

International Consensus (ICON) on Drug Allergy

SUMMARY

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Allergy 2014; 69: 420–437

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Thanks to Dr Rik Schrijvers and Dr Anca Mirela Chiriac, 2 EAACI JMAs and FS recipients, for their precious help for this extensive summary.

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PREFACE

Drug hypersensitivity reactions (DHRs) comprise all drug reactions resembling allergy. DHRs constitute 15% of all adverse drug reactions affecting more than 7% of the general population. DHRs can be allergic or non-allergic with immunologically-mediated DHRs being named **drug allergies**. They are typically unpredictable, necessitate treatment changes and can potentially be life-threatening. A definitive diagnosis enabling the institution of adequate treatment options and proper preventive measures typically requires a complete drug allergy work up. Several guidelines and consensus statements on general or specific drug class-induced DHRs are available to support medical decisions on drug allergy; however, a standardized systematic approach for the diagnosis and management of DHRs is still a major challenge. The **International Collaboration in Asthma, Allergy and Immunology** (iCAALL), formed in 2012 by **EAACI**, **AAAAI**, **ACAAI**, and **WAO**, addresses this unmet need in this **International Consensus (ICON) on Drug Allergy** document. The purpose of this document is to:

- Highlight the key messages that are common to many existing guidelines.
- Critically review and comment on differences, thus providing a concise reference.

DEFINITIONS

- Drug hypersensitivity reactions (DHRs) are adverse effects of drugs that clinically resemble allergic reactions.
- Drug allergies are DHRs for which a definite immunologic mechanism is demonstrated.
- For general communication, when a drug reaction is suspected, DHR is the preferred term.

CLASSIFICATIONS

A generally accepted classification of DHRs is useful for management, comparison of studies and validation of diagnostic techniques.

Clinically: DHRs are classified as immediate or non-immediate/delayed depending on their onset during treatment (Figure 1).

Immediate DHRs occur within 1–6 hours after the last drug administration (typically within the first hour following the first administration of a new course of treatment). Typical symptoms include urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastro-intestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), anaphylaxis or anaphylactic shock. Immediate DHRs are possibly induced by an IgE-mediated mechanism.

The term “anaphylactoid” reactions, considered previously in case of non-IgE-dependent DHRs mimicking anaphylaxis, is abandoned in certain guidelines and the term “non-allergic” DHRs is preferred.

Non-immediate DHRs occur at any time as from 1 hour after the initial drug administration. Common symptoms include maculopapular exanthems and delayed urticaria. Often, a delayed T-cell-dependent type of allergic mechanism is associated.

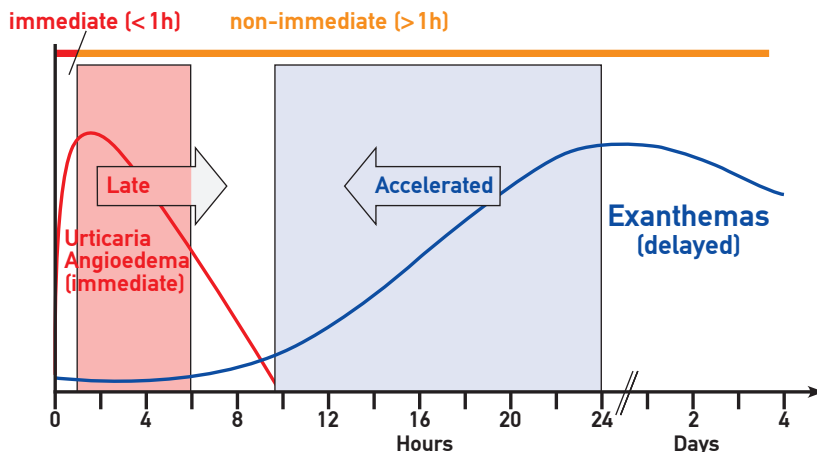


Figure 1 - Chronology of DHRs. Setting the cut-off at 1 hour (between immediate and non-immediate reactions), may not sufficiently reflect the extension of the pathophysiologically determined immediate-type reactions up to 6 hours (Late) and the delayed-type clinical manifestations occasionally starting as early as 8 to 12 hours (Accelerated). However, this approach facilitates the comparison of studies and should help to enhance and validate diagnostic techniques.

