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POSITION PAPER

International Consensus on drug allergy

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Abstract

When drug reactions resembling allergy occur, they are called drug hypersensitivity reactions (DHRs) before showing the evidence of either drug-specific antibodies or T cells. DHRs may be allergic or nonallergic in nature, with drug allergies being immunologically mediated DHRs. These reactions are typically unpredictable. They can be life-threatening, may require or prolong hospitalization, and may necessitate changes in subsequent therapy. Both underdiagnosis (due to under-reporting) and overdiagnosis (due to an overuse of the term 'allergy') are common. A definitive diagnosis of such reactions is required in order to institute adequate treatment options and proper preventive measures. Misclassification based solely on the DHR history without further testing may affect treatment options, result in adverse consequences, and lead to the use of more-expensive or less-effective drugs, in contrast to patients who had undergone a complete drug allergy workup. Several guidelines and/or consensus documents on general or specific drug class-induced DHRs are available to support the medical decision process. The use of standardized systematic approaches for the diagnosis and management of DHRs carries the potential to improve outcomes and should thus be disseminated and implemented. Consequently, the International Collaboration in Asthma, Allergy and Immunology (iCAALL), formed by the European Academy of Allergy and Clinical Immunology (EAACI), the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the World Allergy Organization (WAO), has decided to issue an International CONsensus (ICON) on drug allergy. The purpose of this document is to highlight the key messages that are common to many of the existing guidelines, while critically reviewing and commenting on any differences and deficiencies of evidence, thus providing a comprehensive reference document for the diagnosis and management of DHRs.

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Drugs can induce several different types of immunological reactions that, together with nonallergic drug hypersensitivity reactions (DHRs), comprise 15% of all adverse drug reactions (1). Nonallergic DHRs resemble allergy, but without any proven immunological mechanism.

Drug hypersensitivity reactions are of significant concern for clinicians and patients and are also a significant cause of the postmarketing withdrawal of drugs (2). Even though urticarial and maculopapular eruptions are the most frequent manifestations, there are many other clinical presentations (1). DHRs affect more than 7% of the general population and therefore represent an important public health problem (3). Both underdiagnosis (due to under-reporting (3, 4)) and overdiagnosis (due to an overuse of the term 'allergy', for example, in the presence of symptoms due to co-existing factors such as infections (3, 5)) are potential problems. Misclassification based on the DHR history alone may limit therapeutic options and can lead to the use of more-expensive and potentially less-effective drugs (6). Moreover, one drug allergy may lead to the misconception that the patient is allergic to all drugs.

Few guidelines and/or consensus documents are available to support medical decision making on all aspects of DHR. These documents vary in scope and methodology: They are national (6–10), regional, or international (11–22); concern one specific drug class (7, 8, 14–16, 18, 20, 21, 23); focus specifically on evaluation tools/management (11–13, 17, 19, 23); or are more general (6, 8, 24, 25). Although there is no doubt that the use of common systematic approaches for the diagnosis and management of DHRs can considerably improve outcomes, worldwide dissemination and implementation remain major challenges. For these reasons, the International Collaboration in Asthma, Allergy and Immunology (iCAALL) (26), recently formed by the European Academy of Allergy and Clinical Immunology (EAACI), the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the World Allergy Organization (WAO), has decided to proceed with the compilation of an International CONsensus (ICON) on drug allergy. The purpose of this document is to highlight the key messages that are common to the existing guidelines, while critically reviewing and commenting on any differences, thus providing a comprehensive reference to be disseminated more widely. As for the ICON on pediatric asthma (27), unmet needs, research, and guideline update recommendations are generated.

Methodology

A working committee was formed and approved by the current board of iCAALL and the participating organizations. The criteria used for the formation of the committee were as follows: regional representation, relevance to the field, and previous participation in drug allergy guidelines. The members of the committee proposed relevant documents for appraisal. These included (i) the AAAAI/ACAAI/Joint Council of Allergy, Asthma and Immunology drug allergy updated practice parameters (6, 7), (ii) the WAO drug allergy initiatives (24, 25), (iii) the British Society of Allergy and Clinical Immunology (BSACI) guidelines (8, 9), and (iv) the many task force reports and consensus documents of the EAACI Drug Allergy Interest Group (DAIG) as well as its core group, the European Network of Drug Allergy (ENDA) (11–21, 23). Each member was responsible for the preparation of text and relevant tables comparing the included documents in a specific domain. A draft was subsequently compiled and circulated (in September 2012) among the authors for comments and corrections. The revised document was then sent (in April 2013) to an independent reviewing committee, selected on the basis of their publications over the past 5 years in top peer-reviewed journals as first/last authors. Their comments were taken into account in the final draft, which was then approved by the governing boards of the participating organizations. Recommendations were extrapolated from the reference documents and presented using levels of Evidence A–D (28) (Table 1).

Definition and classifications of drug hypersensitivity reactions

Definition

Drug hypersensitivity reactions (DHRs) are the adverse effects of pharmaceutical formulations (including active drugs and excipients) that clinically resemble allergy (29) (Box 1). DHRs belong to type B adverse drug reactions, which are defined by the World Health Organization as the dose-independent, unpredictable, noxious, and unintended response to a drug taken at a dose normally used in humans (30, 31). A-type reactions, including overdoses and pharmacological reactions, are dose dependent and predictable. However, some dose dependence has been shown repeatedly in DHRs (e.g., for nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptic drugs) and some are

Abbreviations

AAAAI, American Academy of Allergy, Asthma and Immunology; ACAAI, American College of Allergy, Asthma and Immunology; AGEP, acute generalized exanthematous pustulosis; AIDS, acquired immunodeficiency syndrome; BSACI, British Society of Allergy and Clinical Immunology; CD, cluster of differentiation; DAIG, Drug Allergy Interest Group; DHR(s), drug hypersensitivity reaction(s); DPT(s), drug provocation test(s); EAACI, European Academy of Allergy and Clinical Immunology; EBV, Epstein–Barr virus; FcεRI, high-affinity IgE receptor; FDE, fixed drug eruption; HHV, human herpes virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HSS/DRESS/DiHS, hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome; iCAALL, International Collaboration in Asthma, Allergy and Immunology; ICON, International CONsensus; IgE, immunoglobulin E; MCH, major histocompatibility complex; MDH, multiple drug hypersensitivity; NMBA, neuromuscular-blocking agents; NPV, negative predictive value; NSAID(s), nonsteroidal anti-inflammatory drug(s); RCM, radiocontrast media; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; TNF-α, tumor necrosis factor alpha; WAO, World Allergy Organization.

