expansion of few specific T-cell clones,⁹³ while DHRs are more polyclonal.⁹⁴ A recent paper has analyzed this clonal diversity of T-cell repertoire as novel diagnostic tests to distinguish DHRs from GVHD. Chang et al sequenced the CD3 region of the TCR

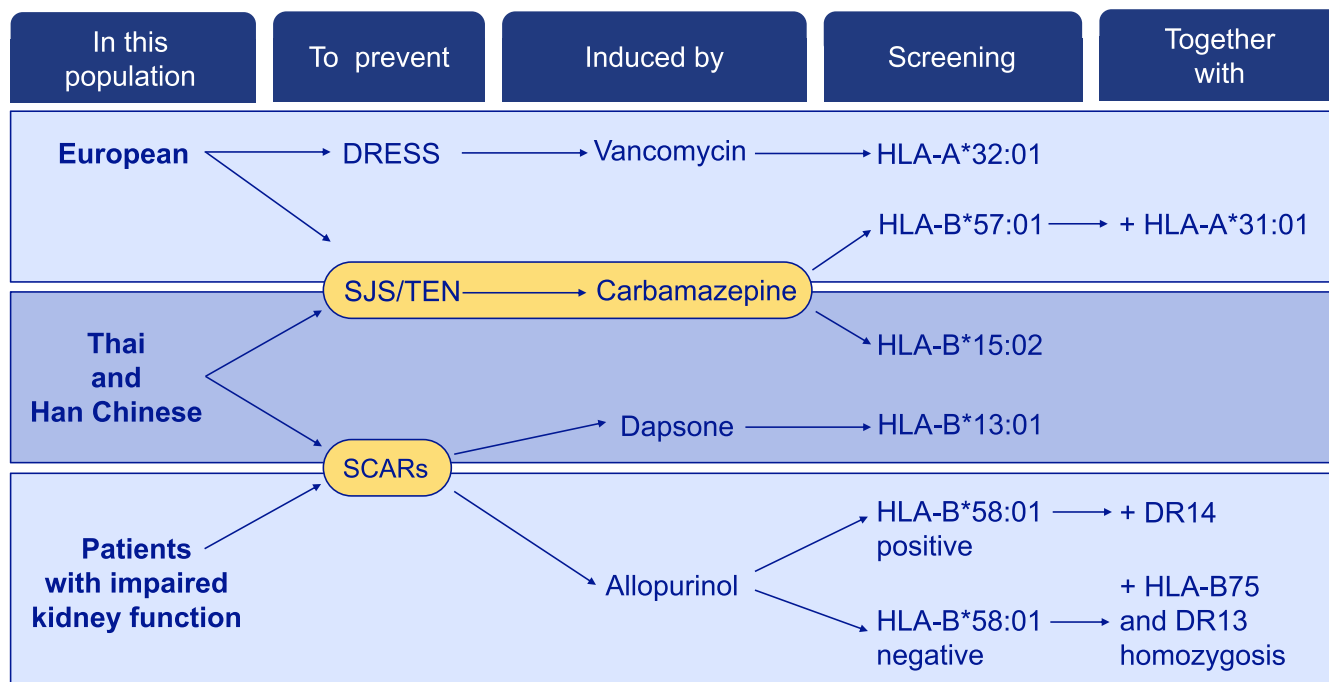


FIGURE 3 Scheme indicating which HLA alleles must be tested in a determined population before the administration of some drugs to prevent NIR, according to studies published in the last two years

β chain from affected skin tissue observing a greater clonal diversity in DHRs compared with GVHD.⁹⁵ This fact could be useful for performing a differential diagnosis between both entities, which have similar clinical and histological characteristics, but different management.

4 | GENETIC SUSCEPTIBILITY

A recent EAACI position paper performed an exhaustive revision about advances on the role of genetic susceptibility in DHRs. Genetic variations in HLA associated with susceptibility to hypersensitivity reactions for some drugs highlight the need to confirm current knowledge and to identify new associations for more accurate diagnosis, treatment, and management⁹⁶ (Figure 3).