The administration route, drug metabolites, or presence of co-factors or co-prescribed drugs altering DHRs' onset or progression must be taken into account when considering this classification.

Mechanistically: DHRs can be defined as allergic (Table) and non-allergic:

Type	Type of immune response	Pathophysiology	Clinical symptoms	Typical chronology of the reaction
I	IgE	Mast cell and basophil degranulation	Anaphylactic shock, Angio-oedema, Urticaria, Bronchospasm	Within 1 to 6 hours 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	Maculo-papular 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	Maculo-papular 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)

DRESS, Drug reaction with Eosinophilia and Systemic Symptoms; SJS, Stevens-Johnson Syndrome; TEN, Toxic Epidermal Necrolysis; MPE, maculo-papular exanthema.

PATHOPHYSIOLOGY

Drug allergies are adverse reactions whereby antibodies and/or activated T-cells are directed against the drugs or against one of its metabolites.

- **Immediate allergic DHRs** develop as a result of IgE production by antigen-specific B-lymphocytes after sensitization. Following subsequent drug exposure, the antigen (presumably a hapten-protein complex) cross-links the IgE bound to mast cells and basophils, stimulating the release of pre-formed mediators (e.g., histamine, tryptase, some cytokines like TNF α) and the production of new mediators (e.g., leukotrienes, prostaglandins, kinins, other cytokines).
- **Non-immediate allergic DHRs** are mostly mediated through the actions of T-lymphocytes.

According to the hapten hypothesis, in order to stimulate a reaction, a drug should act as a hapten and bind irreversibly to proteins, generating antigens. An alternative hypothesis, the pharmacological interaction with immune receptor (p-i) concept, suggests that drugs might interact directly with immune receptors (T-cell receptors or HLA-molecules) and activate T-cells by altering the MHC-peptide groove (e.g., Abacavir binding to HLA-B*5701).

Remarks:

Viral infections can mimic DHRs, but can also interact with drugs, leading to mild (e.g., "ampicillin rash" linked to EBV) and severe reactions (e.g., link between HHV-6 and DRESS).

The pathomechanism of non-allergic DHRs (often erroneously considered to be real drug allergies) may include:

- Non-specific mast cell or basophil histamine release (e.g., opiates, radiocontrast media and vancomycin).
- Bradykinin accumulation (angiotensin-converting enzyme inhibitors).
- Complement activation (e.g., protamine).
- Possibly an alteration of arachidonate metabolism (e.g., aspirin and NSAIDs).
- The pharmacological action of certain substances inducing bronchospasm (e.g., β -blockers, sulphur dioxide released by formulations containing sulphites).

CLINICAL PRESENTATIONS

Immediate DHRs: typically involve urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, gastro-intestinal symptoms (nausea, vomiting, diarrhea), or anaphylaxis which can lead to cardiovascular collapse (anaphylactic shock).

Non-immediate DHRs: often result in variable cutaneous symptoms such as late-occurring or delayed urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, blistering diseases (such as TEN, SJS and generalized bullous fixed drug eruptions), 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.

NATURAL HISTORY

Although the IgE antibody response is not permanent over time, IgE sensitization may persist for years. T-cell memory seems to be even stronger for non-immediate DHRs. Therefore lifelong avoidance of the drug and cross-reactive drugs is recommended when drug allergy has occurred.

DIAGNOSIS

- A **definitive diagnosis** of a DHR is in many cases required in order to institute proper preventive measures.
- 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 work up**.
- The clinical tools allowing a definitive diagnosis include a **thorough clinical history, standardized skin tests, reliable in vitro tests and drug provocation tests**.
- **Screening** subjects without a prior history of allergic drug reactions **is not recommended**.

When to evaluate?