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Table 1 Recommendations for DHR diagnosis and management

No.	Statement	Levels of evidence	Grade of recommendation	References
R1	Lifelong avoidance of the drug and cross-reactive drugs is recommended when drug-induced anaphylaxis has occurred	4	D	(6, 102)
R2	The specific allergy work-up should be carried out 4–6 weeks after complete resolution of all clinical symptoms and signs of a suspected DHR	4	D	(12, 13)
R3	Sensitivity and predictive values of skin tests vary among drug classes: from 'good' for immediate DHRs to β-lactam antibiotics, muscle relaxants, platin salts and heparins, to moderate to low for most other drugs	2++	B	(22)
R4	Skin testing is helpful for diagnosis of immediate DHRs to iodinated RCM	2+	C	(16, 22)
R5	A DPT is the gold standard for the identification of the drug eliciting a DHR	2+	C	(6, 8, 13)
R6	For DPT, the oral route is preferred whenever possible	3	D	(6, 8, 13)
R7	Contraindications must be observed before performing DPT, and immediate treatment available allowing complete and rapid recovery	4	D	(6, 8, 13)
R8	Patients who suffered severe immediate reactions to β-lactams and who displayed negative results at the first evaluation, which included a DPT, can be considered for retesting 2–4 weeks after initial evaluation	2−	D	(6, 18)
R9	For currently available biological methods to diagnose drug allergy, a negative test does not exclude the imputability of the drug, whilst a positive result shows sensitivity to the drug but does not reliably confirm causality	2+ for ß-lactams 2− to 3 for others	C	(6, 8)
R10	HLA-B*5701 screening reduces the risk of DHR to abacavir and is mandatory before starting treatment	1++	A	(47) Not rated in previous consensuses (6–23)
R11	An indicative, regularly updated list of drugs to avoid and the list of possible alternatives should be given to patients with a DHR	4	D	(8)
R12	The search for safe alternatives may require DPTs in a hospital setting when the alternatives belong to the same drug class	2+	C	(6, 8, 13)
R13	Specific questioning for a history of drug allergy by every clinician prior to issuing a prescription is essential from both a medical and a medico-legal view-point	4	D	(6, 8, 20)
R14	Preventive measures by pre-medication (e.g. slow injection and pre-treatment with glucocorticosteroids and H1-antihistamines) are useful mainly for non-allergic DHRs, but corticosteroids and H1-antihistamines may not reliably prevent IgE-dependent anaphylaxis	2+	C	(6, 8, 102)
R15	In the absence of generally accepted protocols for drug desensitization in cases of immediate DHRs, reference to successfully applied existing protocols is recommended	2+	C	(6, 19)
R16	Desensitization to aspirin as a therapeutic intervention may be considered in selected asthmatic patients with aspirin exacerbated respiratory disease or nasal polyps	2−	D	(6, 19)

DHR(s), drug hypersensitivity reaction(s); RCM, radiocontrast media; DPT(s), drug provocation test(s); HLA, human leukocyte antigen.

predictable due to the disease state (e.g., human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), Epstein–Barr virus (EBV) infection) or a similar previous reaction to the same drug or drug class.

Only when a definite immunological mechanism (either drug-specific antibody or T cell) is demonstrated, these reactions should be classified as drug allergy. For general communication, when an allergic drug reaction is suspected,

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DHR is the preferred term, because true drug allergy and nonallergic DHR (29) may be difficult to differentiate based on the clinical presentation alone, especially in cases of acute severe DHR.

Box 1: Definition of drug hypersensitivity reactions

1 Drug hypersensitivity reactions (DHRs) are adverse effects of drugs that clinically resemble allergic reactions.
2 Drug allergies are DHRs for which a definite immunological mechanism (either drug-specific antibody or T cell) is demonstrated.
3 For general communication, when a drug allergic reaction is suspected, DHR is the preferred term.

Classifications

The classification of DHRs is challenging because, for many drugs and clinical presentations, the underlying mechanism is poorly understood (Box 2). A generally accepted classification should facilitate the comparison of studies and help to enhance and validate diagnostic techniques.

Box 2: Classification of drug hypersensitivity reactions

1 Drug hypersensitivity reactions (DHRs) are heterogeneous.
2 Clinically, DHRs can be classified as:
   a Immediate DHRs (urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms [nausea, vomiting, diarrhea, abdominal pain], anaphylaxis, anaphylactic shock); they typically occur within 1–6 h after the last drug administration.
   b Nonimmediate DHRs (delayed urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, and Stevens–Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis and symmetrical drug-related intertriginous and flexural exanthemas; internal organs can be affected either alone or with cutaneous symptoms (DRESS, vasculitis) and include hepatitis, renal failure, pneumonitis, anemia, neutropenia, thrombocytopenia); they may occur at any time as from 1 h after from the initial drug administration.
3 Mechanistically, DHRs can be defined as allergic (Table 2) and nonallergic.

Clinically, DHRs are commonly classified as immediate or nonimmediate/delayed depending on their onset during treatment (18). Immediate DHRs are possibly induced by an IgE-mediated mechanism and occur within 1–6 h after the last drug administration (32) (Fig. 1). Typically, they occur within the first hour following the first administration of a new course of treatment. They usually manifest as isolated symptoms such as urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), or as anaphylaxis or anaphylactic shock. In certain guidelines, when DHR symptoms are systemic, non-IgE-dependent, and mimicking anaphylaxis, they are designated as 'anaphylactoid' reactions (6). This is no longer the case in EAACI and WAO (29) guidelines, where the term 'nonallergic DHRs' is preferred. Nonimmediate DHRs may occur any time as from 1 h after the initial drug administration. They commonly occur after many days of treatment and are often associated with a delayed T-cell-dependent type of allergic mechanism. Maculopapular exanthemas and delayed urticaria are the most common clinical presentations of nonimmediate DHRs. Although artificial, this classification is very important in clinical practice for workup planning. In any case, a precise description of the morphology and chronology of the reaction is mandatory. But there are still limitations, because other factors such as the route of administration, the role of drug metabolites, and the presence of co-factors or co-prescribed drugs may accelerate or slow down the onset or progression of a reaction (32) (Fig. 1).

Mechanistically, drugs are capable of inducing all of the types of immunological reactions described by Gell and Coombs (33), but the most common are IgE- and T-cell-mediated reactions (Table 2). Certain drugs, such as antiepileptic drugs and allopurinol, cause mainly T-cell-mediated reactions, while others, such as neuromuscular-blocking agents (NMBA), provoke mainly IgE-mediated reactions. Some of the others (e.g., β-lactams) may lead to both types of reaction.

Pathogenesis and pathophysiology

Immune/allergic and nonimmune/nonallergic DHRs

Drug allergies are adverse reactions whereby antibodies and/or activated T cells are directed against the drugs or against

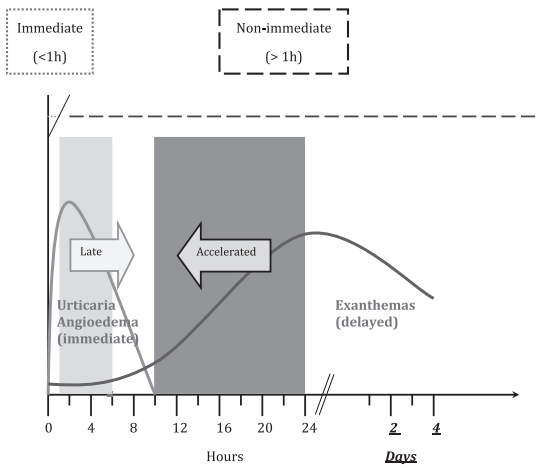


Figure 1 Chronology of DHRs. The separation at 1 h into immediate or nonimmediate reactions although it may not sufficiently reflect the extension of the pathophysiologically determined immediate-type reactions up to 6 h (Late) and the delayed-type clinical manifestations occasionally starting as early as 8–12 h (Accelerated) facilitates the comparison of studies and should help to enhance and validate diagnostic techniques (adapted from (32) with permission).

