**Overview of Drug Allergy: from immunogenetic basis to its clinical translation.**

**Alergia a Fármacos: da imunogenética à clínica.**

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**Overview of Drug Allergy**

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**Overview of Drug Allergy: from immunogenetic basis to its clinical translation. Abstract**

Drug therapy is often a balance between the beneficial and harmful effects of drugs. Drug allergic reactions are adverse reactions that are mediated by immunological mechanisms and usually not related to the pharmacological actions of the drug. They can be classified based either on the clinical presentation or the underlying immunological mechanism. Although uncommon, drug allergic reactions are unpredictable and can be very severe, even life threatening.

A review was conducted on the current literature about the complexity of drug allergy, from the incompletely known physiopathology to the heterogeneous clinical presentation, with a special focus on the drugs most frequently involved.

Despite all advances in this challenger field of allergy and immunology, the complexity of drug allergy is not yet fully established and understood. An exceptional contribution was brought by pharmacogenomics, though for a very limited number of drugs has been defined a specific pharmacogenetic association. Further studies are needed to allow obtaining straighter answers when managing each individual case of drug allergy.

**Resumo**

A terapêutica farmacológica consiste, frequentemente, num balanço entre os efeitos benéficos e prejudiciais dos fármacos. As reações alérgicas a fármacos são reações adversas mediadas por mecanismos imunológicos e habitualmente não relacionadas com as ações farmacológicas do fármaco. Podem ser classificadas quer com base na apresentação clínica, quer no mecanismo imunológico subjacente. Embora pouco comuns, as reações alérgicas a fármacos são imprevisíveis, podendo ser muito graves e potencialmente fatais.

Foi realizada uma revisão da literatura corrente, relativamente à complexidade das reações alérgicas a fármacos, desde a fisiopatologia, não completamente conhecida, à heterogeneidade da apresentação clínica. Foi dada especial atenção aos fármacos mais frequentemente envolvidos.

Apesar de todos os avanços nesta área desafiadora da alergologia e imunologia clínica, a complexidade da alergia a fármacos, não está ainda completamente compreendida e estabelecida. Um contributo excecional foi trazido pela farmacogenómica, embora uma associação farmacogenética esteja definida para um número muito limitado de fármacos. São necessários mais estudos que permitam obter respostas mais diretas na abordagem de cada caso individual de alergia a fármacos.

**Key words:**

Adverse drug reactions

Drug allergy

Drug hypersensitivity

**1 – Introduction**

Drug therapy is often a balance between the beneficial and harmful effects of drugs. Despite the intensive investigation in the field, adverse drug reactions remain a major problem. An adverse drug reaction (ADR) has been defined by the World Health Organization as any noxious, unintended and undesired effect of a drug occurring at doses normally used for prevention, diagnosis or treatment 1. It has been estimated that ADRs account for 3% to 6% of all hospital admissions and occur in 10% to 15% of hospitalized patients, contributing to morbidity and mortality2-3. A widely used classification system divides ADRs in two types: Type A (predictable, common, related to the pharmacological properties of the drug), and Type B (unpredictable, uncommon, usually unrelated to the pharmacological actions of the drug). The first type comprises approximately 80% of all ADRs and includes drug-induced toxicity, side effects and drug interactions 4-7. Drug allergy reactions (DARs) are those mediated by immunological mechanisms and belong to type B. In practice, based on the clinical presentation alone, it is often difficult to differentiate between immune- and non-immune-mediated reactions, thus the term drug hypersensitivity (DH) is applied to drug reactions that clinically seem like allergy, but where an immunological mechanism cannot be demonstrated 4,9. DHRs comprise 15% of all ADR. DARs, although less common (estimated to represent a small percentage of all ADRs), can be very complex and potentially severe, even life-threatening 4.

The study of DARs is challenging5 and is constantly updated as new drugs are developed and drug consumption patterns are changed 6.

A review was conducted on the current literature about the complexity of DARs, from the incompletely known physiopathology to the heterogeneous clinical presentation, with a special focus on the drugs most frequently involved.

**2 – Classification**

A consensus classification is mandatory to guide and validate the diagnostic work-up. DARs can be classified based on the clinical presentation or the underlying immunological mechanism (table 1).