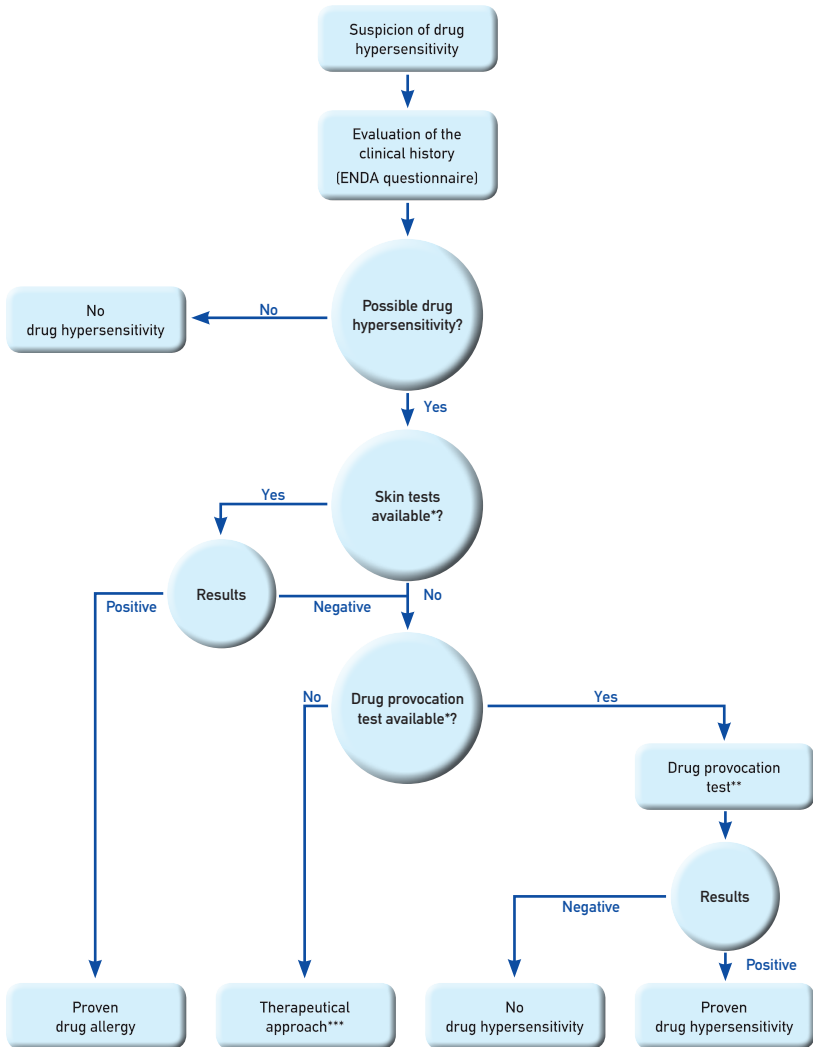
- When there is a history of prior DHR and the drug is required without an equally effective, structurally unrelated alternative, and if the risk/possible benefit ratio is positive.
- When there is a history of prior severe DHR for other drugs (the best way to protect the patient is to find the culprit agents).

When NOT to evaluate?

- Cases with no drug-allergy causality (non compatible symptomatology, non compatible chronology, drugs taken since with no reaction, reaction without having taken the drug).
- Alternative diagnosis (e.g., herpes virus eruption, chronic urticaria).
- For drug provocation every time the reaction was too severe: non-controllable reaction and severe life-threatening reactions.

Timing

- The allergy work-up should ideally be carried out 4-6 weeks after the complete resolution of all clinical symptoms.



* Currently available biological tests to diagnose drug allergy lack sensitivity.

** In the absence of contraindications.

*** If no alternative is available (e.g., neuromuscular blocking agents, chemotherapeutic drugs), readministration of the drug is allowed under surveillance, considering premedication and/or desensitization.

- **Symptomatology:** whether compatible with a DHR.
- **Chronology of 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 as well as other drugs of the same class taken since.
- **Medical background:** including previous allergy or a medical condition such as chronic urticaria/chronic rhinosinusitis that can be aggravated by the intake of certain drugs (e.g., aspirine and non-COX-2 selective nonsteroidal antiinflammatory drugs NSAIDs).

[illegible][illegible]

For immediate DHRs, the skin prick test is recommended for initial screening due to its simplicity, rapidity, low cost and high specificity. Intradermal tests are undertaken when skin prick tests are negative and provide enhanced sensitivity. Sensitivities and predictive values vary and appear to be “good” for immediate DHRs to β -lactam antibiotics, neuromuscular blocking agents, platin salts and heparins, but moderate to low for most other drugs.

