ANNEX 3: DRUG ALLERGY

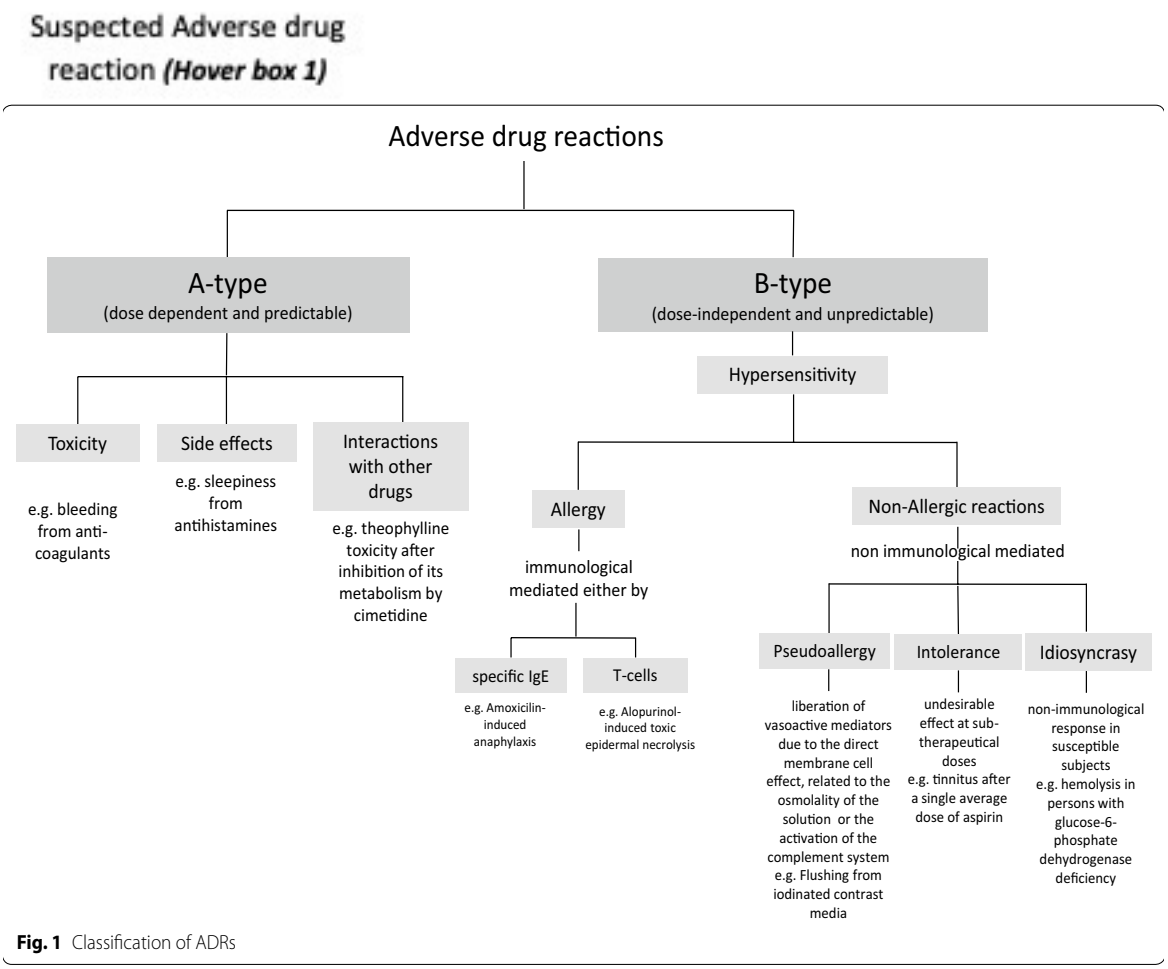

Fig. 1 Classification of ADRs

Doña I. & al., An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity, Clin. Transl. Allergy, 2018.

Predictable (Hover box 2)

A-type reactions are the most common (70-80%), and are a consequence of the pharmacological action of the drug, occurring in otherwise normal patients. They are *dose dependent* and *predictable*.

Table with A-type reactions:

Name of the reaction	Examples
Toxicity	Bleeding from anti-coagulants
Side effects	Sleepiness from antihistamines
Interactions with other drugs	Theophylline toxicity after inhibition of its metabolism by cimetidine

Doña I. et al., An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity, Clin. Transl. Allergy, 2018.

Unpredictable (Hover box 3)

B-type reactions are less common and are considered *dose-independent*, *unpredictable* and *unrelated to the pharmacological effects of the drug* when taken at normal dosage.

