Curr Treat Options Allergy (2019) 6:27–41
DOI 10.1007/s40521-019-0200-1

Drug Allergy (L Mayorga, Section Editor)

Phenotypes and Natural Evolution of Drug Hypersensitivity

Inmaculada Doña, MD, PhD[1,2,*]
María Salas, MD, PhD[1,3]
Natalia Isabel Pérez-Sánchez, MD[1]
Carmen Moreno-Aguilar, MD, PhD[4,5]
María José Torres, MD, PhD[1,2]

Address
[*,1]Allergy Unit, IBIMA-Regional University Hospital of Malaga-UMA, Malaga Regional University Hospital (Pavillion C, Hospital Civil), Pavillion 6, first floor, Plaza del Hospital Civil, 29009, Malaga, Spain
Email: inmadd@hotmail.com
[2]ARADyAL network RD16/0006/0001, Madrid, Spain
[3]ARADyAL network RD16/0006/0021, Madrid, Spain
[4]Allergy Unit, IMIBIC-Reina Sofia University Hospital, Córdoba, Spain
[5]ARADyAL network RD16/0006/0018, Madrid, Spain

Published online: 8 February 2019

This article is part of the Topical Collection on *Drug Allergy*

Keywords Anaphylaxis · Exanthema · Hypersensitivity · Immediate · Non-immediate · Urticaria

Abstracts

Purpose of review Drug hypersensitivity reactions (DHRs) are adverse effects that clinically resemble allergy. They belong to type B adverse drug reactions, which are dose-independent and unpredictable. Misclassification of DHR may lead to under and/or overdiagnosis, which affects the management of patients, leading to higher risk of suffering an allergic reaction or the use of alternative more-expensive and potentially less-effective drugs. A precise phenotype of DHR is required for a better evaluation and proper management of patients experiencing DHR. The purpose of this review is to summarise the different phenotypes of DHR basing on different criterions.
Recent findings The phenotyping of DHRs is challenging as clinical presentations are heterogeneous, the underlying mechanism is poorly understood and terminology varies among different studies. Moreover, natural evolution may be different depending on the phenotype.
Summary This review summarises the complexity of DHR phenotyping, which can be based on different criterions as chronology, mechanism and clinical symptoms as well as natural evolution. A precise phenotyping of DHR is needed to determine the adequate evaluation and management of patients.

Introduction

The World Health Organization defines an adverse drug reaction (ADR) as any noxious, unintended and undesired response to a drug which occurs at normal doses used in humans for diagnosis, prophylaxis and/or treatment [1]. They represent 3–6% of inpatient admissions [2] and occur in about 10–20% of all hospitalised patients [3, 4]. ADRs can be classified, basing on predictability and drug interaction mechanism, in two types [5]: A-type and B-type reactions. A-type reactions are a consequence of the pharmacological action of the drug, and therefore dose-dependent and predictable [6]. They are the most common ones (70–80% approximately) and include unwanted side effects, secondary events due to pharmacological toxicity or drug interactions. B-type reactions are unrelated to the pharmacological effects of the drug when taken at normal dosage, not dose-dependent and unpredictable [6]. However, in some cases, they may be predictable related to the disease state (e.g. human immunodeficiency virus (HIV) or Epstein–Barr virus (EBV) infection), and in some cases, dose dependence has been shown (e.g. for non-steroidal anti-inflammatory drugs (NSAIDs) and antiepileptic drugs) [7••] (Fig. 1).

B-type reactions are less common, representing only 15% of all ADRs. However, they are often severe, accounting for significant morbidity and mortality [7••, 8]. They include drug hypersensitivity reactions (DHRs), which are defined as objectively reproducible symptoms or signs initiated by exposure to a defined drug at a dose tolerated by normal people. This concept implies an individual predisposition [9, 10]. DHRs affect more than 7% of general population, although both under and overdiagnosis exist [11]. This represents an important public health problem as management of patients can be affected due to the use of alternative more-expensive and potentially less-effective drugs.

DHRs can be immunologically mediated or non-immunologically mediated [7••], being termed allergy and non-allergic reactions, respectively [7••, 8, 12] (Fig. 1).

The establishment of phenotypes in DHR is needed to determine the optimal evaluation and management of patients. DHR phenotyping can be based on different criterions: the underlying mechanism of the reaction, the time interval between the drug administration and the onset of the symptomatology (chronology of reactions) and the clinical manifestations experienced by patients after drug intake (Table 1).

DHR Phenotyping by Underlying Mechanism

As mentioned before, DHRs can be immunologically mediated (allergic reaction) or non-immunologically mediated (non-allergic reaction) [7••]. The allergic reactions can be mediated by all of the types of immunological reactions described by Gell and Coombs [13], but the most common ones are IgE-mediated (type I) and T cell-mediated (type IV), being cytotoxic (type II) and immune complex (type III) reactions to drugs rare [7••]. T cell reactions show a very heterogeneous mechanism and have been sub-classified into type IVa to type IVd reactions according to the regulatory mechanisms, composition of the T cell infiltrate and mediator release [14••].