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Table 2 Classification of drug allergies (adapted from (33))

Type	Type of immune response	Pathophysiology	Clinical symptoms	Typical chronology of the reaction
I	IgE	Mast cell and basophil degranulation	Anaphylactic shock Angioedema Urticaria Bronchospasm	Within 1 to 6 h after the last intake of the drug
II	IgG and complement	IgG and complement-dependent cytotoxicity	Cytopenia	5–15 days after the start of the eliciting drug
III	IgM or IgG and complement or FcR	Deposition of immune complexes	Serum sickness Urticaria Vasculitis	7–8 days for serum sickness/urticaria 7–21 days after the start of the eliciting drug for vasculitis
IVa	Th1 (IFN-γ)	Monocytic inflammation	Eczema	1–21 days after the start of the eliciting drug
IVb	Th2 (IL-4 and IL-5)	Eosinophilic inflammation	Maculopapular exanthema, DRESS	1 to several days after the start of the eliciting drug for MPE 2–6 weeks after the start of the eliciting drug for DRESS
IVc	Cytotoxic T cells (perforin, granzyme B, FasL)	Keratinocyte death mediated by CD4 or CD8	Maculopapular exanthema, SJS/TEN, pustular exanthema	1–2 days after the start of the eliciting drug for fixed drug eruption 4–28 days after the start of the eliciting drug for SJS/TEN
IVd	T cells (IL-8/CXCL8)	Neutrophilic inflammation	Acute generalized exanthematous pustulosis	Typically 1–2 days after the start of the eliciting drug (but could be longer)

one of its metabolites. Numerous reactions with symptoms suggestive of allergy are often erroneously considered to be real drug allergies. The suggested pathomechanisms of these reactions include the following: (i) nonspecific mast cell or basophil histamine release (e.g., opiates, radiocontrast media, and vancomycin), (ii) bradykinin accumulation (angiotensin-converting enzyme inhibitors), (iii) complement activation (e.g., protamine), (iv) possibly an alteration in arachidonate metabolism (e.g., aspirin and nonsteroidal anti-inflammatory drugs), and (v) the pharmacological action of certain substances inducing bronchospasm (e.g., β-blockers, sulfur dioxide [$S0_2$] released by pharmaceutical formulations containing sulfites).

Immediate allergic DHRs

Immediate allergic DHRs develop as a result of IgE production by antigen-specific B lymphocytes after sensitization. IgE antibodies bind to the high-affinity Fc RI receptors on the surface of mast cells and basophils, creating a multivalent binding site for the drug antigen (34). Following subsequent drug exposure, the antigen – presumably a hapten–protein complex – cross-links bound IgE, stimulating the release of preformed mediators (e.g., histamine, tryptase, some cytokines such as TNF-α) and the production of new mediators (e.g., leukotrienes, prostaglandins, kinins, other cytokines). The preformed mediators stimulate a response within minutes, whereas the cytokine inflammatory component develops after several hours, the time required for protein synthesis and the recruitment of immune cells. β-Lactam-mediated anaphylaxis is the best defined immediate allergic DHR (18).

Nonimmediate/delayed allergic DHRs

Most nonimmediate/delayed allergic DHRs are mediated through the actions of T lymphocytes (34). The skin is the most commonly targeted organ by drug-responsive T cells, but any organ can be involved. Diclofenac, for example, as well as several other carboxylic acid nonsteroidal anti-inflammatory drugs, can cause immune-mediated liver injury, which may be explained by hepatic metabolism and selective modification of hepatic proteins (35). It is important to note that the same drug might produce different clinical symptoms and signs in different individuals, despite the drug being administered at the same dose via the same route. We are lacking data regarding specific drug processing, but, based on peptide immune recognition, the following scenario is possible. To stimulate naive T cells, dendritic cells first process the drug antigen. The antigen is then internalized and transported to the regional lymph nodes. To develop an effective immune response, the innate immune system needs to be activated, providing important maturation signals, often referred to as 'danger signals' (36) which include direct drug or disease-related stress. On arrival at the lymph nodes, the antigen is presented to naive T cells. Alternatively, some drug antigens might directly stimulate pathogen-specific T cells, thus avoiding the requirement for dendritic cell priming of T cells. However, for some authors, this hypothesis is difficult to reconcile with the time between initial drug exposure and the development of clinical signs (34). Antigen-specific T cells migrate to target organs and, once re-exposed to the antigen, they are activated to secrete cytokines that regulate the response and cytotoxins (e.g., perforin, granzymes, and granulysins) that produce tissue damage.

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Chemical basis of drug allergies

According to the hapten hypothesis, in order to stimulate a reaction, a drug should act as a hapten and bind irreversibly to proteins (34), generating antigens. This theory is relevant for chemical compounds, but not for proteic or carbohydrate compounds of drugs such as insulin, enzymes, monoclonal antibodies, and recombinant proteins. This is also especially relevant for oral drugs that preferentially bind to proteins such as albumin in gastric stomach fluid (37). However, in most cases, the gastric peptic function digests and inactivates the hapten–protein complex. Several drug modifications of the same protein are possible, generating a multivalent antigen for eliciting IgE-mediated immediate DHRs. For the elicitation of delayed-type T-cell-mediated reactions, the role of the carrier protein and/or the hapten has not always been fully defined. Furthermore, it is not known as to whether there is a threshold level of modification that needs to be surmounted to stimulate a T-cell response. The majority of drugs, however, are not directly protein reactive (33), and in such cases, hapten formation is thought to occur as a consequence of metabolic activation (e.g., sulfonamides) (the pro-hapten hypothesis). By generating a reactive metabolite, it is also feasible that activation of the innate immune system occurs, which is a prerequisite for a classical immune response.

An alternative hypothesis (the pharmacological interaction with immune receptor (*p-i*) concept) has evolved from analysis of the response of T-cell clones to drug stimulation, suggesting that drugs, although smaller than traditional antigens, might also interact directly with immunological receptors through a reversible interaction with the immune receptors (33). According to this hypothesis, a drug can directly bind and activate T cells (providing MHC binding as well) or bind to HLA molecules, which then activate T cells indirectly, by altering the MHC–peptide groove. This latter concept was recently further extended by showing that some drugs, when they bind to HLA molecules, promote an exchange of embedded peptides (38). However, the functional consequence of this peptide exchange is still unclear. Abacavir binds at the F pocket antigen-binding site of HLA-B*5701, selecting an array of novel self-peptides that induce the activation of CD8-positive T cells, inducing a severe DHR similar to graft-*vs*-host disease without eosinophilia (38). This recently uncovered mechanism of DHRs may be applicable to other small molecules with HLA allotype preferences.

Pharmaco- and immunogenetic basis of drug allergies

Drug hypersensitivity reactions involve both immune- and nonimmune-mediated mechanisms, with strong genetic interplay in some severe nonimmediate/delayed allergic DHRs. Indeed, a strong association between carbamazepine-induced Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) has been described for HLA-B*1502 in a Han Chinese population (39) and subsequently in Indian (40) and Thai (41), but not in European and Japanese patients (42–45). The association seems to be phenotype specific (SJS, but not hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (HSS/DRESS/DiHS)) (46). In contrast, HLA-A*3101 has been shown to be associated, in northern Europeans, with a spectrum of carbamazepine-induced reactions including maculopapular exanthemas, DRESS/DIHS, and SJS/TEN (42). For the drug abacavir, an association between HLA-B*5701 expression and severe DHRs in Caucasians has been shown (47). The incidence of this allele in abacavir-hypersensitive patients is high (94.4%) (48) in the Australian cohort, but lower (22.2%) in other studies (49), although still significantly higher than in the average population prevalence. Other genetic variants have been associated with DHRs (50) (Table 3). In immediate DHRs, some cytokine gene polymorphisms have been weakly associated with β-lactam-induced anaphylaxis (51, 52).

Role of viruses in the pathogenesis of DHRs

Viral infections can lead to skin eruptions and mimic DHRs if a drug (mostly an antibiotic) is taken at the same time (53). Although they are the leading cause of skin eruptions, viral infections can also interact with drugs, leading to mild eruptions in the case of the 'ampicillin rash' linked to the EBV infection (54) and severe reaction during DRESS (55). The first virus shown to be re-activated in DRESS patients was the human herpesvirus (HHV)-6 (56), but all herpesviruses can be involved (55). Strikingly, it was shown that HHV-6 replication can be induced *in vitro* by amoxicillin (57).