For non-immediate DHRs, patchs test and/or late-reading intradermal tests should be performed.

For many drugs, standardized and validated test conditions are insufficiently studied or are disputed in the literature.

In case the drug is not available in an adequately reactive form, generally because it is the metabolic derivative which is immunogenic and not the parent drug, provocation tests are required to confirm the diagnosis.

III. Drug provocation tests

Drug provocation test (DPT) is the gold standard for the identification of the drug eliciting a DHR. It can confirm or exclude a DHR or demonstrate tolerance to a less likely eliciting drug.

- It is particularly required for NSAIDs, local anaesthetics, antibiotics other than β -lactams, and β -lactams when skin tests are negative.
- When the clinical history has a favourable positive predictive value, DPT can be performed directly with an alternative drug.
- The oral route is preferred whenever possible.

The following precautions and contraindications of DPT are recommended:

- **DPTs are contra-indicated in non controllable and/or severe life-threatening DHRs:**

- Severe cutaneous reactions (e.g., SJS, TEN, DRESS, vasculitis, AGEP).
- Systemic reactions (e.g., DRESS), internal organ involvement, hematologic reactions.
- Anaphylaxis may be tested after risk/benefit analysis.

- **DPTs are not indicated when:**

- The offending drug is unlikely to be needed and several structurally unrelated alternatives exist.
- Severe concurrent illness or pregnancy (unless the drug is essential for the concurrent illness or required during pregnancy or delivery).

- **DPTs should be performed under the highest safety conditions:**

- Trained staff: aware of the tests, ready to identify early signs of a positive reaction and ready to manage a life-threatening reaction.
- Emergency resuscitation equipment available.

Remarks:

- A negative DPT does not prove tolerance to the drug in the future; nevertheless, the negative predictive value (NPV) of for instance β -lactam (94-98%) or NSAIDs DPTs (over 96%) appears to be high.
- Desensitization by testing, as cause of false-negative DPT, is mentioned but no reference to the existing literature is made.
- Regarding β -lactam allergy, resensitization after a negative DPT (i.e., a conversion to skin test positivity) is reported (ranging from 0.9% to 27.9%). Retesting (2 to 4 weeks later) in patients who suffered severe immediate reactions with negative results at the first evaluation is optional (no consensus).

IV. Biological tests

- ***Drug-specific IgE:*** often not available or without evidence of validated assays for most drugs. Validated assays often lack sensitivity but are considered to be quite specific (>90%). Quantitative inhibition tests may explore in vitro cross-reactivities between several drugs, although their predicted clinical outcome is not fully validated.
- ***Tryptase and Histamine:*** in cases of anaphylaxis, blood measurements of histamine and/or tryptase may confirm an involvement of basophils and mast cells whatever the cause of the degranulation.
- ***Drug-induced type II and III allergic reactions:*** Coombs' test, in vitro hemolysis test, complement factors and circulating immune complexes can be performed. Drug-specific IgM or IgG are only of interest in cases of drug-induced cytopenia, type III DHRs to vaccines or allergies to dextrans, although the sensitivity of these tests is unknown.
- ***Genetic markers:*** HLA B*5701 screening reduces the risk of DHRs to abacavir and is mandatory before starting the treatment (positive predictive value 55% and NPV 100% if patch test is negative). DHR to carbamazepine in Han Chinese is associated with HLA B*1502.
- ***Assays involving T-cells:*** promising but only in expert laboratories.
- ***Basophil activation tests:*** promising but currently undergoing validation for certain drugs.

MANAGEMENT

General measures

- Anaphylaxis must be treated promptly and appropriately and all suspected drugs must be stopped.
- In non-anaphylactic reactions 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 (see below) are present.
- General preventive measures include a declaration to the Committee on Safety of Medicine Reports.

Individual preventive measures

- An indicative, regularly updated list of drugs to avoid and the list of possible alternatives should be given to patients with a DHR.
- The search for alternatives may require DPTs in a hospital setting when the alternatives belong to the same drug class.
- The questioning (to elicit any history of medication 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.
- 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.