Differences exist in the mechanisms inducing DHRs in HLA-B*13:01 Thai and Han Chinese patients, as dapsone activated CD8⁺T cells via direct HLA binding, while its reactive metabolite, nitroso dapsone, activated CD4⁺T cells following the hapten concept, finding both types of T-cell clones in the same patient.⁹⁷ This new knowledge could be crucial for developing new diagnostic tools.

Abacavir DHRs have been related with the allele HLA-B*57:01. Recently, abacavir analogues retaining their antiviral capacity but not altering the HLA-B*57:01 peptide binding repertoire, and thus avoiding CD8⁺T-cell activation, were synthesized.⁹⁸ Furthermore, this allele has been associated with SCARs induced by other drugs like carbamazepine (CBZ), increasing the risk of SJS/TEN but not DRESS in the European population.⁹⁹ Combining this result with previous studies,¹⁰⁰ the authors suggest that screening two alleles, HLA-B*57:01 and HLA-A*31:01, could reduce CBZ-induced-SCAR in

Europeans.⁹⁹ HLA-B*15:02 has also been strongly associated with CBZ-induced-SJS/TEN in other ethnic groups such as Han Chinese, Thai, and Malaysian populations.¹⁰¹ These results suggest that screening this allele in populations with high allele frequency could prevent the occurrence of CBZ-induced-SJS/TEN.¹⁰¹

Associations between HLA-B*58:01 and SCARs to allopurinol have been widely described. A "Teachable Moment" article from JAMA Internal Medicine highlighted the importance of screening populations with high prevalence of this allele,¹⁰² especially in case of chronic renal insufficiency.¹⁰³ However, only some allopurinol-treated subjects having this allele develop SCARs and there are allopurinol-induced SCAR cases in the absence of HLA-B*58:01.¹⁰⁴ A study suggests that a secondary screening of HLA-B75, DR13 homozygosity, and DR14 in HLA-B*58:01 patients, especially in those with impaired kidney function, could increase the accuracy of SCAR prediction.¹⁰⁵

Another association found in populations with European ancestry is HLA-A*32:01 allele and vancomycin-induced DRESS. This association was confirmed by in vivo and in vitro tests such as ELISpot assay. The allele was identified in 86% of patients with DRESS, but not in control subjects. This suggests that HLA testing could guide risk stratification after starting vancomycin treatment but before developing vancomycin-induced DRESS.¹⁰⁶ Moreover, low but detectable risk of cross-reactivity among teicoplanin, telavancin, and vancomycin has been detected in these patients.¹⁰⁷

Finally, a genome-wide association study carried out in Spain found associations between three variants of the GNAI2 gene (guanine nucleotide-binding protein (G protein), alpha inhibiting activity polypeptide 2) locus, and the primary risk of NSAID hypersensitivity.¹⁰⁸

5 | CONCLUSIONS

DHRs diagnostic evaluation is complex, time consuming, and costly, and an accurate diagnostic approach is crucial to prevent mislabeling and to reduce morbidity and mortality. It usually includes in vivo (Table 1) and in vitro tests. However, current practice is heterogeneous among centers, being necessary to re-evaluate, update, and standardize protocols on diagnosis and management of patients with suspected drug allergy.

Regarding in vitro tests (Table 2), recent studies have focused on improving sensitivity measuring new molecules or testing metabolites or synthetic determinants besides the suspected culprit. Moreover, different assays have been implemented to test more drugs, trying to establish their sensitivity and specificity. However, most of them are still in-house methods not currently available for clinical practice. Thus, there is still a long way to clinically standardize and validate these tests for applying them in daily clinical practice.

Some new genetic associations have been described, specially related to the risk of suffering SCARs. However, only a low number of SCARs can be prevented using HLA-B prescreening.

Finally, most of the new literature concurs on the fact that combining several tests, in vivo and in vitro, is the best way to perform an accurate diagnosis. Further research is needed to develop a genuinely safe test able to unequivocally diagnose DHRs.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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