Clinical presentations

Acute and delayed manifestations of DHRs

Immediate DHRs usually present in the form of isolated urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea), or anaphylaxis, which can lead to cardiovascular collapse (anaphylactic shock) (58). Nonimmediate DHRs often affect the skin with variable cutaneous symptoms (59–61) such as late-occurring or delayed urticaria, maculopapular eruptions, fixed drug eruptions (FDE), vasculitis, blistering diseases (such as TEN, SJS, and generalized bullous fixed drug eruptions), HSS, acute generalized exanthematous pustulosis (AGEP), and symmetrical drug-related intertriginous and flexural exanthemas (SDRIFE). Internal organs can be affected either alone or with cutaneous symptoms (HSS/DRESS/DiHS, vasculitis, SJS/TEN) and include hepatitis, renal failure, pneumonitis, anemia, neutropenia, and thrombocytopenia.

Danger/severity signs of DHRs

The approach to the patient with a presumed DHR in the acute phase involves the following steps: (i) a complete history of the drugs taken (types, doses, duration), (ii) a detailed description of the symptoms and signs (types, onset, localization, and evolution), with (iii) a complete examination of the skin and the mucous membranes (including the mouth, eyes, and genitals), and (iv) the

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Table 3 Pharmacogenomic biomarkers as predictors of severe DHRs (adapted from (50))

Gene or allele	HLA carriage rate	Relevant drug	% of patients with an ADR	% of association between patients and controls	Relevant ADR and ethnicity	Odds ratio	Negative predictive value %	Positive predictive value %
HLA-B*5701	6–8% Caucasians <1% African-Asian 2.5% African-American	Abacavir	5–8	100	SCAR	960	100 if patch test is negative	55
HLA-B*1502	10–15% Han Chinese <0.1% Caucasians and Japanese	Carbamazepine		100–8.6	SJS-Han Chinese	2504	100 in Han Chinese	3
HLA-B*5801	9–11% Han Chinese 1–6% Caucasians	Allopurinol		100–15 55	SCAR-Han Chinese SJS-Caucasians	580 50	100 in Han Chinese	3
HLA-A*3101	2–5% in northern Europeans	Carbamazepine	1–6/10 000	60.7–12.5 37/41.7-2 to 5	SCAR-Japanese DRESS/SJS-Caucasians	10.8 12.4/25.9		

search for danger/severity signs, which include clinical symptoms as well as some laboratory parameters (Fig. 2) (62). This approach will lead to the correct diagnosis, an appropriate choice of allergy tests later on and, during the acute phase, will facilitate the decision as to whether the drug should be stopped or not. If danger/severity signs are present, the suspected drugs should be stopped immediately.

Multiple drug hypersensitivity syndrome

About one-third of patients consulting in a drug allergy unit report more than one 'drug allergy' (63). First described (64) as drug allergies to two or more chemically different drugs, multiple drug hypersensitivity (MDH) differs from (i) cross-reactivity (due to structural similarities, common metabolic pathways, or pharmacologic mechanisms), (ii) flare-up reactions (exacerbation of an existing drug allergy by the early switch of therapy to a novel drug) (65), and (iii) multiple drug intolerance syndrome (66). Multiple drug intolerance syndrome includes patients with intolerance to three or more neither structurally nor pharmacologically related drugs, with no confirmation after evaluation (67) and possibly driven by patient anxiety (68). In documented DHRs, the prevalence of MDH ranges from 1% to 10% (69) and may relate to moderate and severe DHRs (65).

T-cell activation by different compounds has been clearly demonstrated in MDH (70–72). In these patients, T cells do not appear to have any deficiency in T-reg function or number (73), but the fact that the drug-reactive T cells belong to an *in vivo* preactivated cell fraction ($CD4^+$ $CD25^{dim}$, may be due to *in vivo* occurring T-cell activation) makes them more susceptible to T-cell stimulation via the p-i concept (65).

Natural history of DHRs

The IgE antibody response is not permanent over time, and decreased antibody levels may occur months to years after the occurrence of a DHR, as shown for penicillin allergy (74). However, IgE sensitization may persist for years, as shown for NMBA (75). Experts therefore recommend (R1, Evidence D) lifelong avoidance of the drug and cross-reactive drugs when drug-induced anaphylaxis has occurred (6, 9, 20). T-cell memory seems to be even stronger for nonimmediate/delayed DHRs (76).

In selective responders to amoxicillin, patients are able to tolerate other penicillins and are not at increased risk of allergies upon exposure to closely related penicillins (77). Finally, resensitization studies indicate that some patients with a previous positive history and negatively tested may become positive after therapeutic administration (18). Even if this topic remains debatable, with regard to the time lapse between the tests, the normal sensitization incidence, or the number of subsequent tests, both the EAACI-DAIG/ENDA guideline (18) and the Practice Parameters experts (6) agree that consideration may be given to retesting individuals with particularly severe previous reactions to a β-lactam.

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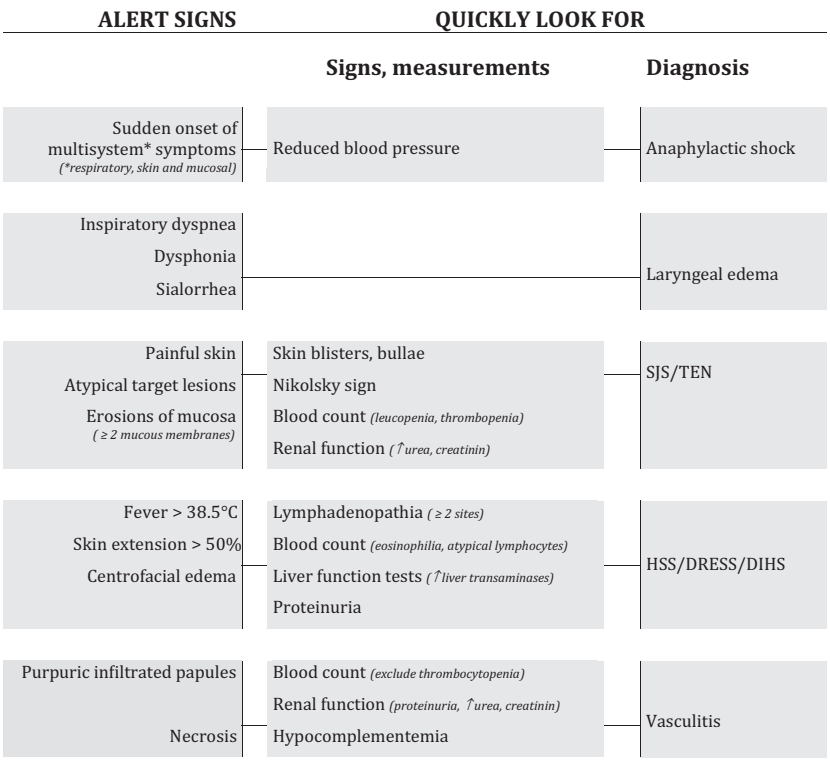


Figure 2 Clinical and biological danger signs suggesting severe cutaneous and/or systemic reactions (created using data from (62)).

Diagnosis

The diagnosis of DHRs requires knowledge of the scientific literature with access to Medline searches and to the Committee on Safety of Medicine and Embase Reports for the more recently introduced drugs. The lack of case studies involving a particular compound does not mean that it cannot induce a DHR, but for a widely used drug, it renders DHRs much less likely. The diagnosis is indeed based on history, on clinical manifestations, and if possible, on *in vivo* tests and some *in vitro* biological tests (Fig. 3) (78). However, only a few clinical and biological tools are available and fully validated. Moreover, a definitive diagnosis of such a reaction is preferred in order to institute proper preventive measures (Box 3).