Non-allergic reactions resemble allergy but no immunological mechanism has been proved. The pathomechanisms of these reactions include [7••]

- Nonspecific mast cell or basophil histamine release (e.g. opiates, radiocontrast media and vancomycin).
- Off-target interactions with Mas-related G protein receptor X2 (MRGPRX2) inducing mast cell activation and degranulation (e.g. quinolones).
- Bradykinin accumulation (e.g. angiotensin-converting enzyme inhibitors)
- Complement activation (e.g. protamine)

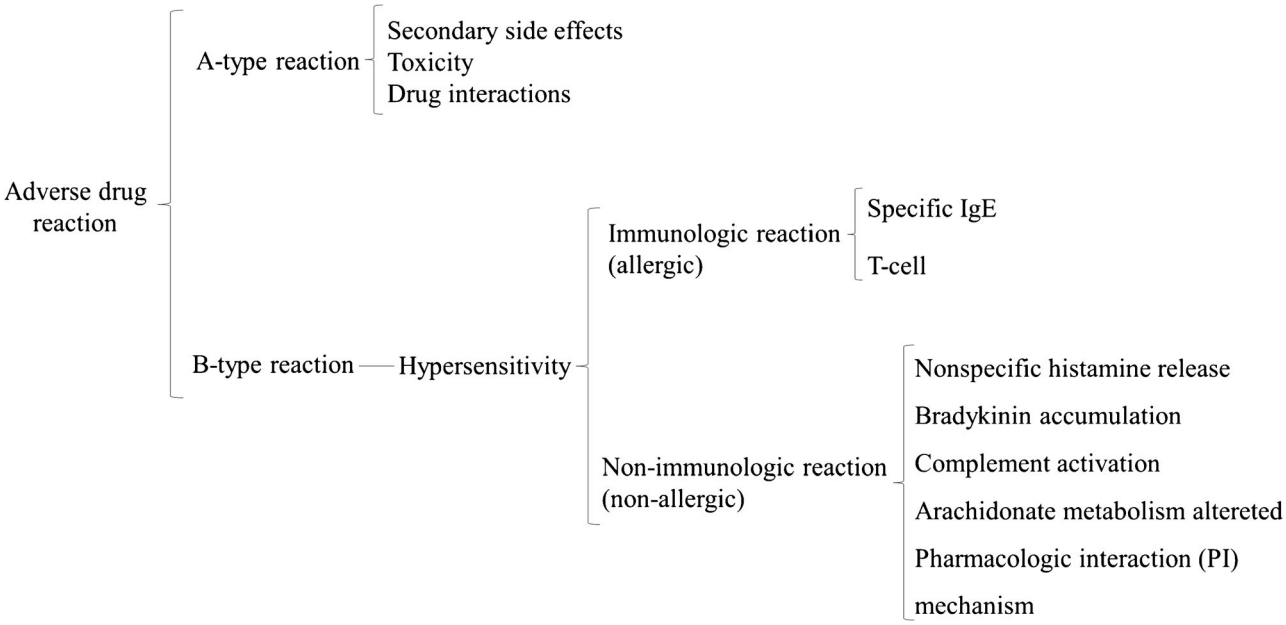

Fig. 1. Classification of ADR

- Possibly an imbalance in the arachidonic acid pathway that could depend on the strength of cyclooxygenase (COX)-1 inhibition by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), independently of the specific chemical structure of the drug. These patients show cross-reactivity with other NSAIDs non-chemically related. This represents the most frequent mechanism involved in NSAIDs-induced hypersensitivity reactions [15] which includes NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD) and NSAID-induced urticaria/angioedema (NIUA) [16].
- Pharmacologic interaction (PI) mechanism. This has been described for non-immediate exanthemas in which an alternative non-allergic HLA-dependent non-covalent mechanism directly activates the T cell receptor as an off-target effect of the drug [14••, 17].

DHR Phenotyping by Chronology

DHR can be classified as immediate and non-immediate according to the time interval between drug intake and onset of reaction [7••, 18]. Initially, immediate reactions were defined as those occurring within 1 h after drug administration and non-immediate as happening any time from 1 h, commonly after many days of treatment [19, 20]. Immediate reactions can be either IgE mediated or non-allergic [21], and non-immediate reactions are usually caused by an allergic type IV reaction or by the PI mechanism [14••].

However, this cut-off point may not reflect sufficiently the pathophysiology of reactions and several considerations must be taken into account. Firstly, reactions can be induced not only by the drug but also by its metabolites, and in

Table 1. Phenotyping DHR base on chronology, underlying mechanism and clinical manifestations induced by drugs

Chronology	Mechanism		Clinical manifestations	Elicitors
Immediate	Non-immunologic	Nonspecific mast cell or basophil histamine release	Urticaria AE Anaphylaxis	Opiates RCM Vancomycin
		Bradykinin accumulation	AE	Angiotensin converting enzyme inhibitors
		Complement activation	Anaphylaxis	Protamine
		Alteration in arachidonate metabolism	Urticaria AE Rhinitis Asthma Anaphylaxis	NSAIDs
	Immunologic	IgE	Urticaria AE Anaphylaxis	Betalactam NMBA Fluoroquinolones NSAIDs PPI
Non-immediate	Immunologic	T-cell	MPE	Betalactams Sulfonamides RCM Antiepileptic drugs
	Non-immunologic	PI reaction	SDRIFE	Aminopenicillins Erythromycin Clindamycin Pseudoephedrine Valacyclovir RCM
			AGEP	Aminopenicillins Cephalosporins Macrolides
			Bullous exanthema (SJS/TEN)	Allopurinol Sulfonamides Oxicam Nevirapine Antiepileptic drugs
			DHIS/DRESS	Antiepileptic drugs Allopurinol Sulfonamides Neviparine Dapsone Vancomycin Minocycline Calcium channel blockers
			Fixed drug eruption	NSAIDs Tetracyclines Sulfonamides Penicillin Phenytoin
			Vasculitis	Betalactams

Table 1. (Continued)

Chronology	Mechanism	Clinical manifestations	Elicitors
			Phenytoin Allopurinol NSAIDs Sulfonamides Diurectis
		Organ-specific	Penicillins Sulfonamides Cytostatic
		Drug-iduced autoimmune disease	TNF-α blockers Interferons Terbinafine