Table with B-reactions:

Name of the reaction	Definitions	Examples
Drug allergy	Hypersensitivity reaction immunologically mediated either - by drug-specific antibodies : - by T-cells:	- Amoxicillin-induced anaphyla - Allopurinol induced toxic epidermal necrolysis
Non-allergic reactions	Others hypersensitivity reactions non immunologically mediated.	
1/ Pseudoallergy	Liberation of vasoactive mediators due to the direct memebrane cell effect, related to the osmolality of the solution or the activation of the complement system.	➔ Flushing from iodinated contrast media
2/ Intolerance	Undesirable effect at sub-therapeutical doses.	➔ Tinnitus after a single averag of dose of aspirin
3/ Idiosyncrasy	Non-immunological response in susceptible subjects.	➔ Hemolysis in persons with glucose-6-phosphate deshydrogenase deficiency

Doña I. et al., An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity, Clin. Transl. Allergy, 2018.

When patient experiencing drug reaction

Red Flag Signs (Hover box 4)

ALERT SIGNS	QUICKLY LOOK FOR	
	Signs, measurements	**Diagnosis**
Sudden onset of multisystem* symptoms *(*respiratory, skin and mucosal)*	Reduced blood pressure	Anaphylactic shock
Inspiratory dyspnea Dysphonia Sialorrhea		Laryngeal edema
Painful skin Atypical target lesions Erosions of mucosa *(≥ 2 mucous membranes)*	Skin blisters, bullae Nikolsky sign Blood count *(leucopenia, thrombopenia)* Renal function *(↑urea, creatinin)*	SJS/TEN
Fever > 38.5°C Skin extension > 50% Centrofacial edema	Lymphadenopathia *(≥ 2 sites)* Blood count *(eosinophilia, atypical lymphocytes)* Liver function tests *(↑liver transaminases)* Proteinuria	HSS/DRESS/DIHS
Purpuric infiltrated papules Necrosis	Blood count *(exclude thrombocytopenia)* Renal function *(proteinuria, ↑urea, creatinin)* Hypocomplementemia	Vasculitis

Definition: Nikolsky sign: It is a clinical dermatological sign characterized by detachment of the epidermis when rubbing the skin with weak or moderate pressure. The sign is positive if when exerting a slight pressure there is detachment of the skin, leaving wet and red areas.

Demoly P. & al., International consensus on drug allergy, Allergy, 2014.

Hypotension or shock (Hover box 4a)

Low blood pressure after exposure to a known allergen for this patient (minutes to a few hours):
° From 1 month to 1 year, PAS <70 mmHg
° From 1 to 10 years old, PAS <70 + (2 x age) mmHg
° From 11 to 17 years old, PAS <90 mmHg
° Adult, PAS <90 mmHg or more than 30% lower than usual.

Gloaguen & al., Prise en charge de l'anaphylaxie en médecine d'urgence. Recommandation de la Société française de médecine d'urgence (SFMU) en partenariat avec la Société française d'allergologie (SFA) et le Groupe francophone de réanimation et d'urgences pédiatriques (GFRUP), et le soutien de la Société pédiatrique de pneumologie et d'allergologie, Ann.Fr.Med.Urgence, 2016.

Mucous membrane lesion (Hover box 4b)

Especially if affecting more than one mucosal area.

Doña I. & al., An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity, Clin. Transl. Allergy , 2018.

Fever (Hover box 4c)

Sudden onset of high fever (>39°C), otherwise explained.

Doña I. & al., An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity, Clin. Transl. Allergy , 2018.

Diffuse erythematous swelling (Hover box 4d)

Facial edema.

Doña I. & al., An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity, Clin. Transl. Allergy , 2018.

Internal organ involvement with disturbeded biomarquers (Hover box 4e)

Hepatocytolysis and renal failure, eosinophilia and hyperlymphocytosis.

Demoly P. & al., International consensus on drug allergy, Allergy, 2014.

Stopping medication (Hove box 4f)

When patients experiencing non anaphylactic 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.***

If danger/severity signs are present, the suspected drugs should be stopped immediately.

Demoly P. et al., International consensus on drug allergy, Allergy, 2014.

Continuing the treatment ("Treating through") (Hover box 4g)

Other options, such as treating through (…) are only used in certain specific situations.

Doña I. et al., An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity, Clin. Transl. Allergy , 2018.

First, continuation of the incriminated antibiotics was **deemed necessary because of their clinical effectiveness** and a **more favorable side effect profile** compared with structurally different alternatives. Second, **an unequivocal diagnosis of maculopapular exanthema was made by exclusion of any clinical and laboratory "danger signs"** indicating a potentially severe drug reaction.
Close and careful monitoring of patients was ensured in the inpatient setting. In addition to cutaneous and overall clinical symptoms, liver and kidney function parameters were regularly evaluated during follow-up.