Evaluation of the clinical history

Clinical history must be carefully obtained and should include the symptomatology (whether compatible with a DHR), the chronology of the symptoms (previous exposure, delay between the last dose and the onset of symptoms, effect of stopping treatment), other medications taken (both at the time of the reaction and other drugs of the same class taken since), and the medical background of the patient (any suggestion of a previous allergy, whether associated with medication or not, or of a medical condition, such as chronic urticaria/chronic rhinosinusitis, that can be aggravated by the intake of certain drugs such as aspirin and noncycloxygenase two selective NSAIDs). Data should ideally be recorded in a uniform format, and in order to harmonize the DHR diagnostic procedures, members of EAACI-DAIG/ENDA have developed a questionnaire (11) available in many different languages (Appendix S1 in the online Supporting Information). Diagnosis is more difficult when patients are not seen during the symptomatic phase, in which case photographs are helpful. When patients are seen during the reaction, the suspected drugs should be stopped after a benefit/risk balance analysis, especially if danger/severity signs are present (Fig. 2) (62).

A large number of reactions are presumed to be drug related and allergic in nature, but closer examination often reveals that they are not (3, 5). The history is often not reliable because different drugs are frequently taken simultaneously and each of them can account for the symptoms, although often with very different *a priori* probabilities. History can also be imprecise in many cases. Finally, the clinical picture of DHRs is very heterogeneous, mirroring many distinct pathophysiological events (Table 2). Thus, for the diagnosis of DHR, many healthcare professionals rely on history and various reference manuals. They do not attempt to prove the relationship between the drug intake and the symptoms or to clarify the underlying

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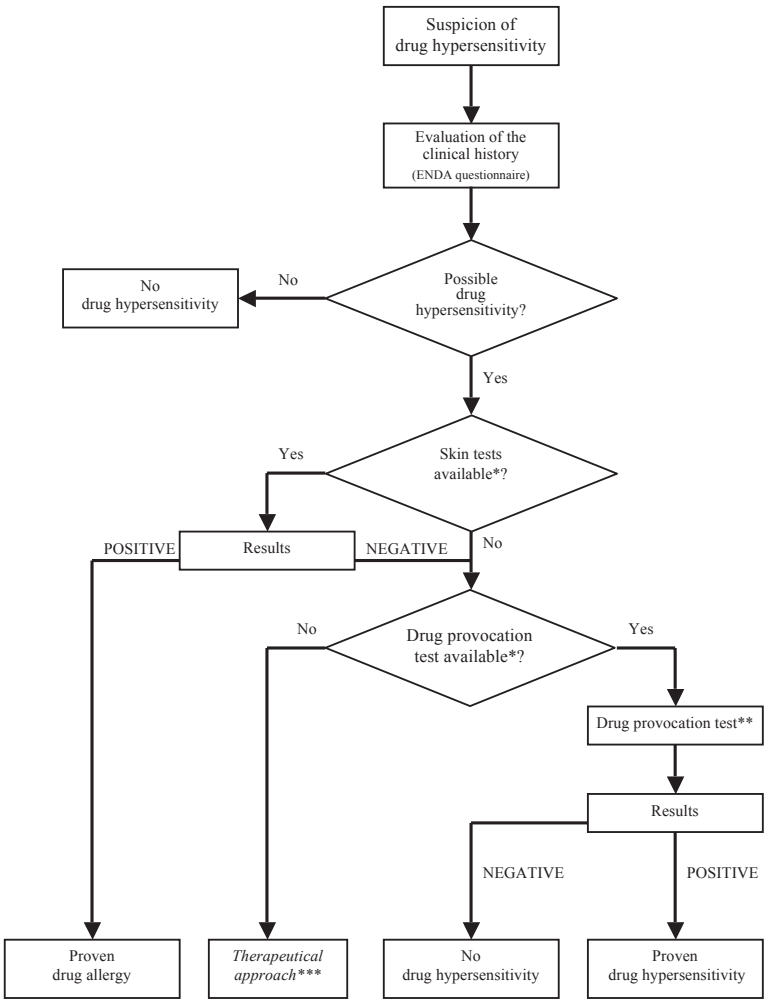


Figure 3 Flow chart when assessing DHRs (adapted from (78) with permission). *Currently available biological tests to diagnose drug allergy lack sensitivity. **In the absence of contraindications (Box 6). ***If no alternative is available (e.g., NMBA, chemotherapeutica drugs), readministration of the drug is allowed under close surveillance, considering premedication and/or desensitization.

pathomechanism of the reaction. Such practice leads to a misunderstanding of the epidemiology and the pathophysiology of this highly relevant field. Members of the panel have listed situations in order to determine when to test and when not to test in suspected DHR (Boxes 4 and 5). An accurate diagnosis of DHRs allows implementation of the best measures required for prevention and treatment. For universal drugs such as β-lactams, NSAIDs, local anesthetics, simply avoiding the drug is not sufficient (Box 4). This procedure could lead to the contraindication of drugs which do not necessarily give rise to reactions and which are widely used. Besides, a false diagnosis can lead to a fake sense of security if other possible causes of serious reactions are not explored and excluded. However, this is a valid option until a specialist consultation can be scheduled.

Box 3: Key points regarding DHR diagnosis

1. A definitive diagnosis of a DHR is in many cases required in order to institute proper preventive measures.
2. Misclassification based on the DHR history alone may have consequences on individual treatment choices and be more detrimental for the patients than a complete drug allergy workup.
3. The clinical tools allowing a definitive diagnosis include a thorough clinical history, standardized skin tests, reliable *in vitro* tests, and drug provocation tests.
4. When properly performed in specialized centers, a reliable diagnosis is often possible and safe alternative medication can be administered.
5. Screening subjects without a prior history of allergic drug reactions is not recommended.

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Box 4: DHR workup: When to evaluate?

1 When there is a history of prior DHR and the drug is required without an equally effective, structurally unrelated alternative, and if the risk/possible benefit ratio is positive:
   - **a** For the majority of patients with β-lactam, NSAIDs, local anesthetics DHRs.
   - **b** For others when drugs are required (depending on an individual medical needs).
2 When there is a history of prior severe DHR for other drugs (the best way to protect the patient is to find the culprit agents).

Box 5: DHR workup: When not to evaluate?

1 Cases with no drug allergy causality:
   - **a** Noncompatible symptomatology
   - **b** Noncompatible chronology
   - **c** Drug taken since with no reaction
   - **d** Reaction without having taken the drug
   - **e** Alternative diagnosis (e.g., herpesvirus eruption, chronic urticaria)
2 For drug provocation, every time the reaction was too severe: noncontrollable reaction and severe life-threatening reactions (Box 6)

The specific allergy workup should be carried out 4–6 weeks after the complete resolution of all clinical symptoms and signs (R2, Evidence D). How early testing can be made without results being falsely negative is unknown. On the other hand, after a time interval of more than 6–12 months, some drug tests may already have turned negative. These could be false-negative results (or true negative) depending on the results of the subsequent drug provocation test. According to the clinical presentations, a hypothesis on pathogenesis should be generated (Table 2) in order to select appropriate testing procedures (12, 62).

Pharmacovigilance algorithms

Pharmacovigilance algorithms for diagnosis are based principally on the clinical history (79); they are rarely specific for DHRs (80). They rarely produce a firm diagnosis of DHRs, and allergy testing is often necessary (79). Indeed, the symptoms are often suggestive, but not necessarily definitive in diagnosing DHR. The effect of discontinuation of the drug is not always conclusive (e.g., rebounds of urticaria after drug withdrawal is possible for a few hours) and no biological examination is reliable and specific. Often there is a lack of accurate information (imprecise chronology, exact name of drug or of corrective treatment not recalled by the patient), making drug causality assessment difficult to ascertain.