**Clinically**, DARs are classified depending on the time elapsed between drug administration and the onset of symptoms: **immediate** (occurring up to one hour after the last drug administration) and **non-immediate** (at any time, after one hour and up to several days of drug administration) 4.

Any of the 4 **immunologic mechanisms** proposed by Gell and Coombs 9, may underlie DARs with IgE- and T-cell-mediated reactions as the most common 4,10. **Type I**, also known as immediate reactions (IRs), are mediated by drug-specific IgE antibodies. **Type II** (cytotoxic) and **Type III** (immune complex) are mediated by drug-specific IgG or IgM antibodies. **Type IV** are mediated primarily by T cells 4-6,10-13 and has been recently classified in 4 subtypes, according to cytokine patterns and the preferential activation of different immunocytes10.

**3 – Clinical Presentation**

**3.1 – Immediate reactions**

IRs present as isolated symptoms (urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm) or as a severe presentation as anaphylaxis. Urticaria/angioedema and anaphylaxis are the most common. The IgE-mediated allergy to β-Lactam (βL) antibiotics is the paradigmatic example 4,14.

**3.2 – Non-immediate reactions**

The skin is the most frequently involved organ in non-immediate reactions (NIRs), with a wide range of clinical manifestations. Maculopapular exanthema (MPE) and delayed urticaria are the most common 4,6,11,14. Fixed drug eruption (FDE), acute generalized exanthematic pustulosis (AGEP), erythema multiforme (EM) and eczema are other presentations 13.

Both skin and other organs can be involved, as in drug rash with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DiHS), vasculitis and Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) 4,6,11,14.

Mild eruptions usually occur one to few days after the drug treatment is started, while most severe reactions often begin later on (SJS/TEN: 4-21 days; DRESS/DiHS: 2-6 weeks) 4,15.

DRESS is an unusual DAR characterized by the presence of morbilliform rash, atypical lymphocytosis, eosinophilia, fever and other organ involvement, usually liver 13,15. A minimum criterion of rash, fever, hepatitis and lymphocytosis has been proposed for DiHS 16.

SJS and TEN, the most severe type of reactions affecting the skin, are characterized by extensive epidermal detachment and mucous membrane erosion, including oral, conjunctival and anal 11,13. Although uncommon (estimated prevalence: 5-6 cases and 1-2 cases per million patients for SJS and TEN, respectively) 17, the morbidity and mortality is high (5-10% mortality for SJS 16-17 and 30–50% for TEN) 13,16-18. Several authors support SJS and TEN are a single disease with common causes and physiopathology, but different spectrums of severity according to the extension of epidermal detachment (<10%:SJS; 10–30%:SJS–TEN overlapping; >30%:TEN) 11,1316-18. Drugs causing SJS/TEN overlap with those causing DRESS/DiHS: aromatic amine anticonvulsants (phenytoin, carbamazepine, phenobarbital), sulfonamides antibiotics, nonsteroidal anti-inflammatory drug (NSAIDs) and antiretroviral agents (abacavir, nevirapine). Allopurinol and lamotrigine were also associated with SJS/TEN  11,13,15-17.

EM is characterized by the presence of target-shaped lesions and, although less severe, can be an early presentation of SJS/TEN. Any of these reactions contraindicate the re-administration of the culprit drug 13.

**4 – Pathogenesis and physiopathology**

**4.1 – Chemical basis**

For a drug to become an antigen, able to elicit an immune response, two main mechanisms have been proposed: 1. The drug, a chemically reactive small-molecule, must bind irreversibly to a protein, generating antigens (hapten concept); 2. The drug, chemically inert, needs to be converted into reactive metabolites before binding irreversibly to proteins (pro-hapten concept) 4-5,19-21.

For T-cell mediated reactions, the role of a carrier-protein/hapten has not been fully defined as for IgE mediated reactions 4,19.

An alternative hypothesis is that some drugs might also originate a direct reversible interaction with the T-cell receptors or HLA-molecules, activating T cells by pharmacological interaction (**p-i concept)** 10. According to this hypothesis, the drug eliciting an immunological response is not dependent on its structural features nor metabolism. Chemically inert drugs are able to directly activate T-cell receptors 4-5,12,20.