AE angioedema, *AGEP* acute generalised exanthematous pustulosis, *DHIS* drug-induced hypersensitivity syndrome, *DRESS* drug reaction with eosinophilia and systemic symptoms, *SDRIFE* symmetric drug-related intertriginous and flexural exanthema, *SJS* Stevens-Johnson syndrome, *MPE* maculopapular exanthema, *NMBA* neuromuscular-blocking agents, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PPI* proton pump inhibitor, *RCM* radiocontrast media, *TEN* toxic epidermal necrolysis

some cases, they might take some hours to be formed. Consequently, a reaction can start much later than 1 h after drug intake even when specific IgE is involved [22•, 23]. Moreover, cofactors such as exercise and food can accelerate or slow down the onset or progression of a reaction [24]. In addition, the onset of the reaction can be influenced by the route of administration as after parenteral administration of the drug, the reaction can start within a few minutes and after oral intake take up to 1–2 h. Indeed, in the recent International Consensus on Drug Allergy (ICON), this interval has been extended up to 6 h for immediate reactions [7••].

Certain drugs cause mainly immediate or non-immediate reactions, e.g. neuromuscular-blocking agents (NMBA), fluoroquinolones such as moxifloxacin and NSAIDs such as ibuprofen, provoke mainly immediate reactions; and antiepileptic drugs and allopurinol, cause most frequently non-immediate reactions. Other drugs such as betalactam antibiotics and dypirone may lead to both types of reaction.

DHR Phenotyping by Clinical Symptoms

Immediate reactions mostly manifest with urticaria, angioedema, or anaphylaxis [21]. Non-immediate reactions are more heterogeneous but usually affect skin, being the most frequent symptoms exanthemas and delayed urticaria [14••, 25, 26]. Internal organs can be affected either alone or with cutaneous symptoms [7••].

Any drug can induce any clinical symptoms; however, as it is explained below, certain drugs are more likely to be associated with specific types of clinical presentations. It is important to note that the same drug at the same dose and route might produce different clinical manifestations in different subjects [7••].

Urticaria and Angioedema

Urticaria is characterised by painless erythematous wheals associated with intensely pruritus that blanches with pressure [27, 28••]. It is caused by edema and vasodilation in the upper part of the dermis. Lesions are transient and a single wheal at one location usually resolves within 24 h; however, migrating lesions may last several days or weeks [28••].

Angioedema is a swelling that does not itch but induces a feeling of pressure. It is caused by a deeper edema of the dermis and subcutaneous tissues, affecting mainly face, lips, tongue or genitalia [28••]. When the mechanism involves bradykinin, angioedema lasts several days.

Urticaria and angioedema are usually induced by either IgE mediated or non-allergic mechanisms. NSAIDs, betalactam antibiotics, NMBA, quinolones and other antibiotics are the most common elicitors [29, 30], and ACE inhibitors are specifically very common inductors for angioedema, even years after the start of intake.

Considering cross-hypersensitivity to NSAIDs, urticaria/angioedema is the most frequent clinical entity (NIUA) [15]. It is important to identify specific underlying diseases, such as chronic spontaneous urticaria, in which up to one-third of the patients experienced exacerbations after NSAID intake (NECD) [16]. The degree of sensitivity may show fluctuations related to the activity to the underlying chronic urticaria [31•].

Anaphylaxis

It is an immediate reaction involving more than one organ apart from skin (pruritus, urticarial, angioedema, erythema): gastrointestinal tract (nausea, vomiting, abdominal pain and/or diarrhoea), respiratory system (rhinoconjuctivitis, dyspnea, wheezing and/or coughing) and cardiovascular system (drop of blood pressure, tachycardia, fainting and unconsciousness) [32]. Severe respiratory and cardiovascular manifestations may be the primary manifestations in perioperative anaphylaxis [33–35].

Anaphylaxis are considered to be IgE-mediated [32]; however, non-allergic mechanisms have also been described [36••]. Penicillins are considered the main triggers of IgE-mediated anaphylaxis induced by drugs [36••]. Recently, fluoroquinolones such as moxifloxacin and proton pump inhibitors such as lansoprazol have been increasingly reported as eliciting anaphylaxis [37–40]. NMBAs have been classically considered as the group that most frequently causes perioperative anaphylaxis [41]. Among the most common causes of non-allergic anaphylaxis are quinolones, opioids, vancomycin, dextrans, radiocontrast media and NMBA. Recently, it has been reported that patients experiencing cross-hypersensitivity to NSAIDS, in which underlying mechanism is possibly related to an alteration in arachidonate metabolism, can manifest as anaphylaxis [42].

Rhinitis and Asthma

Respiratory symptoms are usually associated to skin symptoms in the context of anaphylaxis as described above. However, respiratory symptoms with no other organs involved can occur in patients with cross-hypersensitivity to NSAIDs (NERD) [16]. They usually have underlying chronic rhinosinusitis complicated by polyp formation, and/or asthma usually preceding the development of

hypersensitivity to NSAIDs [16]. NSAID cross-hypersensitivity is strongly associated with near fatal asthma [43]. Reaction can involve exclusively the upper or lower respiratory tract or both. Nasal symptoms include rhinorrhea, nasal congestion, nasal pruritus and sneezing. Bronchial obstruction induced is manifested as dyspnea, cough and wheezings. These symptoms usually appear between 30 and 180 min after ingestion of NSAID, being the patient cross-reactive to other COX-1 inhibitors non-chemically related [16].