Skin tests

Skin tests are the most readily available means for confirming or excluding sensitization (22). Their diagnostic value has not been fully evaluated for all drugs, and over the past decades, experience among different centers has rarely been exchanged in a systematic manner (22). These tests should follow standard procedures and should be performed by trained staff (6, 12). They should be performed 4–6 weeks after the reaction (R2, Evidence D). Skin tests have to be applied depending on the suspected pathomechanism of the DHR.

Skin prick tests and intradermal tests are particularly important for reactive haptens in order to demonstrate an IgE-dependent mechanism (62). Thus, for immediate DHRs, the prick test is recommended for initial screening due to its simplicity, rapidity, low cost, and high specificity. Intradermal tests (12) are undertaken when skin prick tests are negative. Compared to skin prick tests, they provide an enhanced sensitivity for drug-specific IgE (12). They should be performed with the intravenously injectable form of the drug whenever possible (22). Their sensitivity and predictive values vary, depending on the culprit drug and the clinical presentation. They appear to be 'good' for immediate DHRs to β-lactam antibiotics, NMBA, platin salts, and heparins, but moderate to low for most other drugs (R3, Evidence B) (22).

In order to demonstrate a T-cell-dependent mechanism for nonimmediate DHRs (manifesting by cutaneous symptoms such as a maculopapular exanthema occurring within hours after the last drug intake), patch tests and/or late-reading intradermal tests should be performed (15, 62). Unfortunately, apart from allergic reactions to several antibiotics and a few other drugs (81), for most drug allergens, standardized and validated test concentrations and vehicles have not been studied or are disputed in the literature. Sometimes the drug is not available in an adequately reactive form, generally because it is a metabolic derivative which is immunogenic and not the parent drug. In such cases, provocation tests are required to confirm the diagnosis. Available data have been summarized by EAACI-DAIG/ENDA experts (22).

Testing subjects without a prior history of an allergic drug reaction is not supported by available studies and therefore not recommended by any of the societies, in particular in preoperative settings (20).

While there is general agreement among guidelines on the importance of skin testing in the drug allergy workup, some discrepancies arise. The authors of the US Practice Parameters (6) consider that immediate DHRs to iodinated radiocontrast media (RCM) are all nonallergic (described as 'anaphylactoid') in nature and do not include skin testing in the management of a patient having experienced a previous DHR to iodinated RCM. This position is challenged by the multicenter study of EAACI-DAIG/ENDA (82), thus encouraging further studies (R4, Evidence C).

Provocation tests

A drug provocation test (DPT), also referred to as drug challenge, graded challenge, or test dosing, is the gold standard for the identification of the drug eliciting a DHR (R5, Evidence C). Whereas all the guidelines agree that the DPT

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comes at the end of the stepwise approach in drug allergy (due to its inherent risks), it holds a slightly different meaning, depending on different guidelines. The authors of the US Practice Parameters (6) consider that the procedure is intended for patients who, after a full evaluation, are unlikely to be allergic to the given drug, that is, DPT performed to demonstrate tolerance to a less likely eliciting drug. The BSACI (8) guideline considers the primary aim of a DPT as a means to exclude DHR, but it can also be used to confirm a diagnosis. The EAACI-DAIG/ENDA guideline (13) addresses its role as a gold standard to establish or exclude the diagnosis of DHRs, but agrees that in some clinical practice situations, it might be more useful to look for safe alternatives instead of testing with a drug which was the definitive cause of the problem. It also mentions the altruistic and scientific value of the DPT (i.e., other patients might benefit from the obtained knowledge), but in these cases (and not in routine practice), approval by an ethical committee is mandatory.

The DPT is independent of the pathogenesis and consequently cannot differentiate between allergic from nonallergic DHRs. It takes individual factors such as the metabolism and genetic disposition of an individual into account. DPTs have the highest sensitivity, but should only be performed under the most rigorous surveillance conditions (Box 6). They are therefore usually restricted to certain specialist centers in which equipment, supplies, and personnel are present to manage serious reactions, and that personnel are well trained and experienced in performing this procedure in properly selected patients (13).

Box 6: Precautions and contraindications of performing DPTs

1. DPTs are contraindicated in noncontrollable and/or severe life-threatening DHRs:
   - **a** Severe cutaneous reactions such as SJS, TEN, DRESS, vasculitis, AGEP
   - **b** Systemic reactions such as DRESS, any internal organ involvement, hematological reactions
   - **c** Anaphylaxis may be tested after risk/benefit analysis
2. DPTs are not indicated when:
   - **a** The offending drug is unlikely to be needed and several structurally unrelated alternatives exist
   - **b** Severe concurrent illness or pregnancy (unless the drug is essential for the concurrent illness or required during pregnancy or delivery)
3. DPTs should be performed under the highest safety conditions:
   - **a** Trained staff: aware of the tests, ready to identify early signs of a positive reaction, and ready to manage a life-threatening reaction
   - **b** With emergency resuscitative equipment available

These tests are particularly required for nonsteroidal anti-inflammatory drugs (23), local anesthetics, antibiotics other than β-lactams, and β-lactams when skin tests are negative. They should be performed after a certain time interval following the DHR (at least 1 month) (R2, Evidence D) using, whenever possible, the same drug as in the initial reaction (13). Sometimes, when the clinical history has a favorable positive predictive value, performing DPT directly with an alternative drug seems more judicious (e.g., a cycloxygenase-2 antagonist is typically tolerated uneventfully in the case of NSAID cross-reactors). Some authors evoke the option of prolonged DPTs (performed at home) in patients (children especially) with nonimmediate and nonsevere reactions (53, 83–85), sometimes without previous skin tests (53, 85). Recommendations have not yet echoed this strategy.

The route of administration depends on the suspected drug, which should in principle be administered in the same way as it was given when the initial reaction occurred. However, all the guidelines agree that the oral route is preferred whenever possible (R6, Evidence D). The precise challenge procedure varies a great deal from one team to another, and guidelines for the performance of DPTs have been proposed (13). A summary of DPT protocols has been reported in retrospective studies of more than one thousand consecutive patients (5, 85).

There is general consensus regarding the contraindications of DPT (see Box 6), with respect to the severity of the initial reaction and the availability of immediate treatment allowing complete and fast recovery (R7, Evidence D). The US Practice Parameters (6) state that rare exceptions to this may exist, such as treatment of a life-threatening illness, in which case the benefit of treatment outweighs the risk of a potentially life-threatening reaction. Arguments against a DPT would be if the offending drug is infrequently used and several alternatives exist. BSACI (8) and EAACI-DAIG/ENDA guidelines (13) mention that severe concurrent illness and pregnancy are generally considered as contraindications to DPT, unless the drug is essential for the concurrent illness (i.e., neurosyphilis and penicillin therapy, although desensitization may be considered first) or required during pregnancy or delivery (i.e., local anesthetics although it is not a classical DPT because subcutaneous injections are followed by a full dose of epidural anesthetic).

Despite the advantage of DPT over all the other test procedures, it has its limitations. First, the patient does not like to be re-exposed to a drug, which he or she considers harmful. Secondly, severe reactions are not amenable to DPTs (Box 6). Finally, a negative test does not prove tolerance to the drug in the future, but rather that there is no DHR at the time of the challenge and to the doses challenged. Nevertheless, a high negative predictive value (NPV) of β-lactam DPT of 94–98% was found in large studies involving both children and adults (86, 87), and most of the reactions reported by patients were both mild and nonimmediate reactions. Similarly, the NPV of DPT with NSAIDs also appears to be high (over 96%) whatever the NSAID (the one negatively tested or an alternative), and none of the false-negative patients described a life-threatening reaction (88). Desensitization by testing, as cause of false-negative DPT, is mentioned by the EAACI-DAIG/ENDA guideline (13) and the US Practice Parameters (6), but no reference to the existing literature is made. Resensitization by testing is addressed by EAACI-DAIG/ENDA (13) and BSACI (8) guidelines, with

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respect to β-lactam allergy. Several studies have observed re-sensitization (i.e., a conversion to skin test positivity) after a negative DPT (followed by full therapeutic courses), with a frequency ranging from 0.9% (89) to 27.9% (90). Although this view is not mentioned in all guidelines and is not widely accepted, one approach might be to retest (2–4 weeks later) the patients who suffered severe immediate reactions and who displayed negative results at the first evaluation, which included a DPT (18) (R8, Evidence D).