**Cross-reactivity** between drugs is an immunological reaction that occurs on exposure to different drugs with a similar molecular structure. This can happen even without any previous exposure to the cross-reacting drug, allowing some risk prediction of reactivity to chemically related drugs 12.

**4.2 – Immunopathological mechanisms**

It has been proposed that drug-protein conjugates might be processed and presented by antigen-presenting cells to naive T cells, after drug intake, inducing tolerance or effector responses22. In the last case, the immune system develops either immediate T-helper2 (Th2)- type responses, mediated by specific IgE antibodies, or non-immediate Th1-type responses, mainly mediated by specific T cells 5,11. Alternatively, T cells could be directly stimulated by the drug 10.

**4.2.1 – Immediate reactions**

IRs develop as a result of **IgE production.** At an initial **sensitization phase,** B-cells proliferate and differentiate into plasma cells, in the presence of specific Th2-cells. Drug-specific IgE are then produced and bind to the high-affinity FcRI receptors on the surface of mast cells and basophils. On **subsequent drug exposure**, the drug antigen cross-links IgE on the surface of mast cells, activating them which induces the release of preformed mediators (e.g., histamine, tryptase, TNF-α) and the production of new ones (e.g., leukotrienes, prostaglandins, cytokines). The sensitization phase is usually asymptomatic and can have occurred during an earlier drug treatment 4-5,15.

**4.2.2 – Non-immediate reactions**

The majority of NIRs are mediated byT lymphocytes 4,15. Most of the information available concerns to the specific effector immune response **mediated by T cells**. Little is known about the initial steps mediated by the innate immune system, mainly by dendritic cells 11,22.  It has been proposed that these cells can process the drug antigen as first step to stimulate naive T cells 4. The antigen is then internalized and transported to the regional lymph nodes, where is presented to naive T cells. Alternatively, it may stimulate directly pathogen-specific T cells, without priming by dendritic cells. Antigen-specific T cells migrate to target organs and, on **re-exposition** to the drug, are activated to secrete cytokines.

Other immune cells are involved in NIRs, fitting into the four **subtypes of Type IV reactions**10: **Iva**) Th1 cells produce interferon-γ-activated **macrophages**, whose typical clinical manifestation is eczema; **IVb)** Th2 cytokines induce production of antibodies by B cells and the **eosinophil** responses, mainly in MPE and DRESS; **IVc**) CD4+ and CD8+ **T cells** produce **cytotoxic** mediators leading to keratinocyte apoptosis in MPE and massive apoptosis in SJS/TEN; **IVd**) **neutrophil** recruitment and T-cell-induced activation by the production of a chemokine, CXCL8, mainly in AGEP.

Interestingly, the histopathology findings in SJS/TEN show detachment of large portion of epidermis13 induced by massive T-cell mediated keratinocyte apoptosis. Previously, Fas-FasL interaction and perforin-granzyme B were the pathways reported as basic effectors 13,16. More recently, granulysin was described as a key effector responsible for keratinocytes death 16,18,23. Granulysin concentrations in blister fluid seem to correlate with the severity of SJS/TEN23 and high granulysin serum levels may be a useful early diagnostic biomarker 18.

In a minority of NIRs other immune mechanisms may be involved. **Type II** **reactions** concern to IgG-mediated cytotoxicity directed to membranes of erythrocytes, leukocytes and platelets. Drugs typically involved are methyldopa (hemolytic anemia), aminopyrine (leukopenia), and heparin (thrombocytopenia). Such reactions may occur only as long as the drug is present in soluble form. **Type III** **reactions** involve the formation of immune complexes (IC), a common event in a normal immune response, usually asymptomatic. On rare occasions, IC bind to endothelial cells and lead to IC deposition with complement activation in small blood vessels, translated in serum sickness syndrome (SSS), drug-induced lupus erythematosus or vasculitis 5.