Maculopapular Exanthem

It is the most common manifestation in non-immediate DHR, being in most of cases benign [30]. It occurs in 2% of hospitalised patients [44]. The primary lesions are pruritic erythematous macules and papules, affecting most often trunk and the proximal extremities with diffuse and symmetric distribution. Mucous membranes are normally not involved. It usually appears several days (up to 2–3 weeks) after drug exposure; however, in a sensitised subject symptoms already may appear about 6 h after. Desquamation is common in the later clearing phase. It is of note that MPE may be the first indication of a more severe hypersensitivity reaction, such as a drug-induced-hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DHIS/DRESS). Moreover, it is important to make a differential diagnosis of some skin or autoimmune diseases that can be exanthematic in their appearance.

Exanthemas are caused by T cell (type IV) or by the PI mechanism [14••]. Common elicitors are betalactams, sulfonamides, radiocontrast media and antiepileptic drugs.

Symmetric Drug-Related Intertriginous and Flexural Exanthema

It is a rare DHR that typically develops within hours or days after exposure to drugs. The clinical manifestation is an erythema with a characteristic distribution pattern, resembling the shape of a "V", involving perigenital, perianal and inguinal areas. Other flexural areas such as axillae, knees or elbows are affected [46]. It usually evolves to desquamation. Few pustules may be observed and there may be an overlap with acute generalised exanthematous pustulosis. Systemic symptoms are rarely observed. Main elicitors are aminopenicillins, erythromycin and clindamycin [47]. Other drugs reported implicated in SDRIFE are pseudoephedrine, valacyclovir and iodinated contrast media [48].

Acute Generalised Exanthematous Pustulosis

It is a rare non-immediate DHR characterised by disseminated small non-follicular subepidermal and intraepidermal sterile pustules on a widespread confluating erythema [28••, 49•, 50, 51]. The eruption begins on the face or intertriginous area and within 24 h disseminates diffusely, although they have been reported even up to 3 weeks after drug exposure [52]. Palms and soles are rarely affected and at least one mucous membrane is involved in 20–25% of cases [45••]. The pustular eruption is followed by desquamation. Several pustules may confluent resulting in a superficial bullous resembling Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). It is often associated to fever and leukocytosis with neutrophilia and mild eosinophilia [45••, 53].

The pathologic mechanism has not been extensively studied, although a T cell-mediated reaction involving $CD4^+$ T cells, cytotoxic $CD8^+$ T cells and inflammatory chemokines and cytokines such as CXCL18 which leads to the accumulation of neutrophils in tissues has been proposed [54, 55].

It can occur after an infection or after drug administration, being the most frequent ones elicitors aminopenicillins, cephalosporins and macrolides [50, 53].

Bullous Exanthems

They are the most severe non-immediate DHR, with a high mortality. They comprise SJS/TEN [56]. It is rare, with an incidence estimated at 2–7 cases per million persons per years, with SJS occurring three times as often as TEN [57] and incidence being 100-fold higher in human immunodeficiency virus infection [58]. They start within the first 4–6 weeks of treatment with a febrile prodrome preceding the cutaneous eruption. Small blisters arise on purple macules and spread usually to the trunk. Bullous lesions develop fast on the skin and mucous membranes (oral, genital, conjunctival, perianal), causing pain. Atypical flat multiform target lesions often appear and patients usually develop fever. SJS and TEN are considered to be variants of the same disease, distinguished by the percentage of the total corporal surface affected. SJS is the less severe form, with confluated bullae leading to detachment of the skin in less than 10% of the total body surface in SJS, 10–30% in SJS/TEN overlap and > 30% in TEN. Both conditions present extensive necrosis and epidermiolysis, with positive Nicholsky sign, due to keratinocyte necrosis [28••, 45••, 59]. SJS and TEN are differentiated from erythema exsudativum multiforme by the absence of typical target lesions. Erythema exsudativum multiforme is mainly caused by viral infections, whereas SJS and TEN are in the majority of cases caused by drug, being allopurinol, sulfonamides, oxicam, nevirapine and antiepileptics the most frequently involved [49•, 60, 61].

Drug-Induced Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms

It is a rare, potentially life-threatening non-immediate reaction presenting as a rash with the involvement of internal organs [62]. It typically takes 2–6 weeks after the start of the drug intake to develop with an erythematous central facial swelling. This quickly progresses to a diffuse rash that may vary from typical macules and papules to multiform, eczematous or puntiform lesions. Fever, malaise and lymphadenopathy are mostly present as well as eosinophilia, leukocytosis and atypical lymphocytes in peripheral blood [45••, 63]. Agranulocytosis and anaemia may occur. Liver function impairment is generally mild and transient, but some patients develop a potentially life-threatening hepatitis. Other internal organs may be affected, resulting in interstitial nephritis, pericarditis and pulmonary infiltrates. Arthritis and myositis are less frequent. After the discontinuation of the drug involved, further flares commonly appear. This has been linked to herpes virus reactivation, which is considered specific to DRESS [64].

Common elicitors are antiepileptics, allopurinol, sulfonamides and neviparine. Other drugs associated to DRESS have been reported, including

dapsone, vancomycin, lamotrigine, minocycline and calcium channel blockers [63, 65, 66].

Fixed drug eruption

It is a non-immediate DHR characterised by erythematous to violatious well-demarcated macules, which may become bullous in the centre. This lesion always recurs in the same location within several hours or up to 2 days upon re-exposure to the culprit drug. Most often, it affects face, mouth and genital and acral areas [67, 68]. Typically, it leaves a residual hyperpigmentation. Multilocular fixed drug eruptions mimicking SJS/TEN may occur, but patients with fixed drug eruptions have no systemic symptoms, the lesions are well demarcated and the mucous membranes are rarely or only minimally involved [69].

Drugs commonly implicated include NSAIDs, tetracyclines, sulfonamides, penicillin and phenytoin.