Biological tests

It would be highly advantageous to have discriminating biological tests available in order to establish the nature of the culprit agent. This would be helpful particularly for the patient receiving several drugs simultaneously and for severe life-threatening DHRs when skin tests are negative or not possible, and DPT contraindicated (Box 6). However, with some exceptions (e.g., major and minor determinants of penicillin G), the currently available biological methods to diagnose drug allergy lack sensitivity, although they are normally considered to be quite specific (>90%). There are no established methods to predict the immunogenic potential of a drug. It should also be remembered that the results need to be interpreted with caution. A negative test does not exclude the imputability of the drug, while a positive result shows a sensitivity to the drug, but does not reliably confirm its causality (R9, Evidence C).

In vitro assay for drug-specific IgE is not available for many allergenic drugs and, conversely, is offered for many drugs without evidence of validated assays. The demonstration of isolated drug-specific IgE (to penicillins (91), NMBA (92), chymopapain, or tetanus toxoid, for example) does not establish the diagnosis of a drug allergy. However, in conjunction with clinical findings (e.g., typical severe symptoms of rapid onset), an IgE-dependent mechanism can be assumed (particularly if the skin tests to the drug are also positive) (18, 91). Thus, EAACI-DAIG/ENDA advises that skin tests to antibiotics should be performed after IgE testing in severe immediate reactions (22). *In vitro* cross-reactivities between several drugs using quantitative inhibition may also be explored, knowing that its predicted clinical outcome is not fully validated (93). The absence of drug-specific circulating IgE does not rule out a diagnosis of immediate drug allergy (R9, Evidence C). Measurement of drug-specific IgM or IgG is of interest only in cases of drug-induced cytopenia, type III DHRs to vaccines or allergies to dextrans. However, the sensitivity of these tests is unknown and they are not widely available. *In vitro* histamine release from whole blood in the presence of the drug correlates well with skin tests and specific IgE for NMBA, but is not reliable for many other drugs (94). Moreover, it is costly and requires a high level of technical expertise. The usefulness of measuring sulfidopeptide leukotrienes produced *in vitro* by isolated peripheral blood leukocytes after allergenic drug stimulation still requires further validation in both IgE-dependent allergies and non-IgE-dependent DHRs (95). In cases of acute clinical reactions, blood measurements of histamine or tryptase may confirm an involvement of basophils and mast cells whatever the cause of the degranulation (20, 96). Although tests for histamine are not widely commercially available, the test for tryptase is CAP FEIA (20). Basophil activation tests with flow cytometric reading hold promise and are currently undergoing validation for certain drugs (97–99).

For drug-induced type II and III allergic reactions, the following tests can be performed in some centers: Coombs' test, *in vitro* hemolysis test, determination of complement factors and circulating immune complexes. Assays involving T cells (lymphocyte transformation/activation tests) remain the domain of only a few laboratories with experience in DHRs, whereas results from commercial laboratories are generally not reliable (100). Searching for genetic markers may prove helpful, as several strong genetic associations between the expression of a particular HLA allele and the susceptibility to specific forms of DHRs have been recently discovered (Table 3) (50). For the drug abacavir, an association between B*5701 expression and DRESS has prompted the development of predictive testing strategies (47) and labeling changes to drug information sheets. The same is now true for the drug carbamazepine in Han Chinese and the allele B*1502 (101). The positive predictive value of the polymorphisms found so far varies widely (Table 3) and may not always lead to the simple and very successful predictive strategy of abacavir and B*5701 (R10, Evidence A).

Principles of drug allergy management

Acute drug reactions

Anaphylaxis must be treated promptly and appropriately (8), (102, 103), and all suspected drugs must be stopped (102, 104).

When patients experiencing nonanaphylactic reactions are examined during a reaction, the suspected drugs should be stopped if the risks of continuing the administration of the drug outweigh the benefits, and always if danger/severity signs are present (Fig. 2) (62). Indeed, during the acute phase of a severe delayed DHR, the putative drug as well as all 'less necessary' medication should be stopped with no delay in order to improve the prognosis (105).

Supportive treatment for delayed DHRs is not specifically covered by current drug allergy guidelines, but can be found in general reviews (58, 102, 106).

Individual preventive measures

A definitive diagnosis of DHRs allows more targeted preventive measures. Whatever the intensity of the clinical reaction, a state of hypersensitivity is shown toward the particular drug, with the possibility of a more serious reaction in the future. Individual measures include the issue of a written documentation specifying the culprit agent(s), the insertion of the allergy in the tab of the electronic medical record, the drawing up of a list of drugs to avoid, as well as a list of possible alternatives. The lists are only indicative and should be frequently updated (R11, Evidence D). The search for alternatives may require DPTs in a hospital setting when the alternatives belong to the same drug class (R12, Evidence C). The questioning (to elicit

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any history of drug allergy) of every patient by every clinician prior to issuing a prescription is essential from both a medical and a medico-legal point of view (R13, Evidence D). The patient is also asked to make his 'allergies' known prior to all prescriptions and surgical operations.

Preventive measures by premedication (e.g., slow injection and pretreatment with glucocorticosteroids and H1-antihistamines) are useful mainly for nonallergic DHRs (for example to vancomycin, some NMBA, iodinated RCM, and chemotherapy drugs) (R14, Evidence C). Corticosteroids and H1-antihistamines may not reliably prevent IgE-dependent anaphylaxis (103).

Desensitization

Drug desensitization is defined as the induction of a temporary state of clinical unresponsiveness/tolerance to a compound responsible for a DHR (6, 19). Several other terms have been utilized in the past. To encompass classic IgE- and non-IgE-mediated drug desensitization, the Practice Parameters (6) introduced the term 'induction of drug tolerance'. Except for aspirin, the BSACI guidelines only propose desensitization related to an IgE-mediated mechanism (8).

The possibility of desensitization should always be considered when the offending drug is essential and when either no alternatives exist or they are unsatisfactory, as in the following cases (6, 19): sulfonamides in HIV-infected patients (107), quinolone allergies in some patients with cystic fibrosis, serious infections with allergy to β-lactams, antituberculosis drugs, allergy to tetanus vaccine, hemochromatosis with allergy to desferoxamine, taxanes, and platinum salt-based cancer chemotherapeutic agents (108), monoclonal antibodies utilized in several types of hematological and nonhematological neoplasms, aspirin and NSAID hypersensitivity in patients for whom the necessity for these drugs to treat either a cardiac (109) or rheumatic disease is clear.

There are no generally accepted protocols for drug desensitization in immediate DHRs, and guidelines (19) recommend referral to successfully applied existing protocols (R15, Evidence C). For nonimmediate DHRs, the literature is less extensive and more controversial. For EAACI-DAIG/ENDA experts, desensitization in delayed DHRs has to be restricted to uncomplicated exanthemas or fixed drug eruption, due to the unpredictability and limited therapeutic options in severe DHRs (110). Desensitization to aspirin, as a therapeutic intervention for aspirin-exacerbated respiratory disease or nasal polyps, is briefly mentioned by EAACI-DAIG/ENDA guidelines (19), whereas it is recommended in properly selected asthmatic patients by the US Practice Parameter (6), based on certain published data (111) (R16, Evidence D).