**4.3 – Pharmacogenetics**

The finding of strong associations of certain severe reactions, mostly NIRs, with HLA-B alleles has allowed a great progress in drug allergy 4,16-18,20. The association of HLA alleles with SJS/TEN has been reported, for the first time, more than 25 years ago24. Since then, specific HLA alleles have been found to be associated with this disease17. A strong association between carbamazepine (CBZ)-induced SJS/TEN and HLA-B\*1502 has been described in a Chinese population, where this allele was present in all patients suffering from CBZ-induced SJS 25. Subsequently this association was also found in Indian26 and Thai 27, but not in Japanese28 or European patients29. This association seems to be phenotype-specific (SJS/TEN) 4 and is stronger than any other described so far 17.

In northern Europeans, the presence of HLA-A\*3101 has been associated with a wide spectrum of CBZ-induced reactions (MPE, DRESS/DiHS, SJS/TEN)30.

Other important HLA association include HLA-B\*5801and SJS/TEN or DRESS/DiHS with allopurinol, in Asian 31-33 and European populations 34.

Finally, the carriage of HLA-B\*5701 has been strongly associated withflucloxacillin-induced liver injury 35 and with abacavir hypersensitivity syndrome, a severe multi-organic reaction 36-37. This association was higher among Caucasians, where the allele was present in 94.4% cases (positive predictive value ≥ 70%; negative predictive value: 95- 98%)37. International HIV treatment guidelines determine the HLA-B\*5701 screening prior abacavir treatment 38.

Recent pharmacogenomic studies involving from a candidate-gene approach to the genome-wide association study (GWAS) brought great advances in the discovery of genes associated with inter-individual differences in drug response (mainly genes predisposing to ADRs but also genes responsible for drug efficacy). The HLA system has been a major focus for type B reactions, particularly the more severe immune reactions 16-17. A number of polymorphisms located on chromosome 6 have been found in association with SJS/TEN induced by alopurinol 39 and abacavir 40.  In IRs, some polymorphisms in cytokine genes have been weakly associated with βL-induced anaphylaxis 41-42.

This greater knowledge has made some DARs quite predictable 16,20.

**4.5 – Risk factors**

There are few identified factors influencing the risk of sensitization and the severity of DARs. These are the chemical structure of the molecule, the nature of drug exposure (dose, route, frequency and duration), the presence of co-factors (eg. stress, infections), genetic predisposition, immune status and female gender 5, 20. In the “balance” of drug and individual related factors (figure 1), a disturbed immunologic status associated with the development of recurrent infections, decreases the threshold to induce a response. Also the HLA genotype can dictate the way in which a drug can cause allergy 21.

**4.5.1 – The role of viruses**

Viral infections are the main cause of skin reactions, that can mimic DARs if the drug, usually an antibiotic, is taken at the same time. Viruses can also interact with drugs and immune system, leading to allergic reactions such as the mild ampicillin exanthema linked to the Epstein-Barr virus (EBV) infection or DRESS/DiHS 4,11,20-21,43-44. DRESS/DiHS is the best studied DAR associated with viral infection and has been linked to the reactivation of human herpes virus (HHV)-6. EBV, cytomegalovirus and other HHV can be involved, even days or weeks after discontinuation of the drug 4,11,16,21,44.

 The interaction with the immune system can occur at several points: drug metabolism; drug presentation to T cells, by dendritic cells; and effector response (cytokine and chemokine production) 11,45.

**5 – Allergic reactions to specific drugs**

**5.1 –** **Antibiotics**

**5.1.1 – β-Lactams**

βLs are still the most frequent cause of DARs. Benzylpenicillin was the first βL implicated, but amoxicillin has progressively become the most common culprit. A wide range of manifestations can occur, reflecting different underlying immunological mechanisms. They can induce IRs, mediated by IgE (usually urticaria/angioedema and anaphylaxis) and also NIRs (mainly MPE). Severe NIRs (AGEP, SJS/TEN, DRESS) can also occur 6,14.

βLs clearly induce immunological reactions due to hapten-carrier formation which occur through the nucleophilic opening of the βL ring and the generation of reactive intermediates 6,14,21. Recent studies have pointed out the relevance of the three-dimensional shape of the βL, as well as its inherent chemical reactivity, in determining the selectivity of the covalent binding 20. The role of side chains, that distinguish different penicillin compounds, as relevant allergenic determinants is also widely accepted, particularly in IRs to aminopenicillins and cephalosporins. Thus, cephalosporins with a similar side-chain should be avoided in patients with IgE-mediated reactions to penicillin 14,46. Moreover, the Interest group of the European Network of Drug Allergy position paper recommends, in cases of IRs to penicillin, skin testing with the alternative drug (cephalosporins, carbapenems, aztreonam), prior its administration. If negative, drug must be given at increasing doses in an appropriate setting.