Vasculitis

Vasculitis is a typical manifestation in dermatology but rare as a non-immediate reaction induced by drug. It is a type III hypersensitivity reaction characterised by leukocytoclastic vasculitis and it clinically manifests by palpable purpuric macules and papules predominantly in legs. In severe cases, the purpura can progress to form blisters and deep ulcers with hemorrhagia. Fever, arthralgias, lymphadenopathy, headaches, abdominal pain, hematuria or peripherial neuropathy may be also present [28••, 45••]. Clinical manifestations take 1–2 weeks to develop after drug exposure, being the ones most often implicated penicillins, cephalosporins, phenytoin, allopurinol, NSAIDs, sulfonamides and diurectis [70, 71].

Organ-specific and miscellaneous drug reactions

Fever, associated to headaches and myalgias, can be induced by drugs [72], being reported antibiotics, sulfonamides and cytostatics as elicitors.

IgG-mediated cytopenia or cytotoxic immune cytopenia can occur and may manifest as hemolytic anaemia, leukocytopenia or thrombocytopenia.

Internal organ affectations can be involved, being described drug-induced intersticial nephritis and hepatitis [73]. Lymphadenopathy, pneumonitis, pancreatitis, myocarditis, thyroiditis and gastrointestinal tract involvement have also been described.

Fever, arthralgias, macular or urticarial exanthemas and lymphadenopathy are typical for serum sickness syndrome. The most common elicitors are penicillins and cephalosporins (particularly cephaclor) [74].

Drug-Induced Autoimmune Disease

Drugs can induce autoimmune responses such as lupus erythematosus characterised by the sudden onset of fever, malaise, myalgia, arthralgia and erythematous macules on light-exposed skin with atrophy or scaling resembling typical lupus erythematosus lesions [75]. Antinuclear antibodies are commonly positive and directed against nuclear histone H2B for drug-induced systemic lupus, whereas anti-Ro/SSA and anti-La/SSB are more common in cutaneous drug-induced lupus. Reported elicitors of the drug-induced lupus are TNF-α blockers, interferons and terbinfine [76].

Natural Evolution

Although few prospective studies have been carried out to analyse the natural history of DHR, data available suggest that natural evolution differs according to the underlying mechanism involved in DHR.

IgE-Mediated DHRs

IgE antibody response has been reported not to be permanent over time and a loss of sensitivity may occur if the patient is not re-exposed to the drug [77••, 78••, 79, 80, 81••].

Data concerning specific IgE determined by immunoassay have been reported with betalactams [77••, 79] and clorhexidine [80], with differences in the number of patients assessed, the surveillance period and the methods used. Considering betalactams, specific IgE to penicillin and/or amoxicillin in sera was not detected in 50% of patients 3 years after the reactions and in no patients after 4 years [77••]. Regarding clorhexidine, the IgE determination in sera has been recommended within 6 months after the reaction or earlier due to the decline levels [80]. Moreover, the repeat re-exposition to betalactams and chlorhexidine has been related to the maintenance of an IgE level above normal, not showing the gradual decline seen in other patients, presumably due to continued stimulation of IgE production [80, 82].

Data concerning basophil activation test (BAT) show that 60% of the patients who were BAT positive to dipyrone became negative after 6 months of follow-up [78••] whereas negativization with betalactams took longer, since 60% of negativizations occurred after 18 months [77••]. Moreover, the rate of negativization of both BAT and specific IgE determined by immunoassay (radioallergosorbent test, RAST) was different depending on the betalactam involved in the reaction, being faster for amoxicillin in BAT compared to RAST and with no differences for benzylpenicillin comparing both tests [77••]. However, no differences in the negativization rate were found comparing the different clinical manifestations for both tests [77••, 80].

Longer-term rates of negativization have also been found with NMBA in BAT, in which 85% of patients gave positive results within 3 years of the reaction but decreased to 47% after 4 years [81••].

Resensitization studies indicate that some patients with a previous positive history and negatively tested may become positive after therapeutic administration [18]. Therefore, experts recommend lifelong avoidance of the drug and potential cross-reactive drugs in the cases of drug-induced anaphylaxis [7]. However, in selective responders to amoxicillin, patients tolerate other penicillins and are not at increased risk of allergies upon exposure to closely related penicillins [83].

T Cell-Mediated DHRs

Contrary to IgE-mediated responses, evidence suggests that delayed hypersensitivity to betalactams, particularly to aminopenicillins, is long-lasting [84–86]. Indeed, patch tests have been reported to remain positive up to 11 years after the disappearance of cloxacillin-induced DRESS [87].

Non-allergic Reactions

For non-allergic reactions, there are available data about natural history concerning cross-hypersensitivity to NSAIDs. In patients with NIUA, up to one in three patients have been reported to develop chronic spontaneous urticaria over time [88]. However, recently, it has been found that this proportion is similar to the one for patients with IgE-mediated reactions to NSAIDs and healthy subjects [89]. Recent data show that tolerance to NSAIDs can occur in 60% of the patients with NIUA within 6 years after their last reaction. This process seems to be influenced by atopy and type of clinical reaction [90••]. However, in patients with NECD, aspirin hypersensitivity remains present in about two-thirds of patients after 4 years [31•].

Conclusions

Misclassification of DHR may affect proper evaluation of patients and treatment options, resulting in the use of more-expensive or less-effective drugs. Therefore, it is necessary to implement adequate and precise phenotypes in order to improve patient management. However, this is very complex and can be based on different criterions. A better knowledge of the mechanisms involved in DHR as well as the use of consensual terminology would help to better establish phenotypes in DHR.

Funding Information

I Doña holds a Juan Rodes research contract (JR15/00036) and NI Pérez-Sánchez holds a Rio Hortega contract (CM17/00141), both from the Carlos III National Health Institute, Spanish Ministry of Economy and Competitiveness (grants cofounded by European Social Fund, ESF).