General preventive measures

General preventive measures include a declaration to the Committee on Safety of Medicine Reports. The reporting of DHRs leads to public health inquiries and decisions. Some successful examples of proper reports are the rules concerning the use of penicillins during animal feeding, the withdrawal from the market of glafenine, the reformulation of propofol to eliminate the need for Cremophor EL (castor oil) and its replacement with other lipids, and the warnings concerning abacavir, carbamazepine, and nevirapine.

Unmet needs

Unmet clinical needs

Drug hypersensitivity reactions have a significant impact on clinical practice, drug development, and healthcare expenditures. However, epidemiological studies or research to increase understanding and to develop diagnostic and predictive tests has been limited. Epidemiologic risk factors for DHRs are not well characterized and may be influenced by regional/national differences in drug prescriptions and by genetic markers. All drugs can induce DHRs, but the incidence and risk factors for individual drugs remain a major unmet need. As an example, the co-medication of diclofenac with antiulcer medications may present a novel potentiating factor (112), as could the use of over-the-counter pholcodine regarding NMBA-induced anaphylaxis (113). The development of a network to increase the population size from which data on DHRs can be captured would be a major advance. This approach would aim to overcome the major limitation of spontaneous reporting, that is, under-reporting or non-proven case reporting, by engaging with interested clinicians and involving them in the network.

Physicians do not always have the confidence to clarify a suspected reaction. When they do so, and refer the patients to specialized centers, each one of them experiences a limited and partly biased spectrum of the disease (114). Although standardized diagnostic procedures have been published, validation of these clinical tests for all drugs does not exist and multicenter multinational studies are needed for this purpose. Current controversies and disagreements between the guidelines need to be addressed by further research (e.g., skin testing for iodinated RCM, NPV for penicillin skin testing, utility of skin testing for a variety of rare DHRs (steroids, preservatives, etc), and desensitization for delayed DHRs). Standardized diagnostic procedures should be tailored to specific drugs (e.g., β-lactam antibiotics, non-β-lactam antibiotics, NSAIDs, local anesthetics, radiocontrast media, chemotherapeutic agents, vaccines, biological agents), specific manifestations, and specific age groups (children *vs* adults). New diagnostic tools should be developed, in particular for the diagnosis of severe cutaneous DHRs, or DHRs those affecting internal organs including the liver, lungs, kidneys, and bone marrow. The development of tools for skin testing and biological diagnosis is indeed crucial for those cases where DPT is not possible. Standardized and widely accepted drug allergy procedures are crucial for both individual patient genotyping–phenotyping and epidemiological studies. There should be education in medical schools and residencies as well as postgraduate training programs that include aspects of DHR and its treatment, as well as funding for the postgraduate education of specialists.

The impact of DHRs on the quality of life of patients and their cost on the healthcare system, probably substantial, is

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unknown. For this, one must take into account not only the direct costs (treatment of these reactions, hospitalizations, and prolongation of hospitalization), but also the indirect costs (sick leave, invalidity, excessive cost of the choice of alternatives which are not always medically satisfactory and which may lead to specific adverse effects including the induction of microbial resistance and reduced efficacy).

Additionally, most therapeutic recommendations, including new approaches such as drug desensitization, are mostly based on case reports or small case series. As we do not know the natural course of DHRs, it is not clear whether lifelong avoidance is really necessary. Specific research dedicated to the treatment for anaphylaxis should also be supported. DHR research has not been supported for a long time neither by the pharmaceutical industry nor by national programs. There is therefore a clear need for training, standardized criteria, and large, multicenter studies. The establishment of multinational, adequately resourced large DHR databases/registries would enable all observations to be collected, which would in turn facilitate epidemiologic, risk factor, pharmacovigilance, and research analyses.

Unmet basic research needs

The availability of tissue and serum samples from DHR patients is a prerequisite for basic research in the mechanism of DHRs, which may be allergic or nonallergic, with immunological or pharmacological recognition and with the allergenic and genetic determinants mostly unknown.

Evidence over the past ten years suggests that not all drugs need to bind covalently to the MCH in order to induce an immune response. Without undergoing the classical antigen processing and presentation pathway, some drugs may bind directly in a noncovalent fashion to immune receptors, triggering a drug-specific immune reaction (the p-i concept) and promoting an exchange of embedded peptides (38). The functional consequence of this peptide exchange should be further analyzed. This may explain the increased susceptibility of some patients and the frequency of non-IgE-mediated reactions that occur within hours of first exposure. Whether or not this mechanism is also involved in IgE-dependent reactions is not yet known. The prediction of such reactions may also be possible, but has not yet been fully evaluated. The importance here lies in future drug development, the prediction of which molecules may participate in such reactions, and the development of congeners which retain pharmacological activity, but do not cause immune reactions. For most drugs, the allergenic determinants are unknown. The lack of complete understanding of DHR mechanisms probably explains the low sensitivity of many skin tests and *in vitro* assays. There are many examples where existing tests are negative, and this is likely to be related to the use of an inappropriate antigen. Pinpointing the allergenic determinants is of crucial importance; this will allow a better prediction of cross-reactivities and will provide clinicians with tools for skin testing, biomarkers, and biological diagnosis. A better understanding of virus–drug interactions is also crucial. The availability and use of appropriate viral tests are a prerequisite for a proper evaluation of the role of viral infections in DHRs.

Genetic differences can affect individual responses to drugs by influencing the way in which the drug is processed or acts in the body. They may explain why some drugs induce an immune reaction in only a minority of individuals. Genetic variation in the activity of enzymes and carrier substances can be responsible for changes in the absorption, transport, metabolism, and excretion of drugs. Some genetic variants in (i) drug-metabolizing enzymes (pharmacogenetics) interfering with oxidation, conjugation, and hydrolysis (cytochrome P450, glucuronyl transferase, and glutathione S transferase), acetylation; (ii) drug receptors and effector proteins; and (iii) genes controlling the immune response, especially in the MCH molecules (immunogenetics), have been associated with some DHRs (Table 3). This is an emerging field, which holds a great deal of promise for the development of individual predictive tests. However, this will only be possible if we can pool resources to identify and characterize a large cohort of patients with standardized phenotypic definitions to design studies with adequate statistical power (61). This will only be possible through collaboration.

To generate preclinical testing methods to assess the risk of potential DHRs in new drugs, research should encompass the characterization of drug-specific (chemical structure, metabolites, exposure), intrinsic (genetics), and extrinsic (viral infections, other danger signals) risk factors, complemented by preclinical prediction models (2, 115).

Conclusions

The diagnosis of DHRs is often challenging and requires the same careful approach, no matter which specific drug is involved. It remains largely clinical with the help of certain allergy tests that are available for some of the drug classes. Provocation tests are the gold standard for determining current tolerance, but require expertise, carry a certain amount of risk, and are limited to highly specialized centers when used to establish or rule out diagnosis. They cannot be applied for severe cutaneous reactions. New and validated biological tests for diagnosis, available to all clinicians, are necessary in order to improve care for these patients. Recently, HLA typing has provided an important tool for detecting susceptible patient populations. In view of the diagnostic uncertainty of most adverse drug reaction studies (1), the epidemiology of DHRs was not covered in this ICON document. However, understanding the epidemiology of adverse drug reactions in general and DHRs in particular remains an important future research priority. Finally, collaborative basic research into the pathophysiology of DHRs should be intensified in order to better understand this complex set of diseases associated with or induced by drug exposures and mediated (or not) by the immune system.

Conflicts of interest

The authors declare no conflicts of interest for this work.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Drug hypersensitivity questionnaire (adapted from (11) with permission).

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