In NIRs to aminopenicillins, both core structure and the whole molecule (core structure plus the amino-benzyl group of the side-chain) are recognized by T cells, although the latter plays a predominant role14. Despite very rare, cross-reactivity between penicillins, cephalosporins and carbapenems for T-cell reactions, also demands investigation 14, 47.

**5.1.2 – Sulfonamides**

Sulfonamides are defined as drugs with a SO2-NH2 moiety. Sulfonamide antibiotics also contain an aromatic amine (N4 position) and a substituted ring (N1 position) 46. After βLs, sulfonamide antibiotics (namely sulfamethoxazole-SMX) are the most common cause of DARs 46,48. SMX usually cause cutaneous NIRs and rarely IgE-mediated reactions 13,21,46, trough T cells direct activation by covalent binding or acting as pro-hapten, respectively, as SMX is a chemical inert drug 15,21,49-50.  MPE is the most common presentation, but SJS/TEN were also described 13,21,46,48.

About 40-80% of HIV patients treated with trimethoprim (TMP)-SMX develop a generalized MPE, usually accompanied by fever, while the incidence of skin rashes to TMP-SMX in healthy subjects is only 3% to 5%. The increased risk in HIV patients is probably related to immunologic and metabolic factors and to the frequent exposure to TMP-SMX 48.

The N4 aromatic amine is critical for the development of NIRs to sulfonamide antibiotics and the N1 substituted ring appears to be important for IgE-mediated reactions.  As non-antibiotic sulfonamides lack these structural components, they would not be expected to cross-react with sulfonamide antibiotics 13,46,48. On the opposite, all sulfonamide antibiotics should be considered to be cross-reactive 13.

**5.1.3 – Fluoroquinolones**

This widely used class of broad spectrum antibiotics can induce reactions mediated by IgE (hapten-carrier formation) and T cells (p-i mechanism) 6,51-53, that are estimated to occur in 2-3% of the treated patients 51. IgE-mediated reactions are more common and usually severe, with anaphylaxis as the most frequent presentation.  Urticaria/angioedema can also occur. NIRs are less frequent and include MPE, FDE, vasculitis, AGEP and SJS/TEN 6,51-53. Moxifloxacin induces more severe reactions 6 and is the most frequently involved, followed by ciprofloxacin and levofloxacin 6,52.

As cross-reactivity between these antibiotics is common, in the case of a severe reaction, eviction of all the quinolones is advisable 13,54.

**5.2 – Nonsteroidal anti-inflammatory drugs**

NSAIDs are responsible for 21-25% of reported ADRs, including immunological and non-immunological reactions.  Depending on the clinical presentation and the presumable underlying mechanism, hypersensitivity to NSAIDs is classified in 2 groups and 5 subgroups (table 2) 55.  In the first group (≥75% of cases6), the putative mechanism is the inhibition of ciclooxigenase-1, hence hypersensitivity to multiple NSAIDs is observed regardless of their chemical structure and/or anti-inflammatory potency 55.

The second group involves the selective reactions, probably with an underlying **immunological mechanism**: a) **IgE-mediated** is the proposed mechanism in cases of urticaria, angioedema and anaphylaxis induced by a single NSAID or a group of chemically related drugs 55-56. Pyrazolones, paracetamol, ibuprofen, diclofenac and naproxen are the most common55. The last 3 compounds have a heteroaryl acetic group, presumably carrying a higher risk of anaphylaxis (OR 19.7) 57; b) NIRs, probably **T-cell mediated,** were also reported induced by a single NSAID or a group of chemically related drugs 55-56. Cutaneous reactions, particularly MPE are the most frequent reaction. NSAIDs are the main cause of FDE and can also induce SJS/TEN (particularly oxicams) 55.

**5.3 – Neuromuscular Blocking Agents**

Immediate HRs during the perioperative period have been increasingly reported in developed countries 58-59. Most reactions are mediated by IgE and less frequently related to direct stimulation of histamine release 58-60.