Compliance with Ethical Standards

Conflict of Interest
Inmaculada Doña, María Salas, Natalia Isabel Pérez-Sánchez, Carmen Moreno-Aguilar and María José Torres declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. International drug monitoring. The role of national centres Report of a WHO meeting. World Health Organ Tech Rep Ser. 1972;498:1–25.
2. Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. Ann Pharmacother. 2008;42(7):1017–25.
3. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol. 2005;5(4):309–16.
4. Hakkarainen KM, Hedna K, Petzold M, Hägg S. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions–a meta-analysis. PLoS One. 2012;7(3):e33236.
5. Rawlins MD, T.J., *Pathogenesis of adverse drug reactions*, in *Textbook of adverse drug reactions*, D. DM, Editor. 1977, Oxford University Press: Oxford. p. 10.
6. Bernstein JA. Nonimmunologic adverse drug reactions. How to recognize and categorize some common reactions. Postgrad Med. 1995;98(1):120–2 **125-6**.
7. •• Demoly P, et al. International consensus on drug allergy. Allergy. 2014;69(4):420–37

In this position paper, the International Collaboration in Asthma, Allergy and Immunology (iCAALL) critically reviewed guidelines and consensus documents on DHR and compiled an International CONsensus (ICON) providing recommendations on drug allergy.

8. Joint Task Force on Practice, P, et al. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010;105(4):259–73.
9. Bernstein JA. Allergic drug reactions. How to minimize the risks. Postgrad Med. 1995;98(2):159–60 163-6.
10. deShazo RD, Kemp SF. Allergic reactions to drugs and biologic agents. JAMA. 1997;278(22):1895–906.
11. Gomes E, Cardoso MF, Praca F, Gomes L, Marino E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. Clin Exp Allergy. 2004;34(10):1597–601.
12. Johansson SG, et al. Revised nomenclature for allergy for global use: report of the nomenclature review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113(5):832–6.
13. Coombs PR, G.P., *Classification of allergic reactions responsible for clinical hypersensitivity and disease.* . In: Gell RR, editor. Clinical aspects of immunology. Oxford (UK): Oxford University Pess;, 1968: p. 575–96.
14. •• Pichler WJ. Delayed drug hypersensitivity reactions. Ann Intern Med. 2003;139(8):683–93

In this review, concepts of the role of T-cells in various drug-induced hypersensitivity diseases are described.

15. Doña I, Blanca-López N, Cornejo-García JA, Torres MJ, Laguna JJ, Fernández J, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. Clin Exp Allergy. 2011;41(1):86–95.
16. •• Kowalski ML, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy. 2013;68(10):1219–32

This position paper provides a classification of reactions induced by NSAIDs based on clinical manifestations and suspected mechanism.

17. Pichler WJ, Beeler A, Keller M, Lerch M, Posadas S, Schmid D, et al. Pharmacological interaction of drugs with immune receptors: the p-i concept. Allergol Int. 2006;55(1):17–25.
18. Blanca M, Romano A, Torres MJ, Férnandez J, Mayorga C, Rodriguez J, et al. Update on the evaluation of hypersensitivity reactions to betalactams. Allergy. 2009;64(2):183–93.
19. Torres MJ, Blanca M, Fernandez J, Romano A, Weck A, Aberer W, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. Allergy. 2003;58(10):961–72.
20. Romano A, Blanca M, Torres MJ, Bircher A, Aberer W, Brockow K, et al. Diagnosis of nonimmediate reactions to beta-lactam antibiotics. Allergy. 2004;59(11):1153–60.
21. Limsuwan T, Demoly P. Acute symptoms of drug hypersensitivity (urticaria, angioedema, anaphylaxis, anaphylactic shock). Med Clin North Am. 2010;94(4):691–710 **x**.
22. • Blanca-Lopez N, et al. Allergic reactions to Metamizole: immediate and delayed responses. Int Arch Allergy Immunol. 2016;169(4):223–30

In this paper, a clinical characterization of allergic reactions to metamizol is performed, describing the symptoms induced by the drug. In this paper, the authors also discuss about the time interval between the drug intake and the onset of the reaction.

23. Ariza A, García-Martín E, Salas M, Montañez MI, Mayorga C, Blanca-Lopez N, et al. Pyrazolones metabolites are relevant for identifying selective anaphylaxis to metamizole. Sci Rep. 2016;6:23845.
24. Bircher AJ, Scherer Hofmeier K. Drug hypersensitivity reactions: inconsistency in the use of the classification of immediate and nonimmediate reactions. J Allergy Clin Immunol. 2012;129(1):263–4 author reply 265-6.
25. Mockenhaupt M. Severe drug-induced skin reactions: clinical pattern, diagnostics and therapy. J Dtsch Dermatol Ges. 2009;7(2):142–60 quiz 161-2.
26. Bircher AJ, Scherer K. Delayed cutaneous manifestations of drug hypersensitivity. Med Clin North Am. 2010;94(4):711–25 **x**.