Drug desensitization

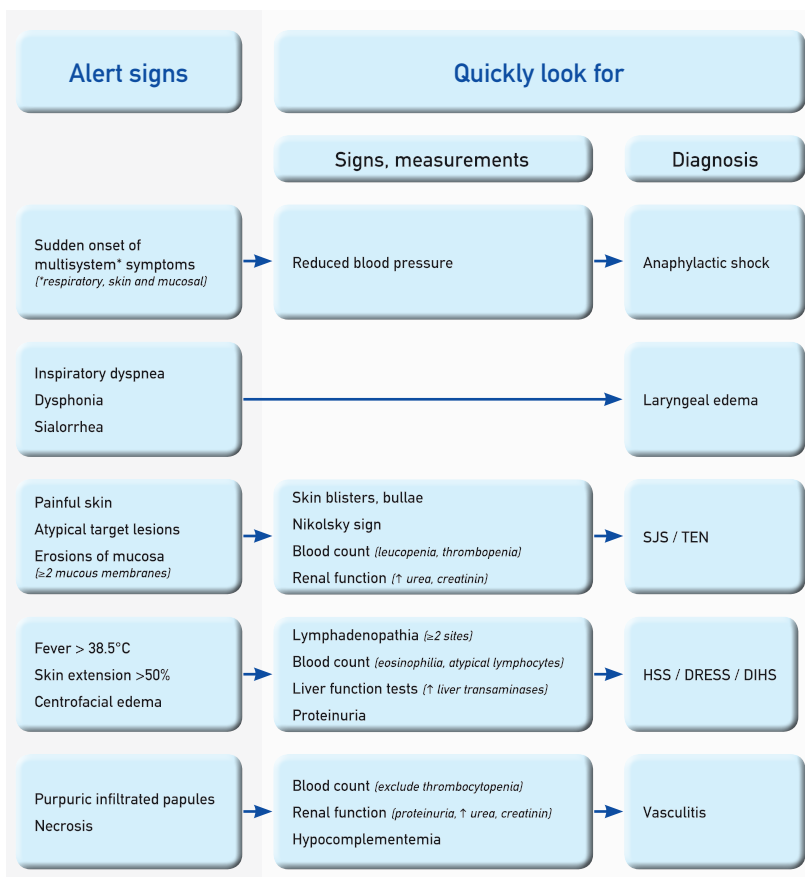
Drug desensitization is defined as the induction of a temporary state of clinical unresponsiveness/tolerance to a compound responsible for a DHR. Desensitization should be considered when the offending drug is essential and when either no alternatives exist or they are unsatisfactory:

- Sulfonamides in HIV-infected patients.
- Quinolone allergies in some cystic fibrosis patients.
- Serious infections with allergy to β -lactams, anti-tuberculosis drugs.
- Allergy to tetanus vaccine.
- Hemochromatosis with allergy to desferoxamine.
- Taxanes and platinum salt-based cancer chemotherapeutic agents.
- Monoclonal antibodies utilized in several types of hematological and non hematological neoplasms.

- Aspirin and NSAID hypersensitivity in patients for whom the necessity for these drugs to treat either a cardiac or rheumatic disease is clear.

Remarks:

- Guidelines recommend referral to successfully applied existing protocols.
- Desensitization to aspirin as a therapeutic intervention for aspirin exacerbated respiratory disease or nasal polyps may be considered in selected asthmatic patients.
- Literature on desensitization in non-immediate DHRs is less extensive and more controversial.



Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms/Drug-induced Hypersensitivity Syndrome (HSS/DRESS/DIHS); SJS, Stevens-Johnson Syndrome; TEN, Toxic Epidermal Necrolysis.

List of abbreviations

- AAAAI:** American Academy of Allergy Asthma and Immunology.
- ACAAI:** American College of Allergy Asthma and Immunology.
- AGEP:** acute generalized exanthematous pustulosis.
- 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.
- ENDA:** European Network of Drug Allergy.
- EBV:** Epstein Barr Virus.
- HHV:** Human Herpes 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.
- MPE:** maculo-papular exanthema.
- NMBA:** neuromuscular blocking agents.
- NPV:** negative predictive value.
- NSAID(s):** nonsteroidal anti-inflammatory drug(s).
- 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.