Trautmann et al., "Treating Through" Decision and Follow-up in Antibiotic Therapy-Associated Exanthemas, J.Allergy Clin Immunol Pract, 2017

Consider differential diagnosis (Hover box 5)

Type of differential diagnosis	Examples
Infectious disease	Measles virus infection, scarlet fever, rubella, erythema infectiosum (parvovirus B19), exanthema subitem (Roseola infantum, HHV-6 infection)
Spontaneous acute urticaria or chronic urticaria	
Other dermatological disease	Psoriasis, lichen planus, eczema, pityriasis rosea, lupus erythematosus, dermatomyositis, bullous pemphigoid, Kawasaki disease

When patient reporting a past history of possible drug hypersensitivity

Document the history with a structured approach (Hover box 8)

Data that should be recorded in the case of a suspected DHR
Date of the reaction
The name of the incriminated drug and reason for prescribing
The number of doses taken before the reaction occurred
Time interval between the last dose of drug intake and the onset of the reaction
The nature and detailed description of the symptoms of the reaction
The treatment needed to resolve the reaction
The time for recovery
Other medications taken (both at the time of the reaction and other chemically related drugs after the reaction)
Underlying conditions (such as chronic urticaria/chronic rhinosinusitis)

Doña I. et al., An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity, Clin. Transl. Allergy , 2018.

Get documentation about clinical manifestations (cutaneous/extra-cutaneous) if available (Hover box 9)

Retrieve structured and precise written information. And for example, when there is a per-operative reaction, it is important to get anesthesia record.

Reproducibility (Hover box 10)

Patient with the same symptoms after taking the same drug or a similar drug class.
Eliminate patients with symptoms appearing without taking the drug or if medication taken since without reaction.

Demoly P. & al., Development of algorithms for the diagnosis and management of acute allergy in primary practice, World Allergy Organ J., 2019.

Time interval (Hover box 11)

Drug hypersensitivity reactions can be classified based on the delay between the last drug administration and the onset of the reaction as either an *immediate reaction,* when occurring up to 1 h after the drug intake, or *a non-immediate reaction*, when occurring after more 1h.

Doña I. & al., An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity, Clin. Transl. Allergy , 2018.

Severity of the reaction (Hover box 12)

For the evaluation of severity it is important to recovered : the treatment needed to resolve the reaction, the nature and detailed description of the symptoms of the reaction, the place of care (need for hospitalization), the time for recovery.

Doña I. et al., An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity, Clin. Transl. Allergy , 2018.

Cofactors (Hover box 13)

Finally, cofactors such **as exercise, food intake, alcohol and co-medications** can speed up or slow down the onset or progression of a reaction. It is also important to identify **specific medical condi- tions that may play a role in DHRs,** such as chronic spontaneous urticaria/chronic rhinosinusitis, autoimmune or infectious diseases such as human immunodeficiency virus infection.

Doña I. et al., An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity, Clin. Transl. Allergy , 2018.

Refer to a specialist (Hover box 14)

Confirm or refute the drug hypersensitivity diagnosis, through skin tests, targeted biological tests and provocation tests. In case of confirmed allergy, avoidance of the drug or of its pharmacological class, substitution treatment or desensitization will be considered.

Demoly P. & al., Development of algorithms for the diagnosis and management of acute allergy in primary practice, World Allergy Organ J., 2019.

Precisions: Iindications to referral the patient to specialist services:

- In General :

Refer people to a specialist drug allergy service if they have had:

- a suspected anaphylactic reaction or
- a severe non-immediate cutaneous reaction (for example, drug reaction with eosinophilia and systemic symptoms [DRESS], Stevens–Johnson Syndrome, toxic epidermal necrolysis).

- For Beta-lactam antibiotics :

Refer people with a suspected allergy to beta-lactam antibiotics to a specialist drug allergy service if they:

  - need treatment for a disease or condition that can only be treated by a beta-lactam antibiotic or
  - are likely to need beta-lactam antibiotics frequently in the future (for example, people with recurrent bacterial infections or immune deficiency).

- For NSAID:

Refer people who need treatment with an NSAID to a specialist drug allergy service if they have had a suspected allergic reaction to an NSAID with symptoms such as anaphylaxis, severe angioedema or an asthmatic reaction.

- For anaesthesic treatment:

Refer people to a specialist drug allergy service if they have had anaphylaxis or another suspected allergic reaction during or immediately after general anaesthesia.

Refer people to a specialist drug allergy service if they need a procedure involving a local anaesthetic that they are unable to have because of suspected allergy to local anaesthetics.

National Clinical Guideline Centre (UK). Drug Allergy: Diagnosis and Management of Drug Allergy in Adults, Children and Young People [Internet]. London: National Institute for Health and Care Excellence (UK); 2014 [cité 28 juill 2019]. (National Institute for Health and Clinical Excellence: Guidance). Disponible sur: http://www.ncbi.nlm.nih.gov/books/NBK248066/

Do not label (Hover box 15)

Update the person's medical records or inform their general practitioner is there is a change in the drug allergy status.

National Clinical Guideline Centre (UK). Drug Allergy: Diagnosis and Management of Drug Allergy in Adults, Children and Young People [Internet]. London: National Institute for Health and Care Excellence (UK); 2014 [cité 28 juill 2019]. (National Institute for Health and Clinical Excellence: Guidance). Disponible sur: http://www.ncbi.nlm.nih.gov/books/NBK248066/