IgE mechanism causes perioperative anaphylaxis with an estimated incidence of 1:10000 to 1:20000 anesthetic procedures. Any drug administered in this period can potentially induce this life-threatening reaction 58-59. Different populations exhibit different patterns of sensitization 7. NMBAs are the most common cause (50-70%), followed by antibiotics and latex. Suxamethonium is the most frequent reported culprit, with a recent increment of rocuronium, vecuronium and pancuronium, translating an increasing use of these drugs 58-62. Sensitization to NMBAs seems to demand the presence of a substituted ammonium ion in the drug molecule. In many cases, the reaction may occur at the first exposure, since a prior sensitization to other compound with a substituted ammonium ion (eg. pholcodine) may have occurred 5,61. Investigation of cross-reactivity between NMBAs is mandatory in diagnostic work-up 58-62.

**5.4 – Radiocontrast media**

In the past the ionic high-osmolar RCM induced a high incidence of IRs due to the nonspecific release of vasoactive mediators 6. Despite the introduction of nonionic (NI) low-osmolar RCM, HRs are still a matter of concern. A recent European multicenter study suggests that at least 50% of the HRs to NI-RCM are caused by an immunological mechanism. Cross-reactivity was pronounced among NI-RCM with a very similar chemical structure 63. It is estimated that NI-RCM can cause IRs and NIRs in about 1–3% of applications 64. IRs are mainly anaphylaxis, whereas NIRs predominantly manifest as mild skin eruptions occurring hours to days after RCM administration 63-67.

**5.5 – Biological Modifiers**

The biologic immune modulator agents have been recently developed and are increasingly used. They comprise proteins such as cytokines and monoclonal antibodies (mAbs) 6,46 that differ from other drugs as they have high molecular-weight with a great immunogenic potential 46. Three major groups of mAbs are in use: chimeric (-ximab), humanized (-zumab) and human antibodies (-mumab). They can induce reactions through different immunological mechanisms 68. IgE-mediated reactions to basiliximab, infliximab, rituximab and cetuximab have been reported 6-7,48. IgE antibodies to cetuximab specific for alpha-1,3-galactose have been found in the majority of anaphylactic reactions 7.

A rare delayed anaphylaxis has been reported in near 0.2% of exposures to omalizumab and also after trastuzumab, daclizumab, infliximab and basiliximab administration13.

NIRS have been described after rituximab (vasculitis, SSS) 7 and infliximab infusion (SSS, SJS, DiHS) 46.

**5.6 – Antineoplastic agents**

HSR to antineoplastic agents are an increasing problem. Any cytostatic can potentially expose the patient to the risk of an immune reaction. They can elicit either immediate (urticaria, bronchospasm, dyspnea, thoracic/abdominal pain, fever, anaphylaxis) or NIRs (macular/MPE, vasculitis). Severity of reactions ranges from mild symptoms to life-threatening anaphylaxis 69.

HSR are more common with platinum compounds (cisplatin, carboplatin, oxaliplatin), epipodophyllotoxins (teniposide, etoposide), asparaginase, taxanes (paclitaxel) and procarbazine. Doxorubicin and 6-mercaptopurine are rare culprits. HSR to carboplatin and oxaliplatin are particularly frequent (incidence: 12-17%), with more than 50% of the reactive patients developing moderate to severe symptoms 70-72.

Most reactions occur during the treatment (platinum derivatives and taxanes), although some appear hours after the drug administration. Reactions to taxanes usually manifest during the first few minutes of the first or second infusion, whereas acute reactions to platinum agents usually occur after several cycles 73.

Since these drugs are usually the first line therapy and when no equally effective alternative drugs are available, patients can be desensitized following the general considerations for these procedures published in a consensus paper for IRs 74and NIRs 75.

**6- Comment:**

Despite all advances, the complexity of drug allergy is not yet fully established and understood. An exceptional contribution was brought by pharmacogenomics, though for a very limited number of drugs has been defined a specific association. Further investigation is needed to obtain straighter answers when managing each individual case of drug allergy. The development of new biomarkers and a “tailored-made” medicine is probably the future.