27. Bircher AJ. Uncomplicated drug-induced disseminated exanthemas. Chem Immunol Allergy. 2012;97:79–97.
28.•• Zalewska-Janowska A, Spiewak R, Kowalski ML. Cutaneous manifestation of drug allergy and hypersensitivity. Immunol Allergy Clin N Am. 2017;37(1):165–81
In this review, the clinical characteristic and mechanisms involved in allergic and non-allergic hypersensitivity reactions to drugs are summarized.
29. Schnyder B. Approach to the patient with drug allergy. Med Clin North Am. 2010;94(4):665–79 **xv**.
30. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. Toxicology. 2005;209(2):123–9.
31.• Setkowicz M, et al. Clinical course and urinary eicosanoids in patients with aspirin-induced urticaria followed up for 4 years. J Allergy Clin Immunol. 2009;123(1):174–8
In this study, it is analyzed the natural evolution of aspirin hypersensitivity in patients with NSAIDs-induced urticaria and underlying chronic spontaneous urticaria (NECD).
32. Khan DA, Solensky R. Drug allergy. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S126–37.
33. Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reactions during anesthesia in Australia. Ann Fr Anesth Reanim. 1993;12(2):97–104.
34. Mertes PM, et al. Perioperative anaphylaxis. Med Clin North Am. 2010;94(4):761–89 xi.
35. Laguna JJ, Archilla J, Doña I, Corominas M, Gastaminza G, Mayorga C, et al. Practical guidelines for perioperative hypersensitivity reactions. J Investig Allergol Clin Immunol. 2018;28(4):216–32.
36.•• Montanez MI, et al. Epidemiology, mechanisms, and diagnosis of drug-induced anaphylaxis. Front Immunol. 2017;8:614
This review focuses in mechanisms involved and management of anaphylaxis induced by drugs.
37. Ewan PW, Dugué P, Mirakian R, Dixon TA, Harper JN, Nasser SM, et al. BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia. Clin Exp Allergy. 2010;40(1):15–31.
38. Bonadonna P, Lombardo C, Bortolami O, Bircher A, Scherer K, Barbaud A, et al. Hypersensitivity to proton pump inhibitors: diagnostic accuracy of skin tests compared to oral provocation test. J Allergy Clin Immunol. 2012;130(2):547–9.
39. Blanca-Lopez N, et al. Hypersensitivity reactions to fluoroquinolones: analysis of the factors involved. Clin Exp Allergy. 2013;43(5):560–7.
40. Doña I, et al. Trends in hypersensitivity drug reactions: more drugs, more response patterns *more heterogeneity*. J Investig Allergol Clin Immunol. 2014;24(3):143–53 quiz 1 p following 153.
41. Caubet JC, Kaiser L, Lemaître B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. J Allergy Clin Immunol. 2011;127(1):218–22.
42. Dona I, et al. NSAIDs-hypersensitivity often induces a blended reaction pattern involving multiple organs. Sci Rep. 2018;8(1):16710.
43. Yoshimine F, et al. Contribution of aspirin-intolerant asthma to near fatal asthma based on a questionnaire survey in Niigata prefecture, Japan. Respirology. 2005;10(4):477–84.
44. Fiszenson-Albala F, Auzerie V, Mahe E, Farinotti R, Durand-Stocco C, Crickx B, et al. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. Br J Dermatol. 2003;149(5):1018–22.
45.•• Peter JG, et al. Severe delayed cutaneous and systemic reactions to drugs: a global perspective on the science and art of current practice. J Allergy Clin Immunol Pract. 2017;5(3):547–63
In this review, the clinical features, underlying mechanisms and management of severe delayed reactions to drugs are described.
46. Hausermann P, Bircher AJ. SDRIFE - another acronym for a distinct cutaneous drug exanthema: do we really need it? Dermatology. 2007;214(1):1–2.
47. Hausermann P, Harr T, Bircher AJ. Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome? Contact Dermatitis. 2004;51(5–6):297–310.
48. Thyssen JP, Maibach HI. Drug-elicited systemic allergic (contact) dermatitis–update and possible pathomechanisms. Contact Dermatitis. 2008;59(4):195–202.
49.• Paulmann M, Mockenhaupt M. Severe drug-induced skin reactions: clinical features, diagnosis, etiology, and therapy. J Dtsch Dermatol Ges. 2015;13(7):625–45
In this review, clinical features and drug involved in severe drug-induced skin reactions are described.
50. Sidoroff A, Dunant A, Viboud C, Halevy S, Bavinck JNB, Naldi L, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). Br J Dermatol. 2007;157(5):989–96.
51. Halevy S. Acute generalized exanthematous pustulosis. Curr Opin Allergy Clin Immunol. 2009;9(4):322–8.
52. Momin SB, del Rosso J, Michaels B, Mobini N. Acute generalized exanthematous pustulosis: an enigmatic drug-induced reaction. Cutis. 2009;83(6):291–8.
53. Roujeau JC, et al. Acute generalized exanthematous pustulosis. Analysis of 63 cases. Arch Dermatol. 1991;127(9):1333–8.
54. Britschgi M, Steiner UC, Schmid S, Depta JPH, Senti G, Bircher A, et al. T-cell involvement in drug-induced acute generalized exanthematous pustulosis. J Clin Invest. 2001;107(11):1433–41.
55. Schmid S, Kuechler PC, Britschgi M, Steiner UC, Yawalkar N, Limat A, et al. Acute generalized exanthematous pustulosis: role of cytotoxic T cells in pustule formation. Am J Pathol. 2002;161(6):2079–86.
56. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol. 1993;129(1):92–6.
57. Chan HL, Stern RS, Arndt KA, Langlois J, Jick SS, Jick H, et al. The incidence of erythema multiforme, Stevens-

Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol. 1990;126(1):43–7.