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**Figure 1**: **Drug Allergy: a balance between drug factors and patient biology** (adapted from 21).

**Legends**:

p-i concept: pharmacological interaction with immune receptors.

**Table 1- Classification of drug allergies** (adapted from 4).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Type** | **Type of immune**  **Response** | **Pathophisiology** | **Timing of reaction** | **Clinical symptoms** | **Typical chronology**  **of the reaction** |
| **I** | IgE | Mast cell and basophil degranulation | Immediate | Anaphylaxis  Urticaria/Angioedema  Bronchospasm  Rhinitis | Between 1 to 6 h after the last drug intake |
| **II** | IgG and complement | IgG and complement-dependent cytotoxicity | Non-immediate | 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 after the start of the eliciting drug for serum sickness/urticaria;  7–21 days for vasculitis |
| **IV a** | Th1 (IFN-gama) | Monocytic inflammation | Eczema | 1–21 days after the start of  the eliciting drug |
| **IV b** | Th2 (IL-4 and IL-5) | Eosinophilic inflammation | MPE  DRESS/ DiHS | 1 to several days after the start of the eliciting drug for MPE;  2–6 weeks for DRESS/DiHS |
| **IV c** | Cytotoxic T cells (perforin, granzyme B, FasL, granulysin) | Keratinocytic death  mediated by  CD4 or CD8 | MPE  FDE  SJS/TEN | 1–2 days after the start of the eliciting  drug for FDE;  4–28 days for SJS/TEN |
| **IV d** | T cells (IL-8/CXCL8) | Neutrophilic  Inflammation | AGEP | 1–2 days after the start of the elicit  ting drug, but can be longer |

**Legends:** IgE- immunoglobulin E; IgM- immunoglobulin M; IgG- immunoglobulin G; Th1- T helper1; Th2- T helper 2; IFN gama – Interferon gama; IL4- Interleukin 4; IL5- Interleukin 5; IL8- Interleukin 8; CXCL8- chemokine motif ligand 8; MPE- maculopapular exanthema; DRESS- drug rash with eosinophilia and systemic symptoms; DiHS- drug-induced hypersensitivity syndrome; FDE-fixed drug eruption; SJS- Stevens-Johnson syndrome; TEN- toxic epidermal necrolysis; AGEP- acute generalized exanthematic pustulosis.

**Table 2- Classification of Hypersensitivity Reactions Induced by NSAIDs** (adapted from 55).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Type of reaction** | **Clinical manifestations** | **Timing of reaction** | **Underlying disease** | **Cross-reactivity** | **Putative** | **Mechanism** |
| **NSAID-exacerbated respiratory disease (NERD)** | Bronchospasm  Nasal symptoms | Acute (usually immediate to several hours after exposure) | Asthma/  rhinosinusitis | Cross-reactive | Non- allergic | COX-1 inhibition |
| **NSAID-exacerbated cutaneous disease (NECD)** | Urticaria and/or angioedema | Chronic urticaria |
| **NSAID-induced urticaria/angioedema (NIUA)** |  | Unknown (probably COX-1 inhibition) |
| **Single NSAID-induced urticaria/angioedema or anaphylaxis**  **(SNIUAA)** | Urticaria and/or angioedema/ anaphylaxis |  | No underlying chronic disease | Non Cross-reactive | Allergic | IgE-mediated |
| **Single NSAID-induced delayed reactions**  **(SNIDR)** | Various symptoms and organs involved (eg. MPE, FDE, SJS/TEN, nephritis) | Delayed onset (usually  >24h after exposure) |  | T  cell-mediated |

**Legends:** NSAID- nonsteroidal anti-inflammatory drug; NERD-NSAID-exacerbated respiratory disease; NECD: NSAID-exacerbated cutaneous disease; NIUA: NSAID-induced urticarial/angioedema; SNIUAA: NSAID-induced urticarial/angioedema or anaphylaxis; SNIDR: Single NSAID-induced delayed-reactions; MPE- Maculopapular exanthema; FDE- fixed drug eruption; SJS- Stevens-Johnson syndrome; TEN- toxic epidermal necrolysis; COX- 1: ciclooxigenase 1; IgE- immunoglobulin E.