58. Mittmann N, Knowles SR, Koo M, Shear NH, Rachlis A, Rourke SB. Incidence of toxic epidermal necrolysis and Stevens-Johnson syndrome in an HIV cohort: an observational, retrospective case series study. Am J Clin Dermatol. 2012;13(1):49–54.
59. Roujeau JC. Stevens-Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. J Dermatol. 1997;24(11):726–9.
60. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bavinck JNB, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol. 2008;128(1):35–44.
61. Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bouwes Bavinck JN, Sidoroff A, et al. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol. 2008;58(1):25–32.
62. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol. 2013;169(5):1071–80.
63. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007;156(3):609–11.
64. Kano Y, Hiraharas K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multiorgan reaction in the same sequential order as in graft-versus-host disease. Br J Dermatol. 2006;155(2):301–6.
65. Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. Neurology. 1997;49(2):542–6.
66. Guberman AH, Besag FMC, Brodie MJ, Dooley JM, Duchowny MS, Pellock JM, et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. Epilepsia. 1999;40(7):985–91.
67. Brahimi N, Routier E, Raison-Peyron N, Tronquoy AF, Pouget-Jasson C, Amarger S, et al. A three-year-analysis of fixed drug eruptions in hospital settings in France. Eur J Dermatol. 2010;20(4):461–4.
68. Khaled A, Kharfi M, Ben Hamida M, el Fekih N, el Aidli S, Zeglaoui F, et al. Cutaneous adverse drug reactions in children. A series of 90 cases. Tunis Med. 2012;90(1):45–50.
69. Lipowicz S, Sekula P, Ingen-Housz-Oro S, Liss Y, Sassolas B, Dunant A, et al. Prognosis of generalized bullous fixed drug eruption: comparison with Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol. 2013;168(4):726–32.
70. Calabrese LH, Duna GF. Drug-induced vasculitis. Curr Opin Rheumatol. 1996;8(1):34–40.
71. Martinez-Taboada VM, et al. Clinical features and outcome of 95 patients with hypersensitivity vasculitis. Am J Med. 1997;102(2):186–91.
72. Johnson DH, Cunha BA. Drug fever. Infect Dis Clin N Am. 1996;10(1):85–91.
73. Podevin P, Biour M. Drug-induced "allergic hepatitis". Clin Rev Allergy Immunol. 1995;13(3):223–44.
74. Parra FM, Igea JM, Martin JA, Alonso MD, Lezaun A, Sainz T. Serum sickness-like syndrome associated with cefaclor therapy. Allergy. 1992;47(4 Pt 2):439–40.
75. Rubin RL. Drug-induced lupus. Expert Opin Drug Saf. 2015;14(3):361–78.
76. Lowe GC, Henderson CL, Grau RH, Hansen CB, Sontheimer RD. A systematic review of drug-induced subacute cutaneous lupus erythematosus. Br J Dermatol. 2011;164(3):465–72.
77.•• Fernandez TD, et al. Negativization rates of IgE radioimmunoassay and basophil activation test in immediate reactions to penicillins. Allergy. 2009;64(2):242–8

In this study, it is analyzed the loss of sensitivity of radioimmunoassay and BAT in patients reporting immediate allergic reactions to penicillin.

78.•• Gomez E, et al. Immunoglobulin E-mediated immediate allergic reactions to dipyrone: value of basophil activation test in the identification of patients. Clin Exp Allergy. 2009;39(8):1217–24

In this study, it is analyzed the negativization rate of BAT in patients reporting immediate allergic reactions to dipyrone.

79. Torres MJ, Padial A, Mayorga C, Fernandez T, Sanchez-Sabate E, Cornejo-Garcia JA, et al. The diagnostic interpretation of basophil activation test in immediate allergic reactions to betalactams. Clin Exp Allergy. 2004;34(11):1768–75.
80. Garvey LH, Krøigaard M, Poulsen LK, Skov PS, Mosbech H, Venemalm L, et al. IgE-mediated allergy to chlorhexidine. J Allergy Clin Immunol. 2007;120(2):409–15.
81.•• Kvedariene V, et al. Diagnosis of neuromuscular blocking agent hypersensitivity reactions using cytofluorimetric analysis of basophils. Allergy. 2006;61(3):311–5

In this study, it is analyzed the role of BAT in the diagnosis of immediate allergic reactions to NMBA, including the negativization rate over time.

82. Antunez C, Fernandez T, Blanca-Lopez N, Torres MJ, Mayorga C, Canto G, et al. IgE antibodies to betalactams: relationship between the triggering hapten and the specificity of the immune response. Allergy. 2006;61(8):940–6.
83. Fernandez T, Torres MJ, R-Pena R, Fuentes MS, Robles S, Mayorga C, et al. Decrease of selective immunoglobulin E response to amoxicillin despite repeated administration of benzylpenicillin and penicillin V. Clin Exp Allergy. 2005;35(12):1645–50.

84. Romano A, et al. Evaluation of adverse cutaneous reactions to aminopenicillins with emphasis on those manifested by maculopapular rashes. Allergy. 1995;50(2):113–8.
85. Romano A, Quaratino D, di Fonso M, Papa G, Venuti A, Gasbarrini G. A diagnostic protocol for evaluating nonimmediate reactions to aminopenicillins. J Allergy Clin Immunol. 1999;103(6):1186–90.
86. Romano A, Viola M, Mondino C, Pettinato R, di Fonso M, Papa G, et al. Diagnosing nonimmediate reactions to penicillins by in vivo tests. Int Arch Allergy Immunol. 2002;129(2):169–74.
87. Barbaud A, Collet E, Milpied B, Assier H, Staumont D, Avenel-Audran M, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. Br J Dermatol. 2013;168(3):555–62.
88. Asero R. Intolerance to nonsteroidal anti-inflammatory drugs might precede by years the onset of chronic urticaria. J Allergy Clin Immunol. 2003;111(5):1095–8.
89. Doña I, Blanca-López N, Torres MJ, Gómez F, Fernández J, Zambonino MA, et al. NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. Allergy. 2014;69(4):438–44.
90.•• Doña I, et al. Natural evolution in patients with nonsteroidal anti-inflammatory drug-induced urticaria/angioedema. Allergy. 2017;72(9):1346–55
In this study, it is analyzed the natural evolution of cross-hypersensitivity to NSAIDs manifested as urtiaria/angioedema (NIUA).